

The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***THE EFFECT OF GABAPENTIN ON PERIOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK SURGERY PATIENTS***

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>The effect of gabapentin on perioperative pain control among head and neck surgery patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.6 (sixth amended version)</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection (mucosal head and neck surgeries)</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing all types of head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 2 or the day of discharge, whichever comes first. Note that on the morning of POD3 at 7am, a VAS will be obtained to reflect the POD 2 7pm dose. The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The perioperative BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be observational, based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing surgical resection of head and neck mucosal surfaces.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck patients undergoing surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

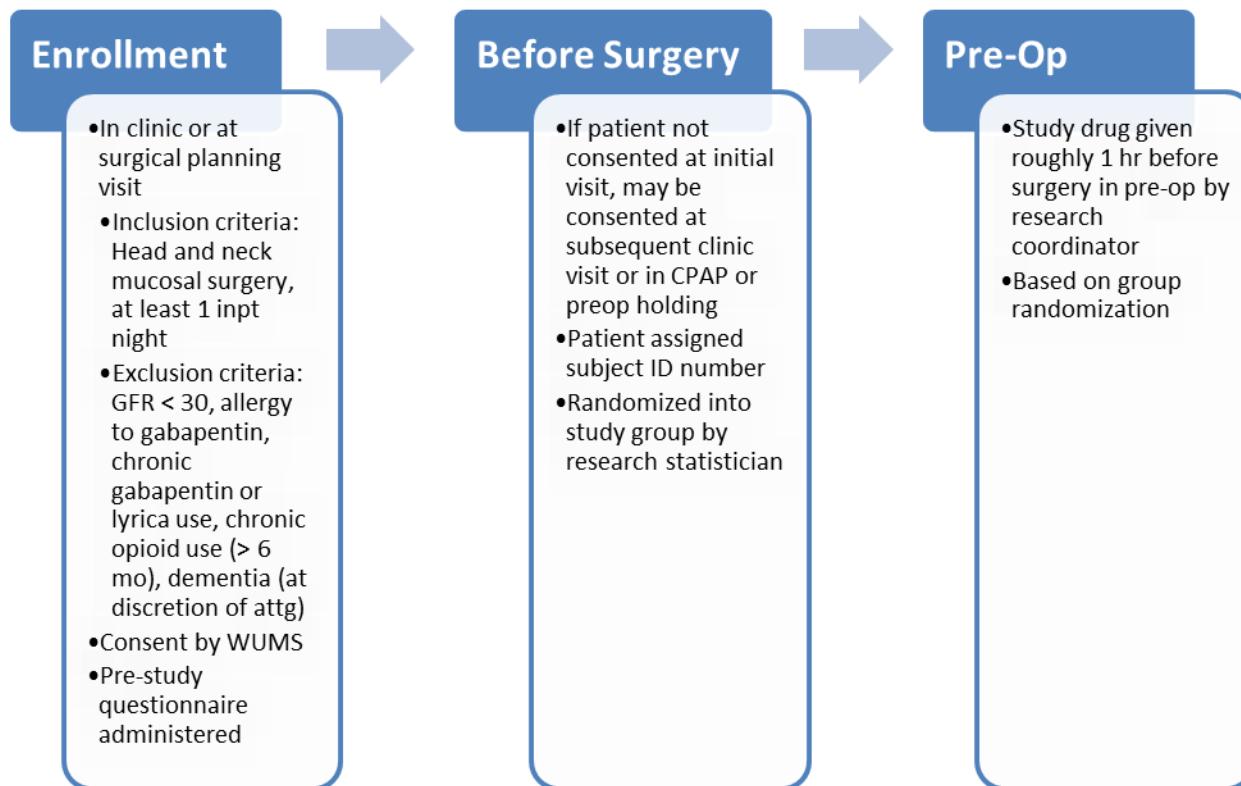
3 Study Design

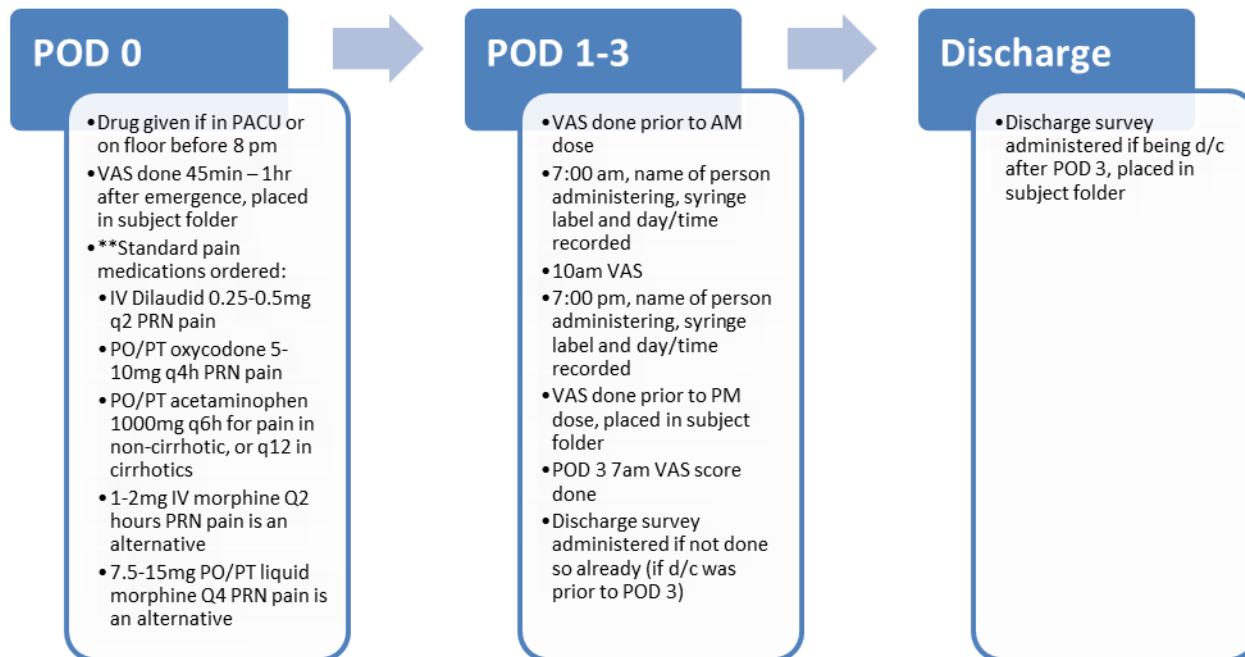
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The duration of subject participation includes the subsequent inpatient hospitalization following definitive

cancer resection up to two days after surgery. Subjects will be given the placebo or gabapentin for up to two days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM, the center for outpatient health or at other outpatient or inpatient sites related to their pre-surgical planning visits. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached either in the exam room during their scheduled appointment with the head and neck surgeons or afterwards via telephone call. The study will be explained to them and a copy of the consent form will be provided after it has been signed. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their head and neck health needs. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in a private room. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and patients will be reassured that their care from their head and neck surgeon will not be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





****Note that IV and PO or per tube morphine will be used in amounts equivalent to the dilaudid and oxycodone medications above if an allergy or intolerance to dilaudid or oxycodone exist.**

Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication approximately 1 hour prior to surgery start time. Patients will not be excluded if surgery start time is delayed past 1 hour. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study member will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain (5mg if pain less than or equal to 5/10, 10mg if greater than 5/10), and dilaudid 0.25-0.5mg Q2 hours PRN breakthrough pain (0.25mg if pain less than or equal to 5/10, 0.5mg if greater than 5/10). Alternatives to these medications in case of allergy or intolerance is 1-2mg IV morphine Q2 hours PRN pain (1mg if pain less than or equal to 5/10, 2mg if greater than 5/10) and 7.5-15mg PO/PT liquid IR morphine Q4 hours PRN pain (7.5mg if pain less than or equal to 5/10, 15mg if greater than 5/10). Additionally, the study team member will place the appropriate investigational drug order in compass. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. Additionally, if the subject is at any point during the study placed on alcohol withdrawal medication protocols, he or she will be withdrawn from the study. The study team member administering the preoperative dose will remind anesthesia to use the same post-operative initial pain management options in the PACU at least initially, again with no restrictions on dose escalations that are needed. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer, and their PACU medication sheet will be copied and added to their hard copy file for use later during

tabulation/data analysis of the pain meds they required. The VAS score obtained after surgery will be completed 45 minutes to 1 hour after extubation in the PACU.

Note that subjects must have completed surgery (extubated) by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS scores can still be obtained at 45 minutes to 1 hour postoperatively, however, even if the case finishes later than 5pm. On POD 1-2, subjects will be given BID medications at 7am and 7pm per the study protocol and VAS scores will be obtained prior to medication administration. A separate VAS will be obtained at 10am on POD1 and POD 2. ON POD 3 a 7am VAS will be obtained but no study medication given. This last VAS concludes participation in the study. Discharge surveys will be administered at this point if they have not been already (ie if the patient remained an inpatient for longer than 2 days postop).

The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to scheduled doses, and the medications will be stored in patient labeled bins in the locked medication refrigerator. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a line measuring 10cm during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" on the far left and "worst pain" on the far right. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

Note that study medication wrappers have patient names on them as a safety mechanism to make sure medications are given to the proper patient. These wrappers and labels will be saved in the patient folders which are secured in a locked cabinet where only study team members have access. Empty and unlabeled medication syringes will be discarded in the red biohazard bins inside patient rooms.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

2. How often did the hospital staff do everything they could to help you with your pain?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

3. How satisfied are you with your overall pain control?

- 0) Very dissatisfied
- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and once on POD 3, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in centimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

- (d) Hospital length of stay will be calculated for each subject.
- (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A safety meeting will be held half way through the study with the PI and all involved faculty mentors to determine if an interim analysis is necessary. This analysis would be considered necessary if a significant number of adverse events likely related to the study medication were occurring, and an analysis to make sure the study was not causing harm to the treatment group was needed.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin or lyric use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited either in the outpatient head and neck clinic prior to their planned surgeries or over the phone after this clinic appointment by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Patient recruited by phone will be able to sign the informed consent prior to surgery either at a subsequent surgical planning visit or in the pre-op holding area on the day of surgery. Eligible subjects will be consented in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. They will also be withdrawn if they remain sedated or intubated after the surgery or are placed on alcohol withdrawal medication protocols, which also cause significant sedation. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

4.4.3 Definitions

Subject withdraw: Withdraw is defined as a subject who signed the informed consent document and for whatever reason dropped out of the study before completion, whether by choice or by exclusion criteria (ie- staying intubated the night after surgery).

Subject screen fail: A screen fail is defined as a subject who has been recruited to participate and approached but does not meet all inclusion criteria.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication syringe or in a marked bag with a capsule. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area approximately 1 hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening (ie not extubated before 5pm), and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 2. Dosing will end either on POD 2 after the PM dose or on day of discharge after the AM dose, whichever comes first. VAS scores will be collected 45 minutes- 1 hour post extubation on POD as well as TID on POD 1-2 and one time at 7am on POD 3 (see above protocol flowsheet).

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assigned an enrollment ID. The enrollment ID is given to any subject who signs consent. If the subject then proceeds to start the study and receive a medication dose, they will also be given a subject ID which reflects their randomization group. The study ID reflects randomization while the enrollment ID is used to enter them into OnCore and track their consent.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the preop holding unit or the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN breakthrough pain (pain equal to or less than 5/10 will get 0.25mg and pain >5/10 will get 0.5mg).
- PO/PT oxycodone 5-10mg q4h PRN pain (pain equal to or less than 5/10 will get 5mg, and pain greater than 5/10 will get 10mg).
- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients
- Morphine IV and PO liquid equivalents will be substituted in cases of oxycodone or dilaudid allergies. 1-2mg IV morphine Q2 hours PRN will be substituted for 0.25-0.5mg dilaudid for breakthrough pain (pain equal to or less than 5/10 will get 1mg and pain >5/10 will get 2mg). PRN liquid IR morphine 7.5-15mg will be substituted Q4 hours for oxycodone PRN for pain (pain equal to or less than 5/10 will get 7.5mg, and pain greater than 5/10 will get 15mg)
- Study team members will place an order in compass for study investigation drug administration as per BJC protocol for investigational drug use.

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid or capsule form. Gabapentin comes as a standard liquid form of 250mg/5ml. Capsules will be used for the pre-operative dose, and will come as single capsules in bags labeled with study ID and name. For post-operative doses, 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic syringe. Each syringe will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at

4 degrees Celsius. The medications will be stored prior to dosing on the floor in a locked fridge in patient specific compartments, as per the floor medication protocol.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medications, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to planned doses. They will be alerted to upcoming procedures that involve study subjects. They will be responsible for delivering the medication to the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius. They will be stored on the inpatient floor in a locked, 4 degree fridge in patient specific compartments per the floor medication storage protocols.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication syringes will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files. Any labels or bags with patient names will be discarded in the shred bins on the 6200 floor or in the preop holding unit.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group approximately 1 hour prior to procedure start time. The coordinator administering the medication will tape a study reminder sheet for anesthesia to the chart and will place an order in the chart that allows the participant to take the preop medication dose, and the RN to chart this dose as a study medication.

- Standard pain medications orders will be provided. Morphine will be used as a substitute for dilaudid or oxycodone allergies or intolerances. These will be up-titrated as needed per discretion of service residents and attending physicians.
- One VAS score will be obtained 45 minutes to 1 hour postoperatively regardless of extubation time.
- One postoperative dose of study drug and VAS will be administered at 7pm if subjects are extubated by 5PM

Post-Operative Day (POD) 1-2

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3

- POD 3 VAS at 7am will be obtained.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dose on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadid et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size $d=0.6$) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

Note that IV morphine equivalents will be used rather than PO.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

Note that in discrepancies of data between reports, such as pack years smoked by a patient, an average of the reported amounts will be used to ensure consistency between data reporting fluctuations.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries that occur during the study period will be regarded as adverse events (meaning that the event does not necessarily have to be likely related to the study drug to be considered an adverse event). However, not all adverse events will meet criteria for reporting. Abnormal results of diagnostic procedures will be reported as adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (see definition below)
- is associated with clinical signs or symptoms that are considered significant and likely related to study participation
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious, moderate or mild. . A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Mild and Moderate adverse events:

A moderate adverse event is one that requires a medical intervention such as medication for nausea, but that does not cause permanent clinical harm and that does resolve in a reasonable amount of time.

A mild adverse event is one that causes mild clinical effect and may or may not require medical intervention. It is expected to resolve completely with observation or medical treatment.

Adverse Event Reporting

The study period during which adverse events that are deemed reportable will be the period from the day of surgery to the end of the study, which is POD 3 or sooner if discharge is sooner than POD 3. Ideally, these events will be reported to the PI within 24 hours of their occurrence. Serious AE must be reported within 24 hours, however. Additionally, subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced after discharge so that the study members can be alerted to any events that may be related to the medication. Any severe adverse events or moderate events thought likely to be related to the study medication that are reported to the PI during this 30 day window will be recorded. Adverse events that occur during the inpatient study period and are significant/severe as defined above or that are unusual will be required to be reported in the adverse events log. The PI will be made aware of all of these events immediately after they occur. All adverse events regardless of grade and attribution will be collected. The PI will sign off on all adverse events that are recorded in the adverse event log.

For all severe AEs or AEs that are unexpected and thought likely related to the study medication, an IRB reportable event form will be submitted. All adverse events, whether mild, moderate or severe, will be reviewed at the safety meeting by all team members and faculty advisors to ensure that proper reporting has occurred.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study in the 30 days window follow discharge.

8.2 Eliciting Adverse Events from Subjects

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the data recording form that is used to record subject data at each interaction. Reporting of these events is as outlined above. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

8.3 Unblinding Procedures

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% by the PI and at 50% enrollment by the entire team to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A safety meeting will be held half way through enrollment as described above,

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, these records will be destroyed in the proper manner in shred it bins where patient information is normally placed. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort

- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at <https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf>

11 Medication processing

11.1 Medication Processing

All unused medications will be picked up from the pharmacy within 12 hours of the time they are determined to be not needed or not used. The pharmacy will be alerted in real time that the medication was not needed so that they can expect to pick it up. A confirmation communication will be sent to the study team once the medication is retrieved to ensure that it is properly picked up.

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The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***THE EFFECT OF GABAPENTIN ON PERIOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK SURGERY PATIENTS***

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>The effect of gabapentin on perioperative pain control among head and neck surgery patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.5 (fifth amended version)</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection (mucosal head and neck surgeries)</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing all types of head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 2 or the day of discharge, whichever comes first. Note that on the morning of POD3 at 7am, a VAS will be obtained to reflect the POD 2 7pm dose. The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The perioperative BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be observational, based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing surgical resection of head and neck mucosal surfaces.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck patients undergoing surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

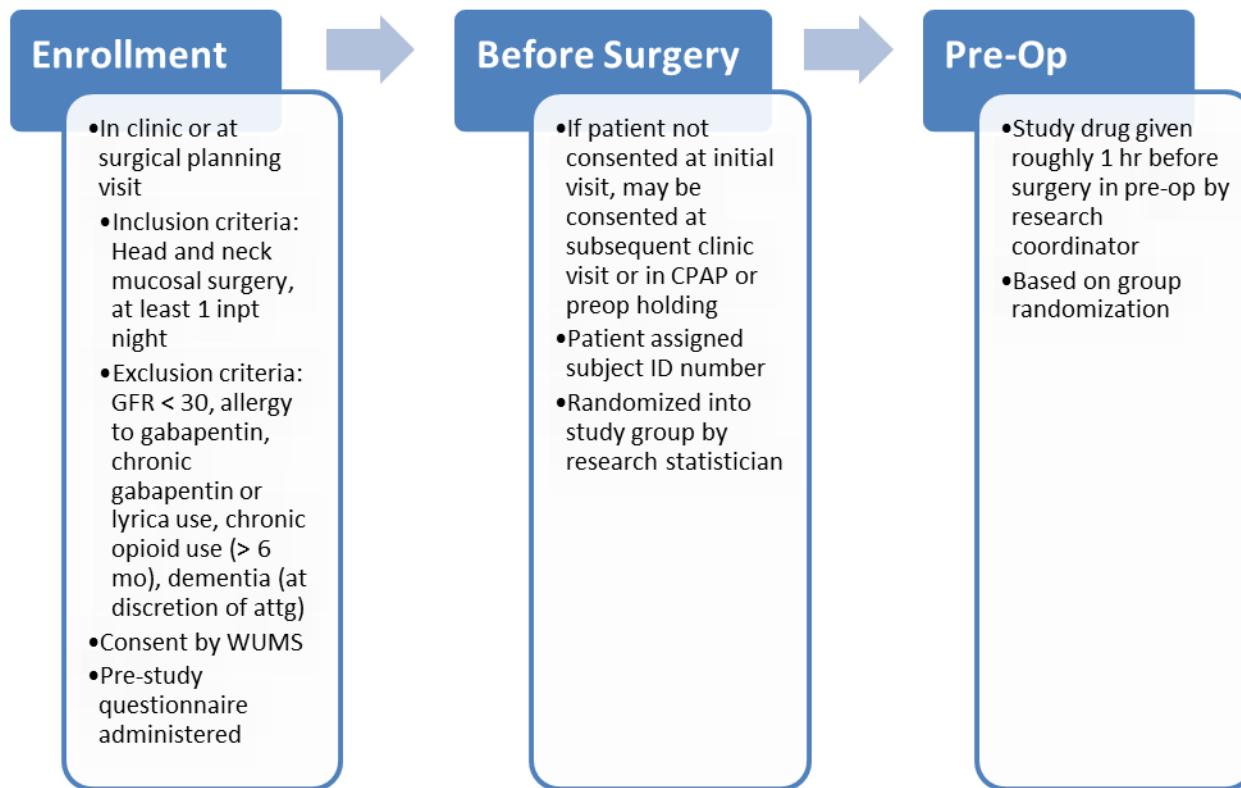
3 Study Design

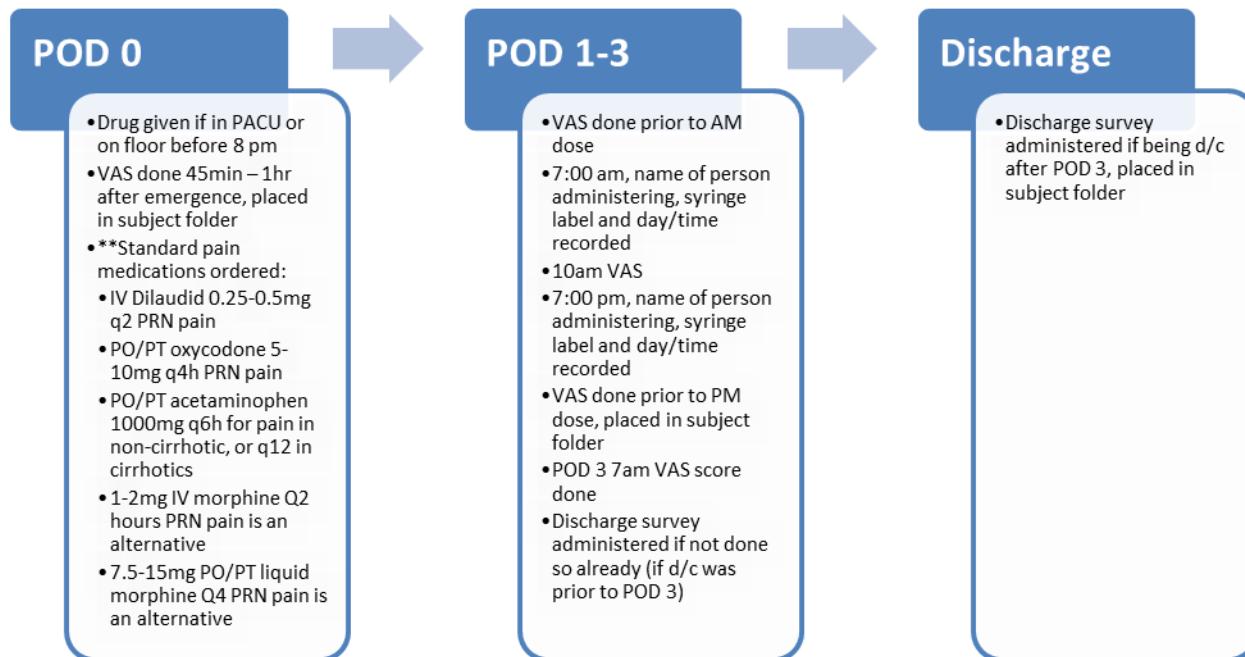
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The duration of subject participation includes the subsequent inpatient hospitalization following definitive

cancer resection up to two days after surgery. Subjects will be given the placebo or gabapentin for up to two days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM, the center for outpatient health or at other outpatient or inpatient sites related to their pre-surgical planning visits. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached either in the exam room during their scheduled appointment with the head and neck surgeons or afterwards via telephone call. The study will be explained to them and a copy of the consent form will be provided after it has been signed. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their head and neck health needs. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in a private room. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and patients will be reassured that their care from their head and neck surgeon will not be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





****Note that IV and PO or per tube morphine will be used in amounts equivalent to the dilaudid and oxycodone medications above if an allergy or intolerance to dilaudid or oxycodone exist.**

Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication approximately 1 hour prior to surgery start time. Patients will not be excluded if surgery start time is delayed past 1 hour. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study member will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain (5mg if pain less than or equal to 5/10, 10mg if greater than 5/10), and dilaudid 0.25-0.5mg Q2 hours PRN breakthrough pain (0.25mg if pain less than or equal to 5/10, 0.5mg if greater than 5/10). Alternatives to these medications in case of allergy or intolerance is 1-2mg IV morphine Q2 hours PRN pain (1mg if pain less than or equal to 5/10, 2mg if greater than 5/10) and 7.5-15mg PO/PT liquid IR morphine Q4 hours PRN pain (7.5mg if pain less than or equal to 5/10, 15mg if greater than 5/10). Additionally, the study team member will place the appropriate investigational drug order in compass. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. Additionally, if the subject is at any point during the study placed on alcohol withdrawal medication protocols, he or she will be withdrawn from the study. The study team member administering the preoperative dose will remind anesthesia to use the same post-operative initial pain management options in the PACU at least initially, again with no restrictions on dose escalations that are needed. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer, and their PACU medication sheet will be copied and added to their hard copy file for use later during

tabulation/data analysis of the pain meds they required. The VAS score obtained after surgery will be completed 45 minutes to 1 hour after extubation in the PACU.

Note that subjects must have completed surgery (extubated) by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS scores can still be obtained at 45 minutes to 1 hour postoperatively, however, even if the case finishes later than 5pm. On POD 1-2, subjects will be given BID medications at 7am and 7pm per the study protocol and VAS scores will be obtained prior to medication administration. A separate VAS will be obtained at 10am on POD1 and POD 2. ON POD 3 a 7am VAS will be obtained but no study medication given. This last VAS concludes participation in the study. Discharge surveys will be administered at this point if they have not been already (ie if the patient remained an inpatient for longer than 2 days postop).

The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to scheduled doses, and the medications will be stored in patient labeled bins in the locked medication refrigerator. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a line measuring 10cm during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" on the far left and "worst pain" on the far right. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

Note that study medication wrappers have patient names on them as a safety mechanism to make sure medications are given to the proper patient. These wrappers and labels will be saved in the patient folders which are secured in a locked cabinet where only study team members have access. Empty and unlabeled medication syringes will be discarded in the red biohazard bins inside patient rooms.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

2. How often did the hospital staff do everything they could to help you with your pain?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

3. How satisfied are you with your overall pain control?

- 0) Very dissatisfied
- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and once on POD 3, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in centimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

- (d) Hospital length of stay will be calculated for each subject.
- (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A safety meeting will be held half way through the study with the PI and all involved faculty mentors to determine if an interim analysis is necessary. This analysis would be considered necessary if a significant number of adverse events likely related to the study medication were occurring, and an analysis to make sure the study was not causing harm to the treatment group was needed.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin or lyrica use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited either in the outpatient head and neck clinic prior to their planned surgeries or over the phone after this clinic appointment by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Patient recruited by phone will be able to sign the informed consent prior to surgery either at a subsequent surgical planning visit or in the pre-op holding area on the day of surgery. Eligible subjects will be consented in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. They will also be withdrawn if they remain sedated or intubated after the surgery or are placed on alcohol withdrawal medication protocols, which also cause significant sedation. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

4.4.3 Definitions

Subject withdraw: Withdraw is defined as a subject who signed the informed consent document and for whatever reason dropped out of the study before completion, whether by choice or by exclusion criteria (ie- staying intubated the night after surgery).

Subject screen fail: A screen fail is defined as a subject who has been recruited to participate and approached but does not meet all inclusion criteria.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication syringe or in a marked bag with a capsule. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area approximately 1 hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening (ie not extubated before 5pm), and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 2. Dosing will end either on POD 2 after the PM dose or on day of discharge after the AM dose, whichever comes first. VAS scores will be collected 45 minutes- 1 hour post extubation on POD as well as TID on POD 1-2 and one time at 7am on POD 3 (see above protocol flowsheet).

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assigned an enrollment ID. The enrollment ID is given to any subject who signs consent. If the subject then proceeds to start the study and receive a medication dose, they will also be given a subject ID which reflects their randomization group. The study ID reflects randomization while the enrollment ID is used to enter them into OnCore and track their consent.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the preop holding unit or the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN breakthrough pain (pain equal to or less than 5/10 will get 0.25mg and pain >5/10 will get 0.5mg).
- PO/PT oxycodone 5-10mg q4h PRN pain (pain equal to or less than 5/10 will get 5mg, and pain greater than 5/10 will get 10mg).
- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients
- Morphine IV and PO liquid equivalents will be substituted in cases of oxycodone or dilaudid allergies. 1-2mg IV morphine Q2 hours PRN will be substituted for 0.25-0.5mg dilaudid for breakthrough pain (pain equal to or less than 5/10 will get 1mg and pain >5/10 will get 2mg). PRN liquid IR morphine 7.5-15mg will be substituted Q4 hours for oxycodone PRN for pain (pain equal to or less than 5/10 will get 7.5mg, and pain greater than 5/10 will get 15mg)
- Study team members will place an order in compass for study investigation drug administration as per BJC protocol for investigational drug use.

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid or capsule form. Gabapentin comes as a standard liquid form of 250mg/5ml. Capsules will be used for the pre-operative dose, and will come as single capsules in bags labeled with study ID and name. For post-operative doses, 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic syringe. Each syringe will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at

4 degrees Celsius. The medications will be stored prior to dosing on the floor in a locked fridge in patient specific compartments, as per the floor medication protocol.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medications, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to planned doses. They will be alerted to upcoming procedures that involve study subjects. They will be responsible for delivering the medication to the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius. They will be stored on the inpatient floor in a locked, 4 degree fridge in patient specific compartments per the floor medication storage protocols.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication syringes will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files. Any labels or bags with patient names will be discarded in the shred bins on the 6200 floor or in the preop holding unit.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group approximately 1 hour prior to procedure start time. The coordinator administering the medication will tape a study reminder sheet for anesthesia to the chart and will place an order in the chart that allows the participant to take the preop medication dose, and the RN to chart this dose as a study medication.

- Standard pain medications orders will be provided. Morphine will be used as a substitute for dilaudid or oxycodone allergies or intolerances. These will be up-titrated as needed per discretion of service residents and attending physicians.
- One VAS score will be obtained 45 minutes to 1 hour postoperatively regardless of extubation time.
- One postoperative dose of study drug and VAS will be administered at 7pm if subjects are extubated by 5PM

Post-Operative Day (POD) 1-2

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3

- POD 3 VAS at 7am will be obtained.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dose on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadid et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size $d=0.6$) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

Note that IV morphine equivalents will be used rather than PO.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

Note that in discrepancies of data between reports, such as pack years smoked by a patient, an average of the reported amounts will be used to ensure consistency between data reporting fluctuations.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries that occur during the study period will be regarded as adverse events (meaning that the event does not necessary have to be likely related to the study drug to be considered an adverse event). However, not all adverse events will meet criteria for reporting. Abnormal results of diagnostic procedures will be reported as adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (see definition below)
- is associated with clinical signs or symptoms that are considered significant and likely related to study participation
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious, moderate or mild. . A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a new congenital anomaly or birth defect
- an important medical event

Mild and Moderate adverse events:

A moderate adverse event is one that requires a medical intervention such as medication for nausea, but that does not cause permanent clinical harm and that does resolve in a reasonable amount of time.

A mild adverse event is one that causes mild clinical effect and may or may not require medical intervention. It is expected to resolve completely with observation or medical treatment.

Adverse Event Reporting

The study period during which adverse events that are deemed reportable must be reported will be the period from the day of surgery to the end of the study, which is POD 3 or sooner if discharge is sooner than POD 3. Ideally, these events will be reported to the PI within 24 hours of their occurrence. Serious AE must be reported within 24 hours, however. Additionally, subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced after discharge so that the study members can be alerted to any events that may be related to the medication. Any severe adverse events or moderate events thought likely to be related to the study medication that are reported to the PI during this 30 day window will be recorded. Adverse events that occur during the inpatient study period and are significant/severe as defined above or that are unusual will be required to be reported in the adverse events log. The PI will be made aware of all of these events immediately after they occur. Events that are mild will not be required to be recorded in the adverse events log. Events that are moderate and thought likely related to the study medication will be reported. Events that are moderate but deemed unlikely to be due to the study medication will not be required to be reported in the adverse events log. However, these events may still be recorded in the adverse events log at the discretion of the PI. The PI will sign off on all adverse events that are recorded in the adverse event log.

For all severe AE or AE that are unexpected and thought likely related to the study medication, an IRB event form will be submitted. For moderate events thought likely to be due to the medication or unexpected, an event form will be submitted at the discretion of the PI. This design is intended to make sure that if subjects seem to be having symptoms that aren't expected to be caused by study participation but are noted in multiple subjects, then this gets reported. However, those side effects that are common after surgery (such as sedation or nausea) that could also be related to study medications are noted in the AE log when appropriate but not generating multiple IRB reportable event forms. The goal is to ensure subject safety and also only report appropriate events to the IRB. All adverse events, whether mild, moderate or severe, will be reviewed at the safety meeting by all team members and faculty advisors to ensure that proper reporting has occurred.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study in the 30 days window follow discharge.

8.2 *Eliciting Adverse Events from Subjects*

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the data recording form that is used to record subject data at each interaction. Reporting of these events is as outlined above. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

8.3 *Unblinding Procedures*

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% by the PI and at 50% enrollment by the entire team to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A safety meeting will be held half way through enrollment as described above,

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, these records will be destroyed in the proper manner in shred it bins where patient information is normally placed. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

This study will be monitored in real time for each subject by the PI and study team. At minimum, with 25% accrual goal all adverse events and data collection forms will be reviewed by the PI and discussed among the study team. At our interim safety meeting, we determined by our AE log that significant adverse events were not occurring to study patients and events that were moderate and likely related to the medication also were extremely infrequent. We determined at that time that a third party officer review was unnecessary, especially in light of the fact that we were aware at that point that an audit would occur. We will proceed to study completion without this third party review. We also will be reporting our study events and AE events in a DSM log to the Siteman monitoring committee, which will also serve as a third party review.

11 Medication processing

11.1 Medication Processing

All unused medications will be picked up from the pharmacy within 12 hours of the time they are determined to be not needed or not used. The pharmacy will be alerted in real time that the medication was not needed so that they can expect to pick it up. A confirmation communication will be sent to the study team once the medication is retrieved to ensure that it is properly picked up.

12 References

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The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***THE EFFECT OF GABAPENTIN ON PERIOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK SURGERY PATIENTS***

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>The effect of gabapentin on perioperative pain control among head and neck surgery patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.4 (fourth amended version)</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection (mucosal head and neck surgeries)</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing all types of head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 2 or the day of discharge, whichever comes first. Note that on the morning of POD3 at 7am, a VAS will be obtained to reflect the POD 2 7pm dose. The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The perioperative BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be observational, based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing surgical resection of head and neck mucosal surfaces.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck patients undergoing surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

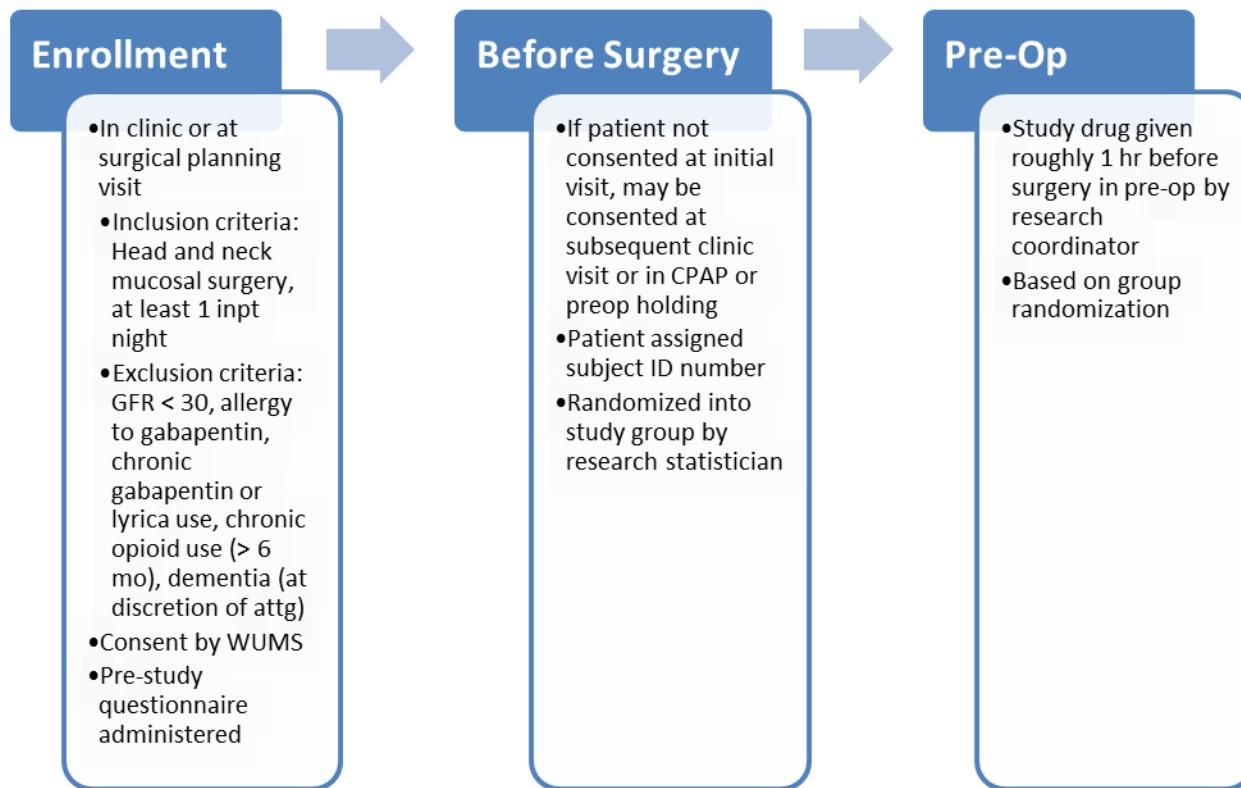
3 Study Design

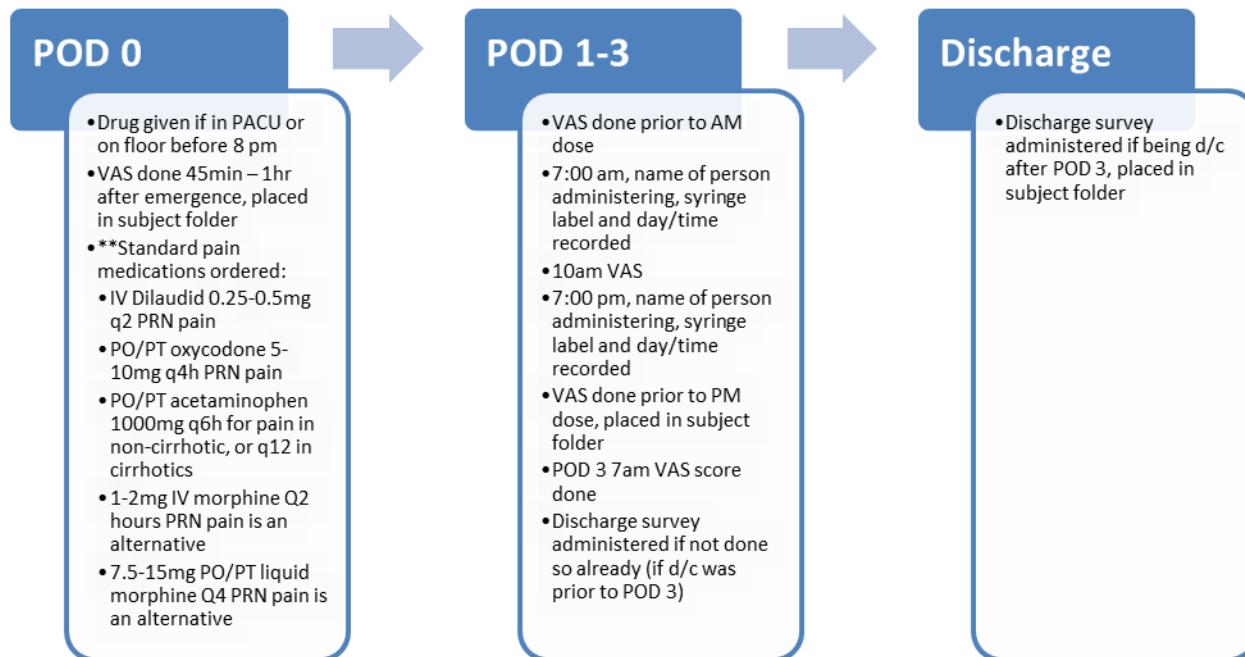
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The duration of subject participation includes the subsequent inpatient hospitalization following definitive

cancer resection up to two days after surgery. Subjects will be given the placebo or gabapentin for up to two days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM, the center for outpatient health or at other outpatient or inpatient sites related to their pre-surgical planning visits. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached either in the exam room during their scheduled appointment with the head and neck surgeons or afterwards via telephone call. The study will be explained to them and a copy of the consent form will be provided after it has been signed. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their head and neck health needs. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in a private room. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and patients will be reassured that their care from their head and neck surgeon will not be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





****Note that IV and PO or per tube morphine will be used in amounts equivalent to the dilaudid and oxycodone medications above if an allergy or intolerance to dilaudid or oxycodone exist.**

Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication approximately 1 hour prior to surgery start time. Patients will not be excluded if surgery start time is delayed past 1 hour. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study member will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain (5mg if pain less than or equal to 5/10, 10mg if greater than 5/10), and dilaudid 0.25-0.5mg Q2 hours PRN breakthrough pain (0.25mg if pain less than or equal to 5/10, 0.5mg if greater than 5/10). Alternatives to these medications in case of allergy or intolerance is 1-2mg IV morphine Q2 hours PRN pain (1mg if pain less than or equal to 5/10, 2mg if greater than 5/10) and 7.5-15mg PO/PT liquid IR morphine Q4 hours PRN pain (7.5mg if pain less than or equal to 5/10, 15mg if greater than 5/10). Additionally, the study team member will place the appropriate investigational drug order in compass. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. Additionally, if the subject is at any point during the study placed on alcohol withdrawal medication protocols, he or she will be withdrawn from the study. The study team member administering the preoperative dose will remind anesthesia to use the same post-operative initial pain management options in the PACU at least initially, again with no restrictions on dose escalations that are needed. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer, and their PACU medication sheet will be copied and added to their hard copy file for use later during

tabulation/data analysis of the pain meds they required. The VAS score obtained after surgery will be completed 45 minutes to 1 hour after extubation in the PACU.

Note that subjects must have completed surgery (extubated) by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS scores can still be obtained at 45 minutes to 1 hour postoperatively, however, even if the case finishes later than 5pm. On POD 1-2, subjects will be given BID medications at 7am and 7pm per the study protocol and VAS scores will be obtained prior to medication administration. A separate VAS will be obtained at 10am on POD1 and POD 2. ON POD 3 a 7am VAS will be obtained but no study medication given. This last VAS concludes participation in the study. Discharge surveys will be administered at this point if they have not been already (ie if the patient remained an inpatient for longer than 2 days postop).

The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to scheduled doses, and the medications will be stored in patient labeled bins in the locked medication refrigerator. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a line measuring 10cm during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" on the far left and "worst pain" on the far right. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

Note that study medication wrappers have patient names on them as a safety mechanism to make sure medications are given to the proper patient. These wrappers and labels will be saved in the patient folders which are secured in a locked cabinet where only study team members have access. Empty and unlabeled medication syringes will be discarded in the red biohazard bins inside patient rooms.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

2. How often did the hospital staff do everything they could to help you with your pain?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

3. How satisfied are you with your overall pain control?

- 0) Very dissatisfied
- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and once on POD 3, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in centimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

- (d) Hospital length of stay will be calculated for each subject.
- (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A safety meeting will be held half way through the study with the PI and all involved faculty mentors to determine if an interim analysis is necessary. This analysis would be considered necessary if a significant number of adverse events likely related to the study medication were occurring, and an analysis to make sure the study was not causing harm to the treatment group was needed.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin or lyrica use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited either in the outpatient head and neck clinic prior to their planned surgeries or over the phone after this clinic appointment by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Patient recruited by phone will be able to sign the informed consent prior to surgery either at a subsequent surgical planning visit or in the pre-op holding area on the day of surgery. Eligible subjects will be consented in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. They will also be withdrawn if they remain sedated or intubated after the surgery or are placed on alcohol withdrawal medication protocols, which also cause significant sedation. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

4.4.3 Definitions

Subject withdraw: Withdraw is defined as a subject who signed the informed consent document and for whatever reason dropped out of the study before completion, whether by choice or by exclusion criteria (ie- staying intubated the night after surgery).

Subject screen fail: A screen fail is defined as a subject who has been recruited to participate and approached but does not meet all inclusion criteria.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication syringe or in a marked bag with a capsule. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area approximately 1 hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening (ie not extubated before 5pm), and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 2. Dosing will end either on POD 2 after the PM dose or on day of discharge after the AM dose, whichever comes first. VAS scores will be collected 45 minutes- 1 hour post extubation on POD as well as TID on POD 1-2 and one time at 7am on POD 3 (see above protocol flowsheet).

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assigned an enrollment ID. The enrollment ID is given to any subject who signs consent. If the subject then proceeds to start the study and receive a medication dose, they will also be given a subject ID which reflects their randomization group. The study ID reflects randomization while the enrollment ID is used to enter them into OnCore and track their consent.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the preop holding unit or the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN breakthrough pain (pain equal to or less than 5/10 will get 0.25mg and pain >5/10 will get 0.5mg).
- PO/PT oxycodone 5-10mg q4h PRN pain (pain equal to or less than 5/10 will get 5mg, and pain greater than 5/10 will get 10mg).
- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients
- Morphine IV and PO liquid equivalents will be substituted in cases of oxycodone or dilaudid allergies. 1-2mg IV morphine Q2 hours PRN will be substituted for 0.25-0.5mg dilaudid for breakthrough pain (pain equal to or less than 5/10 will get 1mg and pain >5/10 will get 2mg). PRN liquid IR morphine 7.5-15mg will be substituted Q4 hours for oxycodone PRN for pain (pain equal to or less than 5/10 will get 7.5mg, and pain greater than 5/10 will get 15mg)
- Study team members will place an order in compass for study investigation drug administration as per BJC protocol for investigational drug use.

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid or capsule form. Gabapentin comes as a standard liquid form of 250mg/5ml. Capsules will be used for the pre-operative dose, and will come as single capsules in bags labeled with study ID and name. For post-operative doses, 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic syringe. Each syringe will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at

4 degrees Celsius. The medications will be stored prior to dosing on the floor in a locked fridge in patient specific compartments, as per the floor medication protocol.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medications, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to planned doses. They will be alerted to upcoming procedures that involve study subjects. They will be responsible for delivering the medication to the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius. They will be stored on the inpatient floor in a locked, 4 degree fridge in patient specific compartments per the floor medication storage protocols.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication syringes will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files. Any labels or bags with patient names will be discarded in the shred bins on the 6200 floor or in the preop holding unit.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group approximately 1 hour prior to procedure start time. The coordinator administering the medication will tape a study reminder sheet for anesthesia to the chart and will place an order in the chart that allows the participant to take the preop medication dose, and the RN to chart this dose as a study medication.

- Standard pain medications orders will be provided. Morphine will be used as a substitute for dilaudid or oxycodone allergies or intolerances. These will be up-titrated as needed per discretion of service residents and attending physicians.
- One VAS score will be obtained 45 minutes to 1 hour postoperatively regardless of extubation time.
- One postoperative dose of study drug and VAS will be administered at 7pm if subjects are extubated by 5PM

Post-Operative Day (POD) 1-2

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3

- POD 3 VAS at 7am will be obtained.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dose on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadid et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size $d=0.6$) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

Note that IV morphine equivalents will be used rather than PO.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

Note that in discrepancies of data between reports, such as pack years smoked by a patient, an average of the reported amounts will be used to ensure consistency between data reporting fluctuations.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries that occur during the study period will be regarded as adverse events (meaning that the event does not necessary have to be likely related to the study drug to be considered an adverse event). However, not all adverse events will meet criteria for reporting. Abnormal results of diagnostic procedures will be reported as adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (see definition below)
- is associated with clinical signs or symptoms that are considered significant and likely related to study participation
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious, moderate or mild. . A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Mild and Moderate adverse events:

A moderate adverse event is one that requires a medical intervention such as medication for nausea, but that does not cause permanent clinical harm and that does resolve in a reasonable amount of time.

A mild adverse event is one that causes mild clinical effect and may or may not require medical intervention. It is expected to resolve completely with observation or medical treatment.

Adverse Event Reporting

The study period during which adverse events that are deemed reportable must be reported will be the period from the day of surgery to the end of the study, which is POD 3 or sooner if discharge is sooner than POD 3. Ideally, these events will be reported to the PI within 24 hours of their occurrence. Serious AE must be reported within 24 hours, however. Additionally, subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced after discharge so that the study members can be alerted to any events that may be related to the medication. Any severe adverse events or moderate events thought likely to be related to the study medication that are reported to the PI during this 30 day window will be recorded. Adverse events that occur during the inpatient study period and are significant/severe as defined above or that are unusual will be required to be reported in the adverse events log. The PI will be made aware of all of these events immediately after they occur. Events that are mild will not be required to be recorded in the adverse events log. Events that are moderate and thought likely related to the study medication will be reported. Events that are moderate but deemed unlikely to be due to the study medication will not be required to be reported in the adverse events log. However, these events may still be recorded in the adverse events log at the discretion of the PI. The PI will sign off on all adverse events that are recorded in the adverse event log.

For all severe AE or AE that are unexpected and thought likely related to the study medication, an IRB event form will be submitted. For moderate events thought likely to be due to the medication or unexpected, an event form will be submitted at the discretion of the PI. This design is intended to make sure that if subjects seem to be having symptoms that aren't expected to be caused by study participation but are noted in multiple subjects, then this gets reported. However, those side effects that are common after surgery (such as sedation or nausea) that could also be related to study medications are noted in the AE log when appropriate but not generating multiple IRB reportable event forms. The goal is to ensure subject safety and also only report appropriate events to the IRB. All adverse events, whether mild, moderate or severe, will be reviewed at the safety meeting by all team members and faculty advisors to ensure that proper reporting has occurred.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study in the 30 days window follow discharge.

8.2 *Eliciting Adverse Events from Subjects*

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the data recording form that is used to record subject data at each interaction. Reporting of these events is as outlined above. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

8.3 *Unblinding Procedures*

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% by the PI and at 50% enrollment by the entire team to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A safety meeting will be held half way through enrollment as described above,

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, these records will be destroyed in the proper manner in shred it bins where patient information is normally placed. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

This study will be monitored in real time for each subject by the PI and study team. At minimum, with 25% accrual goal all adverse events and data collection forms will be reviewed by the PI and discussed among the study team. ~~A designated, third party safety officer will review the study approximately half way through to ensure that subjects are not being harmed by this study. At our interim safety meeting, we determined by our AE log that significant adverse events were not occurring to study patients and events that were moderate and likely related to the medication also were extremely infrequent. We determined at that time that a third party officer review was unnecessary, especially in light of the fact that we were aware at that point that an audit would occur. We will proceed to study completion without this third party review. We also will be reporting our study events and AE events in a DSM log to the Siteman monitoring committee, which will also serve as a third party review.~~

11 Medication processing

11.1 Medicaiton Processing

All unused medications will be picked up from the pharmacy within 12 hours of the time they are determined to be not needed or not used. The pharmacy will be alerted in real time that the medication was not needed so that they can expect to pick it up. A confirmation communication will be sent to the study team once the medication is retrieved to ensure that it is properly picked up.

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The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***THE EFFECT OF GABAPENTIN ON PERIOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK SURGERY PATIENTS***

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>The effect of gabapentin on perioperative pain control among head and neck surgery patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.3 (third amended version)</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection (mucosal head and neck surgeries)</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing all types of head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 2 or the day of discharge, whichever comes first. Note that on the morning of POD3 at 7am, a VAS will be obtained to reflect the POD 2 7pm dose. The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The perioperative BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be observational, based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing surgical resection of head and neck mucosal surfaces.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck patients undergoing surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

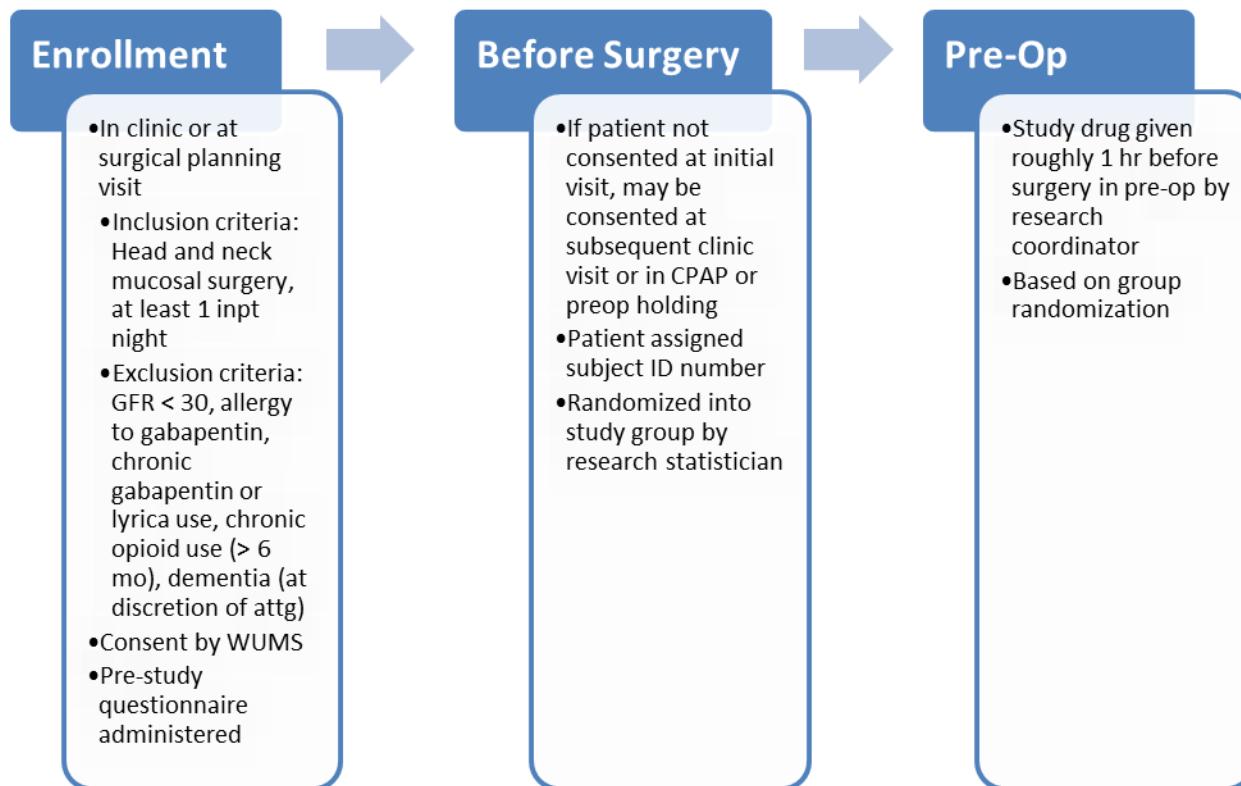
3 Study Design

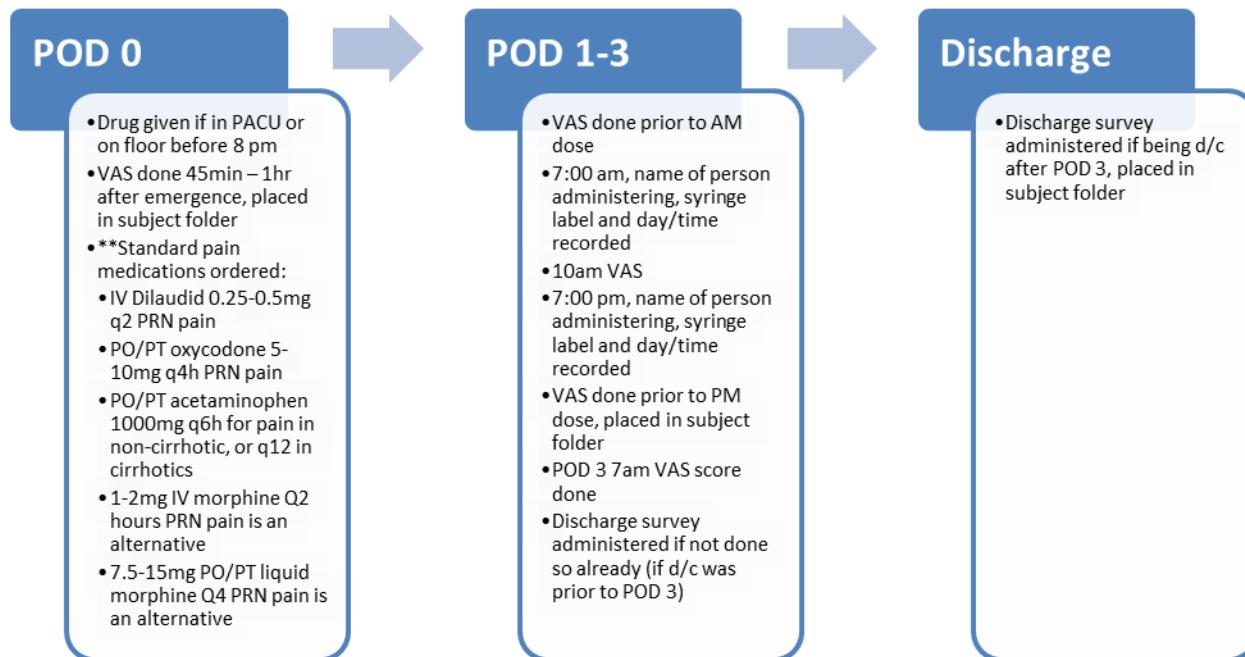
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The duration of subject participation includes the subsequent inpatient hospitalization following definitive

cancer resection up to two days after surgery. Subjects will be given the placebo or gabapentin for up to two days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM, the center for outpatient health or at other outpatient or inpatient sites related to their pre-surgical planning visits. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached either in the exam room during their scheduled appointment with the head and neck surgeons or afterwards via telephone call. The study will be explained to them and a copy of the consent form will be provided after it has been signed. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their head and neck health needs. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in a private room. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and patients will be reassured that their care from their head and neck surgeon will not be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





****Note that IV and PO or per tube morphine will be used in amounts equivalent to the dilaudid and oxycodone medications above if an allergy or intolerance to dilaudid or oxycodone exist.**

Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication approximately 1 hour prior to surgery start time. Patients will not be excluded if surgery start time is delayed past 1 hour. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study member will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain (5mg if pain less than or equal to 5/10, 10mg if greater than 5/10), and dilaudid 0.25-0.5mg Q2 hours PRN breakthrough pain (0.25mg if pain less than or equal to 5/10, 0.5mg if greater than 5/10). Alternatives to these medications in case of allergy or intolerance is 1-2mg IV morphine Q2 hours PRN pain (1mg if pain less than or equal to 5/10, 2mg if greater than 5/10) and 7.5-15mg PO/PT liquid IR morphine Q4 hours PRN pain (7.5mg if pain less than or equal to 5/10, 15mg if greater than 5/10). Additionally, the study team member will place the appropriate investigational drug order in compass. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. Additionally, if the subject is at any point during the study placed on alcohol withdrawal medication protocols, he or she will be withdrawn from the study. The study team member administering the preoperative dose will remind anesthesia to use the same post-operative initial pain management options in the PACU at least initially, again with no restrictions on dose escalations that are needed. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer, and their PACU medication sheet will be copied and added to their hard copy file for use later during

tabulation/data analysis of the pain meds they required. The VAS score obtained after surgery will be completed 45 minutes to 1 hour after extubation in the PACU.

Note that subjects must have completed surgery (extubated) by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS scores can still be obtained at 45 minutes to 1 hour postoperatively, however, even if the case finishes later than 5pm. On POD 1-2, subjects will be given BID medications at 7am and 7pm per the study protocol and VAS scores will be obtained prior to medication administration. A separate VAS will be obtained at 10am on POD1 and POD 2. ON POD 3 a 7am VAS will be obtained but no study medication given. This last VAS concludes participation in the study. Discharge surveys will be administered at this point if they have not been already (ie if the patient remained an inpatient for longer than 2 days postop).

The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to scheduled doses, and the medications will be stored in patient labeled bins in the locked medication refrigerator. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a line measuring 10cm during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" on the far left and "worst pain" on the far right. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

Note that study medication wrappers have patient names on them as a safety mechanism to make sure medications are given to the proper patient. These wrappers and labels will be saved in the patient folders which are secured in a locked cabinet where only study team members have access. Empty and unlabeled medication syringes will be discarded in the red biohazard bins inside patient rooms.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

2. How often did the hospital staff do everything they could to help you with your pain?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

3. How satisfied are you with your overall pain control?

- 0) Very dissatisfied
- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and once on POD 3, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in centimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

- (d) Hospital length of stay will be calculated for each subject.
- (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A safety meeting will be held half way through the study with the PI and all involved faculty mentors to determine if an interim analysis is necessary. This analysis would be considered necessary if a significant number of adverse events likely related to the study medication were occurring, and an analysis to make sure the study was not causing harm to the treatment group was needed.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin or lyrica use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited either in the outpatient head and neck clinic prior to their planned surgeries or over the phone after this clinic appointment by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Patient recruited by phone will be able to sign the informed consent prior to surgery either at a subsequent surgical planning visit or in the pre-op holding area on the day of surgery. Eligible subjects will be consented in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. They will also be withdrawn if they remain sedated or intubated after the surgery or are placed on alcohol withdrawal medication protocols, which also cause significant sedation. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

4.4.3 Definitions

Subject withdraw: Withdraw is defined as a subject who signed the informed consent document and for whatever reason dropped out of the study before completion, whether by choice or by exclusion criteria (ie- staying intubated the night after surgery).

Subject screen fail: A screen fail is defined as a subject who has been recruited to participate and approached but does not meet all inclusion criteria.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication syringe or in a marked bag with a capsule. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area approximately 1 hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening (ie not extubated before 5pm), and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 2. Dosing will end either on POD 2 after the PM dose or on day of discharge after the AM dose, whichever comes first. VAS scores will be collected 45 minutes- 1 hour post extubation on POD as well as TID on POD 1-2 and one time at 7am on POD 3 (see above protocol flowsheet).

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assigned an enrollment ID. The enrollment ID is given to any subject who signs consent. If the subject then proceeds to start the study and receive a medication dose, they will also be given a subject ID which reflects their randomization group. The study ID reflects randomization while the enrollment ID is used to enter them into OnCore and track their consent.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the preop holding unit or the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN breakthrough pain (pain equal to or less than 5/10 will get 0.25mg and pain >5/10 will get 0.5mg).
- PO/PT oxycodone 5-10mg q4h PRN pain (pain equal to or less than 5/10 will get 5mg, and pain greater than 5/10 will get 10mg).
- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients
- Morphine IV and PO liquid equivalents will be substituted in cases of oxycodone or dilaudid allergies. 1-2mg IV morphine Q2 hours PRN will be substituted for 0.25-0.5mg dilaudid for breakthrough pain (pain equal to or less than 5/10 will get 1mg and pain >5/10 will get 2mg). PRN liquid IR morphine 7.5-15mg will be substituted Q4 hours for oxycodone PRN for pain (pain equal to or less than 5/10 will get 7.5mg, and pain greater than 5/10 will get 15mg)
- Study team members will place an order in compass for study investigation drug administration as per BJC protocol for investigational drug use.

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid or capsule form. Gabapentin comes as a standard liquid form of 250mg/5ml. Capsules will be used for the pre-operative dose, and will come as single capsules in bags labeled with study ID and name. For post-operative doses, 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic syringe. Each syringe will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at

4 degrees Celsius. The medications will be stored prior to dosing on the floor in a locked fridge in patient specific compartments, as per the floor medication protocol.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medications, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to planned doses. They will be alerted to upcoming procedures that involve study subjects. They will be responsible for delivering the medication to the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius. They will be stored on the inpatient floor in a locked, 4 degree fridge in patient specific compartments per the floor medication storage protocols.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication syringes will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files. Any labels or bags with patient names will be discarded in the shred bins on the 6200 floor or in the preop holding unit.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group approximately 1 hour prior to procedure start time. The coordinator administering the medication will tape a study reminder sheet for anesthesia to the chart and will place an order in the chart that allows the participant to take the preop medication dose, and the RN to chart this dose as a study medication.

- Standard pain medications orders will be provided. Morphine will be used as a substitute for dilaudid or oxycodone allergies or intolerances. These will be up-titrated as needed per discretion of service residents and attending physicians.
- One VAS score will be obtained 45 minutes to 1 hour postoperatively regardless of extubation time.
- One postoperative dose of study drug and VAS will be administered at 7pm if subjects are extubated by 5PM

Post-Operative Day (POD) 1-2

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3

- POD 3 VAS at 7am will be obtained.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dose on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadid et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size $d=0.6$) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be

included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Mild and Moderate adverse events:

A moderate adverse event is one that requires a medical intervention such as medication for nausea, but that does not cause permanent clinical harm and that does resolve in a reasonable amount of time.

A mild adverse event is one that causes mild clinical effect and may or may not require medical intervention. It is expected to resolve completely with observation or medical treatment.

Adverse Event Reporting Period

The study period during which adverse events that are deemed likely related to the study medication and unexpected or significant must be reported will be the period from the day of surgery to the end of the study, which is POD 3 or sooner if discharge is sooner than POD 3. Additionally, subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced after discharge so that the study members can be alerted to any events that may be related to the medication. Reporting of these events via an adverse event report will be up to the discretion of the PI. Subjects will be advised that the medication does not remain in the

body several days after discontinuation, but they will be able to report events at any point after study participation.

For all severe or unexpected adverse events, an IRB event form will be submitted. For mild or moderate events, an event form will be submitted if the event is one that is likely related to the medication and is an event that is not considered an expected side effect of gabapentin. Mild or moderate events that do not resolve within an appropriate time frame will also be reported to the IRB. Mild and moderate events will be reviewed by the PI and deemed appropriate for reporting. All adverse events, whether mild, moderate or severe, will be reviewed at the safety meeting by all team members and faculty advisors to ensure that proper reporting has occurred.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.2 Recording of Adverse Events

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document located on the secure wustl box for this study. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

The clinical course of any adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study drug or study participation will be recorded and reported immediately to the IRB.

8.3 Unblinding Procedures

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% by the PI and at 50% enrollment by the entire team to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10

Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A safety meeting will be held half way through enrollment as described above,

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, these records will be destroyed in the proper manner in shred it bins where patient information is normally placed. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

This study will be monitored in real time for each subject by the PI and study team. At minimum, with 25% accrual goal all adverse events and data collection forms will be reviewed by the PI and discussed among the study team. A designated, third party safety officer will review the study approximately half way through to ensure that subjects are not being harmed by this study.

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The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***THE EFFECT OF GABAPENTIN ON PERIOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK SURGERY PATIENTS***

Initial version: 3/31/2016

Amended: [7/31/2016]

Amended: [12/1/2016]

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>The effect of gabapentin on perioperative pain control among head and neck surgery patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.2 (first amended version)</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial followed by observational follow up study</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay. Observation of post op swallow function.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection (mucosal head and neck surgeries)</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing all types of head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 2 or the day of discharge, whichever comes first. Note that on the morning of POD3 at 7am, a VAS will be obtained to reflect the POD 2 7pm dose. The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The perioperative BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be observational, based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing surgical resection of head and neck mucosal surfaces.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck patients undergoing surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

Observational outcomes

Hospital length of stay and post-operative swallow function if assessed.

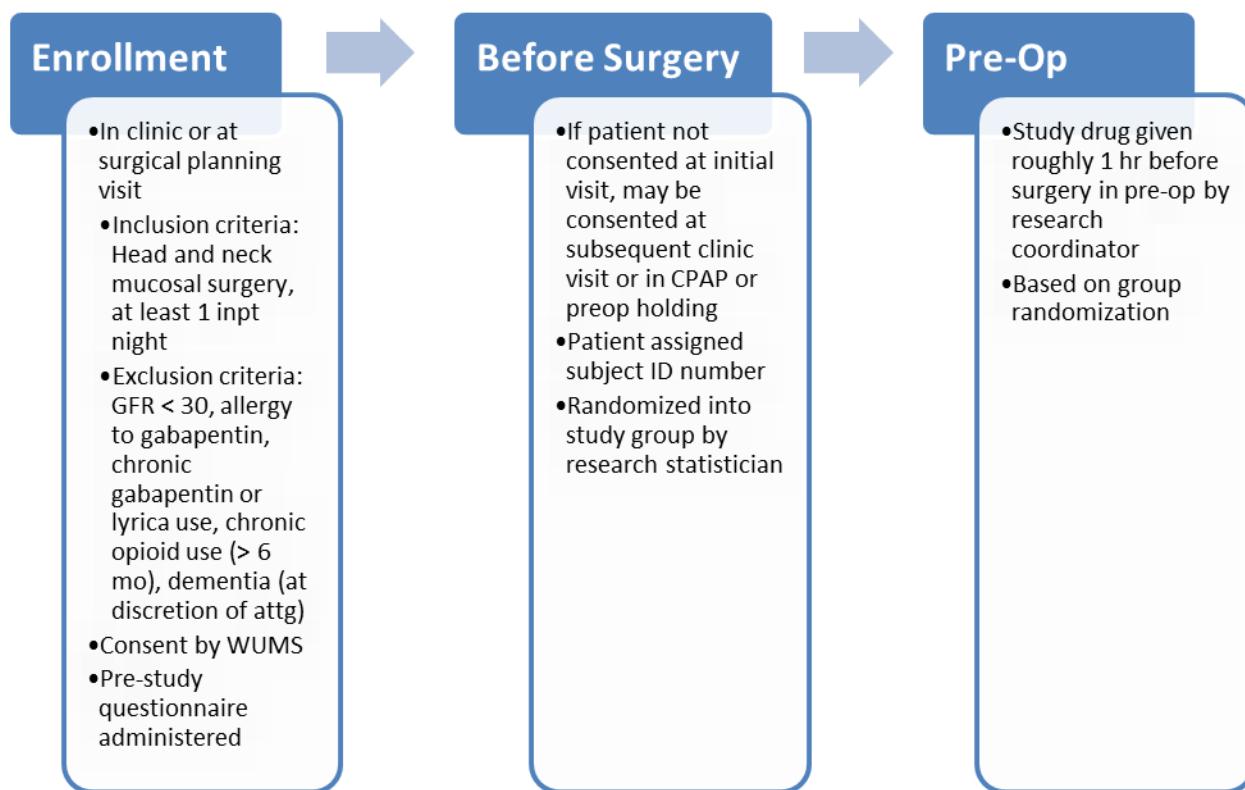
3 Study Design

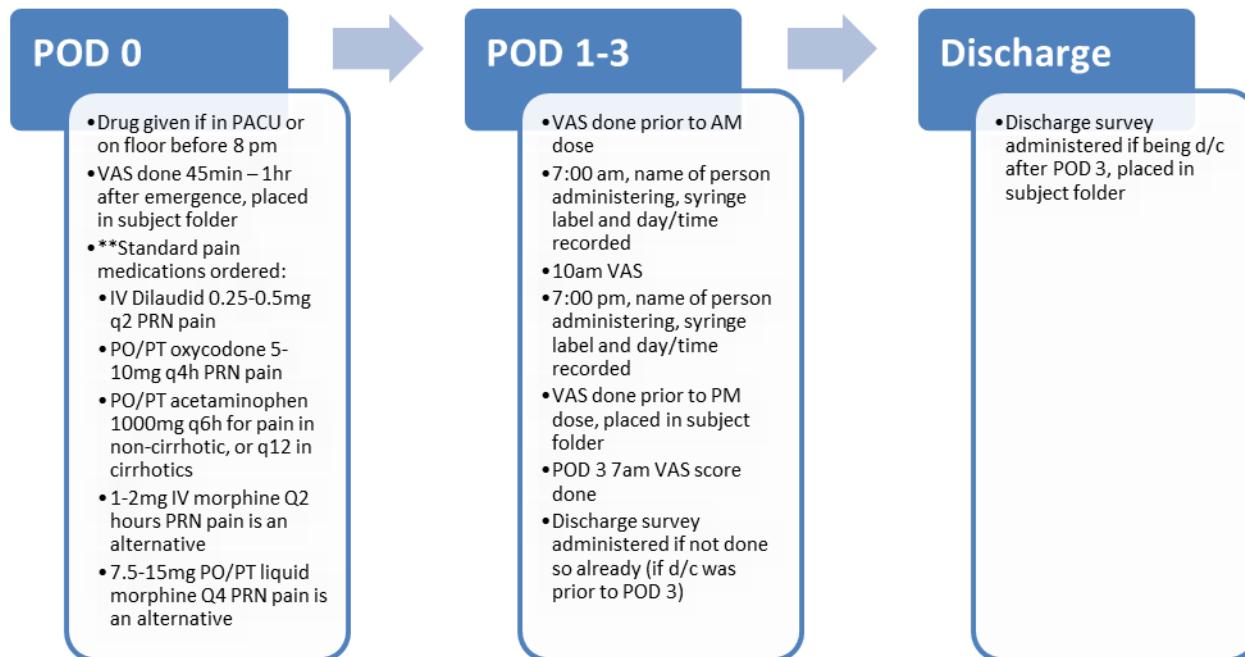
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The

duration of subject participation includes the subsequent inpatient hospitalization following definitive cancer resection up to two days after surgery. Subjects will be given the placebo or gabapentin for up to two days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM, the center for outpatient health or at other outpatient or inpatient sites related to their pre-surgical planning visits. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached either in the exam room during their scheduled appointment with the head and neck surgeons or afterwards via telephone call. The study will be explained to them and a copy of the consent form will be provided after it has been signed. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their head and neck health needs. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in a private room. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and patients will be reassured that their care from their head and neck surgeon will not be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





****Note that IV and PO or per tube morphine will be used in amounts equivalent to the dilaudid and oxycodone medications above if an allergy or intolerance to dilaudid or oxycodone exist.**

Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication approximately 1 hour prior to surgery start time. Patients will not be excluded if surgery start time is delayed past 1 hour. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study member will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain (5mg if pain less than or equal to 5/10, 10mg if greater than 5/10), and dilaudid 0.25-0.5mg Q2 hours PRN breakthrough pain (0.25mg if pain less than or equal to 5/10, 0.5mg if greater than 5/10). Alternatives to these medications in case of allergy or intolerance is 1-2mg IV morphine Q2 hours PRN pain (1mg if pain less than or equal to 5/10, 2mg if greater than 5/10) and 7.5-15mg PO/PT liquid IR morphine Q4 hours PRN pain (7.5mg if pain less than or equal to 5/10, 15mg if greater than 5/10). Additionally, the study team member will place the appropriate investigational drug order in compass. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. Additionally, if the subject is at any point during the study placed on alcohol withdrawal medication protocols, he or she will be withdrawn from the study. The study team member administering the preoperative dose will remind anesthesia to use the same post-operative initial pain management options in the PACU at least initially, again with no restrictions on dose escalations that are needed. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer, and their PACU medication sheet will be copied and added to their hard copy file for use later during

tabulation/data analysis of the pain meds they required. The VAS score obtained after surgery will be completed 45 minutes to 1 hour after extubation in the PACU.

Note that subjects must have completed surgery (extubated) by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS scores can still be obtained at 45 minutes to 1 hour postoperatively, however, even if the case finishes later than 5pm. On POD 1-2, subjects will be given BID medications at 7am and 7pm per the study protocol and VAS scores will be obtained prior to medication administration. A separate VAS will be obtained at 10am on POD1 and POD 2. ON POD 3 a 7am VAS will be obtained but no study medication given. This last VAS concludes participation in the study. Discharge surveys will be administered at this point if they have not been already (ie if the patient remained an inpatient for longer than 2 days postop).

The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to scheduled doses, and the medications will be stored in patient labeled bins in the locked medication refrigerator. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a line measuring 10cm during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" on the far left and "worst pain" on the far right. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

Note that study medication wrappers have patient names on them as a safety mechanism to make sure medications are given to the proper patient. These wrappers and labels will be saved in the patient folders which are secured in a locked cabinet where only study team members have access. Empty and unlabeled medication syringes will be discarded in the red biohazard bins inside patient rooms.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

2. How often did the hospital staff do everything they could to help you with your pain?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

3. How satisfied are you with your overall pain control?

- 0) Very dissatisfied
- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and once on POD 3, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in centimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

- (d) Hospital length of stay will be calculated for each subject.
- (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A project safety review will be conducted by a third party safety officer approximately half way through the study, or sooner if necessary.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin or lyric use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited either in the outpatient head and neck clinic prior to their planned surgeries or over the phone after this clinic appointment by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Patient recruited by phone will be able to sign the informed consent prior to surgery either at a subsequent surgical planning visit or in the pre-op holding area on the day of surgery. Eligible subjects will be consented in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. They will also be withdrawn if they remain sedated or intubated after the surgery or are placed on alcohol withdrawal medication protocols, which also cause significant sedation. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

4.4.3 Definitions

Subject withdraw: Withdraw is defined as a subject who signed the informed consent document and for whatever reason dropped out of the study before completion, whether by choice or by exclusion criteria (ie- staying intubated the night after surgery).

Subject screen fail: A screen fail is defined as a subject who has been recruited to participate and approached but does not meet all inclusion criteria.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication syringe or in a marked bag with a capsule. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area approximately 1 hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening (ie not extubated before 5pm), and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 2. Dosing will end either on POD 2 after the PM dose or on day of discharge after the AM dose, whichever comes first. VAS scores will be collected 45 minutes- 1 hour post extubation on POD as well as TID on POD 1-2 and one time at 7am on POD 3 (see above protocol flowsheet).

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assign a subject study number. The subject study number will be used to identify which subjects are to receive which medication.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the preop holding unit or the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN breakthrough pain (pain equal to or less than 5/10 will get 0.25mg and pain >5/10 will get 0.5mg).
- PO/PT oxycodone 5-10mg q4h PRN pain (pain equal to or less than 5/10 will get 5mg, and pain greater than 5/10 will get 10mg).
- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients
- Morphine IV and PO liquid equivalents will be substituted in cases of oxycodone or dilaudid allergies. 1-2mg IV morphine Q2 hours PRN will be substituted for 0.25-0.5mg dilaudid for breakthrough pain (pain equal to or less than 5/10 will get 1mg and pain >5/10 will get 2mg). PRN liquid IR morphine 7.5-15mg will be substituted Q4 hours for oxycodone PRN for pain (pain equal to or less than 5/10 will get 7.5mg, and pain greater than 5/10 will get 15mg)
- Study team members will place an order in compass for study investigation drug administration as per BJC protocol for investigational drug use.

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid or capsule form. Gabapentin comes as a standard liquid form of 250mg/5ml. Capsules will be used for the pre-operative dose, and will come as single capsules in bags labeled with study ID and name. For post-operative doses, 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic syringe. Each syringe will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at 4 degrees Celsius. The medications will be stored prior to dosing on the floor in a locked fridge in patient specific compartments, as per the floor medication protocol.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medications, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to planned doses. They will be alerted to upcoming procedures that involve study subjects. They will be responsible for delivering the medication to the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius. They will be stored on the inpatient floor in a locked, 4 degree fridge in patient specific compartments per the floor medication storage protocols.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication syringes will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files. Any labels or bags with patient names will be discarded in the shred bins on the 6200 floor or in the preop holding unit.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group approximately 1 hour prior to procedure start time. The coordinator administering the medication will tape a study reminder sheet for anesthesia to the chart and will place an order in the chart that allows the participant to take the preop medication dose, and the RN to chart this dose as a study medication.

- Standard pain medications orders will be provided. Morphine will be used as a substitute for dilaudid or oxycodone allergies or intolerances. These will be up-titrated as needed per discretion of service residents and attending physicians.
- One VAS score will be obtained 45 minutes to 1 hour postoperatively regardless of extubation time.
- One postoperative dose of study drug and VAS will be administered at 7pm if subjects are extubated by 5PM

Post-Operative Day (POD) 1-2

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3

- POD 3 VAS at 7am will be obtained.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dose on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadid et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size $d=0.6$) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be

included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Mild and Moderate adverse events:

A **moderate adverse event** is one that requires a medical intervention such as medication for nausea, but that does not cause permanent clinical harm and that does resolve in a reasonable amount of time.

A **mild adverse event** is one that causes mild clinical effect and may or may not require medical intervention. It is expected to resolve completely with observation or medical treatment.

Adverse Event Reporting Period

The study period during which adverse events must be reported will be the period from the day of surgery to the end of the study treatment follow-up. For this study, the study follow-up is defined as 30 days following the last administration of study drug. Subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced.

For all severe adverse events, an IRB event form will be submitted. For mild or moderate events, an event form will be submitted if the event is one that is likely related to the medication and is an event that

is not considered an expected side effect of gabapentin. Mild or moderate events that do not resolve within an appropriate time frame will also be reported to the IRB. Mild and moderate events will be reviewed by the PI and deemed appropriate for reporting.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.2 Recording of Adverse Events

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

The clinical course of any adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study drug or study participation will be recorded and reported immediately to the IRB.

8.3 Unblinding Procedures

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% and 50% enrollment to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A designated, third party safety officer will review the study approximately half way through to ensure that subjects are not being harmed by this study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, these records will be destroyed in the proper manner in shred it bins where patient information is normally placed. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

This study will be monitored in real time for each subject by the PI and study team. At minimum, with 25% accrual goal all adverse events and data collection forms will be reviewed by the PI and discussed among the study team. A designated, third party safety officer will review the study approximately half way through to ensure that subjects are not being harmed by this study.

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The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***THE EFFECT OF GABAPENTIN ON PERIOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK SURGERY PATIENTS***

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>The effect of gabapentin on perioperative pain control among head and neck surgery patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.1 (first amended version)</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial followed by observational follow up study</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay. Observation of post op swallow function.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection (mucosal head and neck surgeries)</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing all types of head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 2 or the day of discharge, whichever comes first. **Note that on the morning of POD3 at 7am, a VAS will be obtained to reflect the POD 2 7pm dose.** The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The perioperative BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be observational, based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing surgical resection of head and neck mucosal surfaces.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck patients undergoing surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

Observational outcomes

Hospital length of stay and post-operative swallow function if assessed.

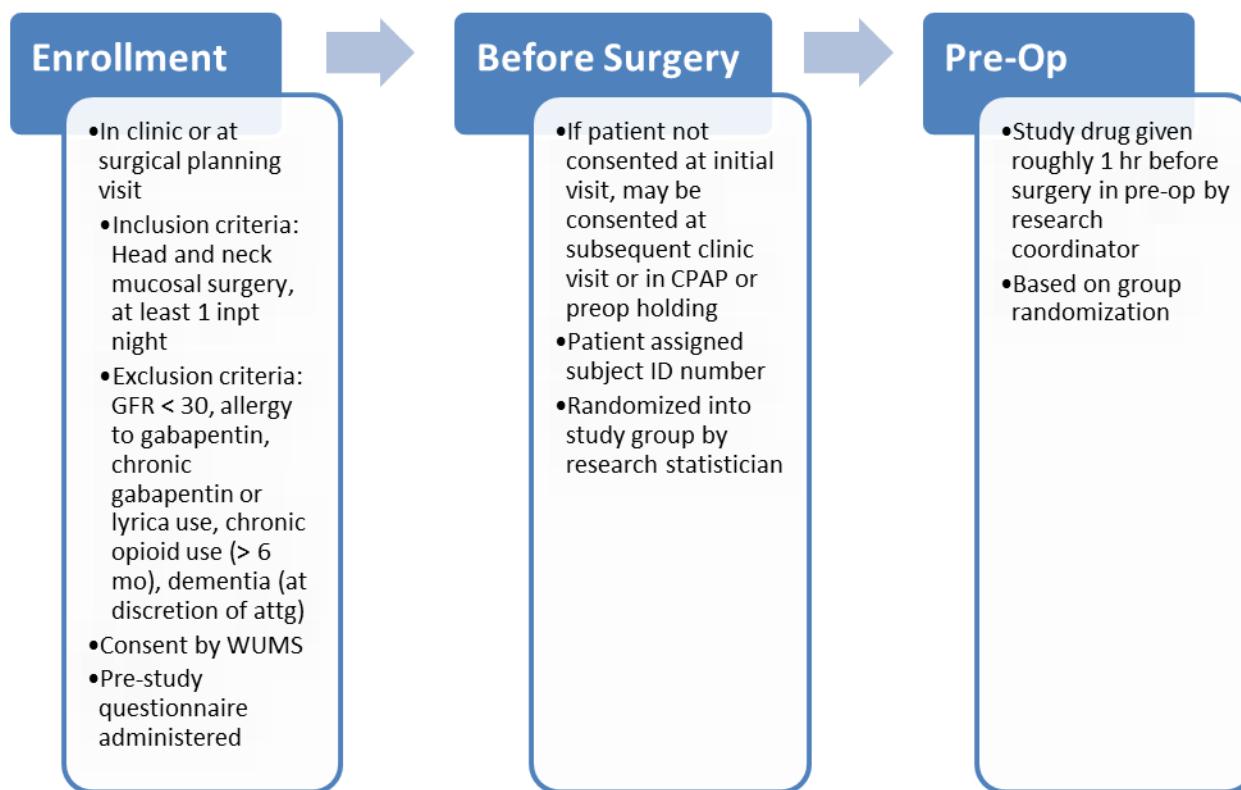
3 Study Design

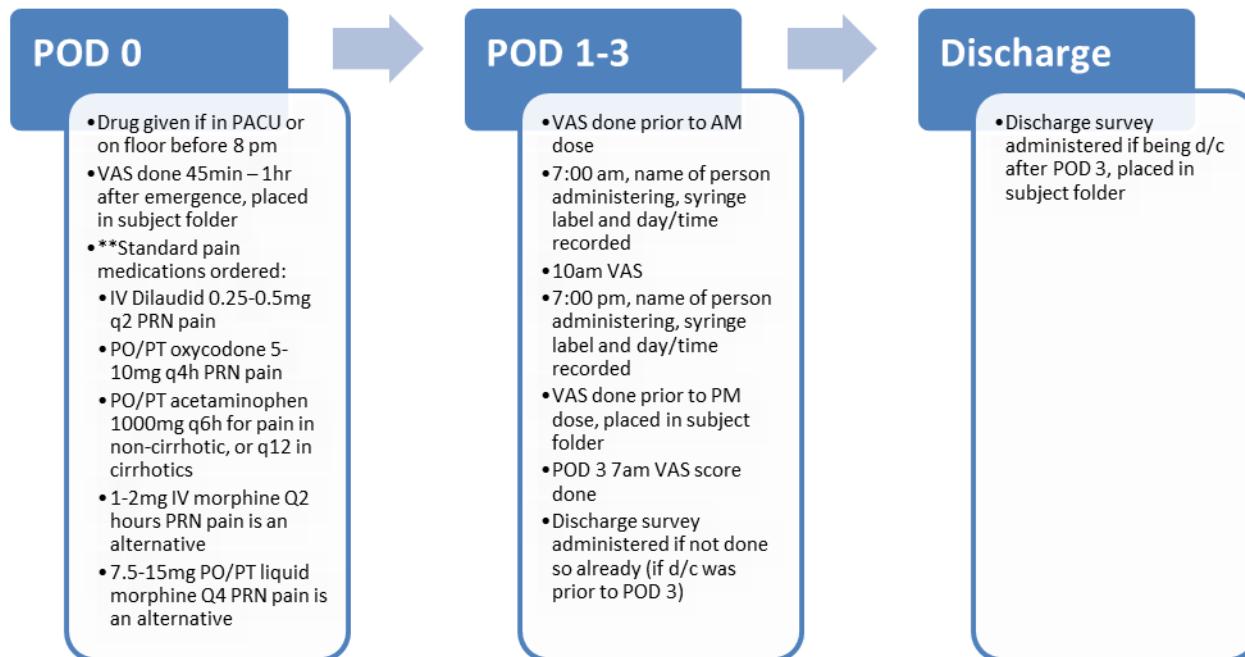
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The

duration of subject participation includes the subsequent inpatient hospitalization following definitive cancer resection up to two days after surgery. Subjects will be given the placebo or gabapentin for up to two days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM, the center for outpatient health or at other outpatient or inpatient sites related to their pre-surgical planning visits. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached either in the exam room during their scheduled appointment with the head and neck surgeons or afterwards via telephone call. The study will be explained to them and a copy of the consent form will be provided after it has been signed. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their head and neck health needs. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in a private room. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and patients will be reassured that their care from their head and neck surgeon will not be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





****Note that IV and PO or per tube morphine will be used in amounts equivalent to the dilaudid and oxycodone medications above if an allergy or intolerance to dilaudid or oxycodone exist.**

Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication approximately 1 hour prior to surgery start time. Patients will not be excluded if surgery start time is delayed past 1 hour. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study member will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain (5mg if pain less than or equal to 5/10, 10mg if greater than 5/10), and dilaudid 0.25-0.5mg Q2 hours PRN breakthrough pain (0.25mg if pain less than or equal to 5/10, 0.5mg if greater than 5/10). Alternatives to these medications in case of allergy or intolerance is 1-2mg IV morphine Q2 hours PRN pain (1mg if pain less than or equal to 5/10, 2mg if greater than 5/10) and 7.5-15mg PO/PT liquid IR morphine Q4 hours PRN pain (7.5mg if pain less than or equal to 5/10, 15mg if greater than 5/10). Additionally, the study team member will place the appropriate investigational drug order in compass. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. Additionally, if the subject is at any point during the study placed on alcohol withdrawal medication protocols, he or she will be withdrawn from the study. The study team member administering the preoperative dose will remind anesthesia to use the same post-operative initial pain management options in the PACU at least initially, again with no restrictions on dose escalations that are needed. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. **Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer. The VAS score obtained after surgery will be completed 45 minutes to 1 hour after extubation in the PACU.**

Note that subjects must have completed surgery (extubated) by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS scores can still be obtained at 45 minutes to 1 hour postoperatively, however, even if the case finishes later than 5pm. On POD 1-2, subjects will be given BID medications at 7am and 7pm per the study protocol and VAS scores will be obtained prior to medication administration. A separate VAS will be obtained at 10am on POD1 and POD 2. **ON POD 3 a 7am VAS will be obtained but no study medication given. This last VAS concludes participation in the study. Discharge surveys will be administered at this point if they have not been already (ie if the patient remained an inpatient for longer than 2 days postop).**

The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to scheduled doses, and the medications will be stored in patient labeled bins in the locked medication refrigerator. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a line measuring 10cm during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" on the far left and "worst pain" on the far right. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

Note that study medication wrappers have patient names on them as a safety mechanism to make sure medications are given to the proper patient. These wrappers and labels will be saved in the patient folders which are secured in a locked cabinet where only study team members have access. Empty and unlabeled medication syringes will be discarded in the red biohazard bins inside patient rooms.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?
 - 0) Never
 - 1) Sometimes

- 2) Usually
- 3) Always

2. How often did the hospital staff do everything they could to help you with your pain?

- 0) Never
- 1) Sometimes
- 2) Usually
- 3) Always

3. How satisfied are you with your overall pain control?

- 0) Very dissatisfied
- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and **once on POD 3**, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in centimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. **In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?**
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

- (d) Hospital length of stay will be calculated for each subject.
- (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A project safety review will be conducted by a third party safety officer approximately half way through the study, or sooner if necessary.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin or lyrica use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited either in the outpatient head and neck clinic prior to their planned surgeries or over the phone after this clinic appointment by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Patient recruited by phone will be able to sign the informed consent prior to surgery either at a subsequent surgical planning visit or in the pre-op holding are on the day of surgery. Eligible subjects will be consented in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. They will also be withdrawn if they remain sedated or intubated after the surgery or are placed on alcohol withdrawal medication protocols, which also cause significant sedation. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication syringe or in a marked bag with a capsule. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area approximately 1 hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening (ie not extubated before 5pm), and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 2. Dosing will end either on POD 2 after the PM dose or on day of discharge after the AM dose, whichever comes first. **VAS scores will be collected 45 minutes- 1 hour post extubation on POD as well as TID on POD 1-2 and one time at 7am on POD 3 (see above protocol flowsheet).**

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assign a subject study number. The subject study number will be used to identify which subjects are to receive which medication.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the preop holding unit or the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN breakthrough pain (pain equal to or less than 5/10 will get 0.25mg and pain >5/10 will get 0.5mg).
- PO/PT oxycodone 5-10mg q4h PRN pain (pain equal to or less than 5/10 will get 5mg, and pain greater than 5/10 will get 10mg).
- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients
- Morphine IV and PO liquid equivalents will be substituted in cases of oxycodone or dilaudid allergies. 1-2mg IV morphine Q2 hours PRN will be substituted for 0.25-0.5mg dilaudid for breakthrough pain (pain equal to or less than 5/10 will get 1mg and pain >5/10 will get 2mg). PRN liquid IR morphine 7.5-15mg will be substituted Q4 hours for oxycodone PRN for pain (pain equal to or less than 5/10 will get 7.5mg, and pain greater than 5/10 will get 15mg)
- Study team members will place an order in compass for study investigation drug administration as per BJC protocol for investigational drug use.

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid or capsule form. Gabapentin comes as a standard liquid form of 250mg/5ml. Capsules will be used for the pre-operative dose, and will come as single capsules in bags labeled with study ID and name. For post-operative doses, 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic syringe. Each syringe will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at 4 degrees Celsius. The medications will be stored prior to dosing on the floor in a locked fridge in patient specific compartments, as per the floor medication protocol.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medications, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to planned doses. They will be alerted to upcoming procedures that involve study subjects. They will be responsible for delivering the

medication to the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius. They will be stored on the inpatient floor in a locked, 4 degree fridge in patient specific compartments per the floor medication storage protocols.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication syringes will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files. Any labels or bags with patient names will be discarded in the shred bins on the 6200 floor or in the preop holding unit.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group approximately 1 hour prior to procedure start time. The coordinator administering the medication will tape a study reminder sheet for anesthesia to the chart and will place an order in the chart that allows the participant to take the preop medication dose, and the RN to chart this dose as a study medication.
- Standard pain medications orders will be provided. Morphine will be used as a substitute for dilaudid or oxycodone allergies or intolerances. These will be up-titrated as needed per discretion of service residents and attending physicians.
- **One VAS score will be obtained 45 minutes to 1 hour postoperatively regardless of extubation time.**
- One postoperative dose of study drug and VAS will be administered at 7pm if subjects are extubated by 5PM

Post-Operative Day (POD) 1-2

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3

- POD 3 VAS at 7am will be obtained.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dose on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadid et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size d=0.6) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Adverse Event Reporting Period

The study period during which adverse events must be reported will be the period from the day of surgery to the end of the study treatment follow-up. For this study, the study follow-up is defined as 30 days following the last administration of study drug. Subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.2 Recording of Adverse Events

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

The clinical course of any adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study drug or study participation will be recorded and reported immediately to the IRB.

8.3 Unblinding Procedures

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% and 50% enrollment to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A designated, third party safety officer will review the study approximately half way through to ensure that subjects are not being harmed by this study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, these records will be destroyed in the proper manner in shred it bins where patient information is normally placed. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

This study will be monitored in real time for each subject by the PI and study team. At minimum, with 25% accrual goal all adverse events and data collection forms will be reviewed by the PI and discussed among the study team. A designated, third party safety officer will review the study approximately half way through to ensure that subjects are not being harmed by this study.

11 References

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The effect of gabapentin on perioperative pain control among head and neck surgery patients

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***A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL ON
THE EFFECT OF GABAPENTIN ON POSTOPERATIVE PAIN
CONTROL AMONG HEAD AND NECK CANCER PATIENTS***

Initial version: 3/31/2016

Amended: [date]

Amended: [date]

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List of Abbreviations

- HCAHPS- Hospital Consumer Assessment of Healthcare Providers and Systems
- PRC-Professional Research Consultants
- FDA – Food and Drug Administration
- VAS – Visual Analog Scale
- POD – post-operative day

Study Summary

Title	<i>A prospective randomized controlled trial on the effect of gabapentin on postoperative pain control among head and neck cancer patients</i>
Short Title	<i>Gaba RCT</i>
Protocol Number	<i>1.0</i>
Phase	<i>Phase 4</i>
Methodology	<i>Prospective randomized double-blind controlled trial followed by observational follow up study</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>Barnes Jewish Hospital</i>
Objectives	<i>Determine the effectiveness of gabapentin for reducing narcotic requirements and subjective pain scores in postoperative head and neck mucosal cancer patients. Determine the ability of gabapentin to improve patient satisfaction with pain management. Track inpatient length of stay. Observation of post op swallow function.</i>
Number of Subjects	<i>120</i>
Diagnosis and Main Inclusion Criteria	<i>Adult head and neck mucosal cancer patients undergoing oral cavity, oropharynx, larynx and hypopharynx resection</i>
Study Product, Dose, Route, Regimen	<i>Gabapentin liquid by mouth or Per Tube 300mg BID vs placebo</i>
Duration of administration	<i>Day of surgery and up to three days post operatively depending on the hospital stay.</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare between treatment groups</i>

1 Introduction

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice compliant to all associated Federal and applicable local and University research requirements, approved by the Institutional Review Board.

1.1 Background

High-quality healthcare is accessible, safe, efficient, patient-centered and imperative for good treatment outcomes. In this era of healthcare reform, patient satisfaction has increasingly become an important metric of hospital performance. The Medicare Hospital Value Based Purchasing Program utilizes patient reported satisfaction scores as a reflection of the quality of care delivered by hospital systems and clinician teams. The scores resulting from these reports are integrated into the formula with which hospitals are reimbursed for Medicare patients.

An important patient-physician interface in quality healthcare is the treatment of pain, and the treatment of acute postoperative pain is particularly relevant for surgical specialties. Effective management of postoperative pain increases patient satisfaction, reduces hospital costs, reduces postoperative morbidity and shortens hospitalizations⁸. HCAHP and PRC data from the Barnes Jewish Hospital otolaryngology inpatient unit reveals that postoperative otolaryngology patient satisfaction with pain control is routinely lower than the 75th percentile of all hospitals nationally surveyed. Traditionally, pain regimens rely heavily on the use of narcotics, which are associated with nausea, vomiting, delirium, and decreased bowel motility. These side effects have the potential to increase length of hospitalization and decrease patient satisfaction. Moreover, otolaryngology patients often undergo very painful and functionally debilitating surgeries of the head and neck and are at increased risk for postoperative pain due to both the neuroanatomy of this region and the need to swallow postoperatively⁸. Postoperative pain control in this population is critical for patient satisfaction and an expedited return to a functional swallowing status.

Within the field of pain management is the practice of multimodal pain therapy. This strategy employs non-narcotic medications working synergistically to improve pain control, decreasing narcotic medication requirements and narcotic-associated side effects⁸. Studies utilizing multimodal pain regimens demonstrate such benefits in acute postoperative pain management²⁻⁵. Gabapentin is a non-narcotic pain medication often used in multimodal pain regimens that has been shown to reduce acute postoperative pain.

1.2 Investigational Agent

Gabapentin is a non-narcotic medication developed to target neuropathic pain¹. It is an amino acid 1-(aminomethyl)cyclohexaneacetic acid that is structurally related to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), without modifying the binding, metabolism, or elimination of GABA. In vitro studies have demonstrated gabapentin binding sites in the rat brain, but the functional implication and the mechanism of its analgesic and anticonvulsant activity remains unknown in humans. The oral bioavailability of gabapentin decreases as dose increases. Its half-life is 5-7 hours, and it is eliminated by renal excretion without chemical alteration. Dose adjustments are recommended for creatinine clearance less than 30 mL/min. It is FDA approved since 1993 for post-herpetic neuralgia and epilepsy, and has been widely applied in neuropathic pain management. It is also frequently used for acute postoperative pain, and meta-analysis of randomized controlled trials shows it to be an effective pain management strategy in postoperative patients. The major adverse reactions reported were, in descending frequency, dizziness, sedation, asthenia, diarrhea, dry mouth, constipation, nausea, and vomiting²³.

1.3 Clinical Data to Date

Numerous randomized controlled trials demonstrated that gabapentin effectively reduced narcotic use and improved subjective pain in various surgical populations, such as gynecology-oncology and orthopedic surgery⁹⁻¹⁵. Meta-analyses of these pooled trials reported an overall trend toward improved pain control and decreased postoperative narcotic use with gabapentin, despite the heterogeneity of the included studies^{6,16-19}. A small number of studies have examined the use of gabapentin in postoperative

otolaryngology patients and suggest a potential benefit in improving postoperative pain control after thyroidectomy, endoscopic sinus surgery, oral cavity resection with reconstruction, and tonsillectomy⁹⁻¹⁵. Most of the studies demonstrated an improvement with only one preoperative dose. To date, no randomized control trials have been conducted with gabapentin use in adult otolaryngology patients undergoing head and neck mucosal surgeries, which is an at-risk population for high levels of postsurgical pain.

1.4 Dose Rationale and Risk/Benefits

Dosing regimen of gabapentin will be 300 mg PO preoperatively, followed by 300 mg BID until POD 3 or the day of discharge, whichever comes first. The liquid formulation will be used postoperatively given the possibility of dysphagia or postoperative NPO status potentially requiring a feeding tube. The optimal dosage for gabapentin in acute postoperative pain is unknown. Recommended gabapentin regimen for treatment of post-herpetic neuralgia is a 300 mg/day on day 1, 300 mg BID on day 2, 300 mg TID on day 3, and subsequently up-titrated as needed to 600 mg TID²³. Prior studies using gabapentin for postoperative pain control in otolaryngology patients have primarily administered a single preoperative dose ranging from 100 mg to 1200 mg⁹⁻¹⁵. Data was inconsistent as some studies showed efficacy at low dosages and some showed no difference at high dosages, and an optimal dose regimen remains to be determined. For this study a relatively low dosage was chosen to minimize sedation side effects, as included participants are likely to be gabapentin-naïve. The postoperative 3-day BID dosing period was chosen to better elucidate the effects of gabapentin in the acute, postoperative period, as many head and neck mucosal resections cause significant pain for several days after the procedure. The majority of head and neck inpatient stays are between 2-3 days, with some staying as short as 1 day and some as long as a few weeks. At this dose and schedule, gabapentin side effects are minimized so that subject risk is also minimized without compromising medication analgesic abilities. Collaboration with the inpatient pain management team also supports the expectation that this dose and time regimen will be effective and will minimize side effects.

Post-operative swallow results will be collected from the medical record on those patients receiving post op swallow therapy per routine care. The post-operative swallow evaluation will be based solely on the discretion of the surgeon and is not required per the research protocol.

2 Study Objectives

This investigation is a quality improvement initiative designed to elucidate the benefit of gabapentin in pain management in subjects undergoing definitive surgical resection of head and neck mucosal malignancies.

Primary Objective

To assess the efficacy of gabapentin on decreasing narcotic requirements for treatment of acute postoperative pain in head and neck cancer patients undergoing definitive surgical resection of mucosal surfaces.

Secondary Objectives

To assess subjective pain scores and participant satisfaction with pain control.

Observational outcomes

Hospital length of stay and post-operative swallow function if assessed.

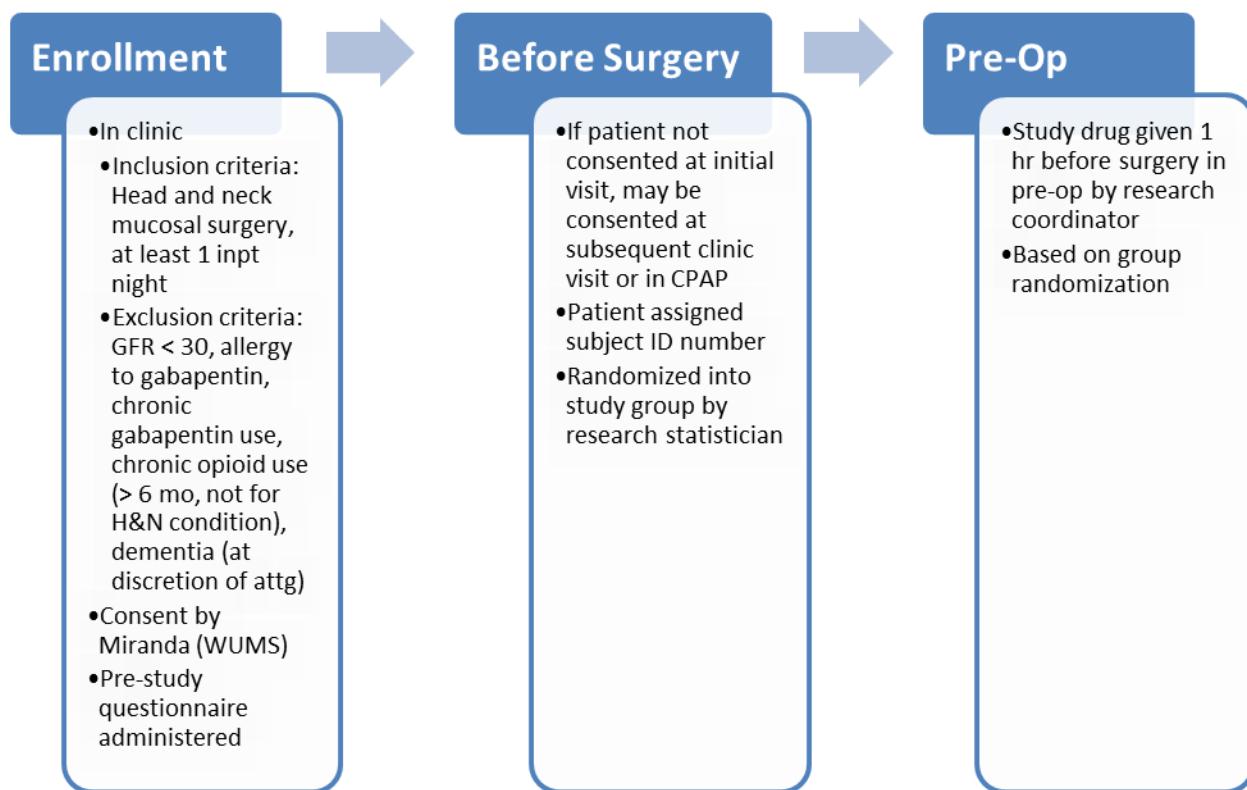
3 Study Design

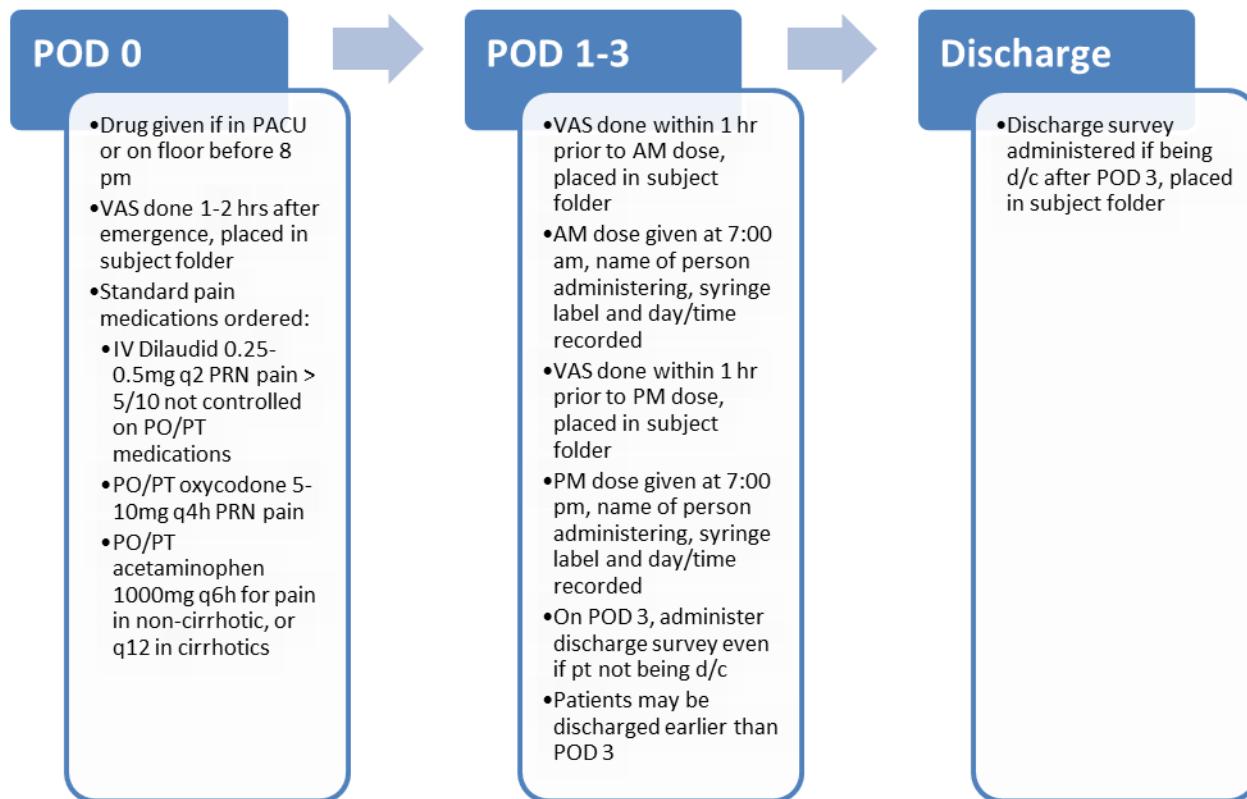
3.1 General Design

This is a prospective, randomized, double-blind, placebo-controlled study with the intent of providing high quality and reproducible data. The study subjects include adult otolaryngology patients over the age of 18 years undergoing open or endoscopic/robotic tumor resection involving the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx in a single tertiary academic center. Participants are

recruited from the otolaryngology head and neck cancer clinic during their preoperative visits. The duration of subject participation includes the subsequent inpatient hospitalization following definitive cancer resection up to three days after surgery. Subjects will be given the placebo or gabapentin for up to three days post op or until discharge, whichever comes first.

Potential subjects will be recruited from the patient population in the head and neck surgery clinic, 11th floor CAM. Eligible patients will be identified before their scheduled appointments via review of medical records in Allscripts by a study team member and approached in the exam room during their scheduled appointment with the head and neck surgeons. The study will be explained to them and a copy of the consent form will be provided. Patients will be reminded that participation is voluntary and will in no way affect their current or future care related to their disease. Patients will be given time to ask questions and will have the option to consider participation and enroll at a subsequent appointment before their planned procedure. The consent process will take place in private clinical exam room. Patients will be able to choose to participate up to 24 hours prior to their scheduled procedure, as this will give the study team enough time to alert the pharmacy and the study coordinators of their case. Steps to avoid coercion include proper training in informed consent, private discussion rooms in which the surgeon is not present, and no involvement of the surgeon will occur to ensure that patients do not feel as though their care from that surgeon will be affected by their decision to participate or to not participate. Patients will be made aware that their postoperative care will not be limited by participation in this study, meaning that they will not be denied needed and appropriate narcotic pain medications simply because they are enrolled. Written informed consent will be obtained prior to the start of research related procedures.





Subjects will present for their planned procedures to the pre-op surgery office and will be taken to the pre-op holding area as per usual hospital procedure. A study team member will meet the subject in the pre-op holding area and will administer the pre-op medication at 6AM and no later than 630AM. An investigational pharmacist will deliver the medication appropriately labeled with patient name and study number to the pre-op holding area. This oral administration is safe per consultation with the anesthesia faculty member of this project. Additionally, on the day of surgery a study Sub-Investigator will place pain medication orders in compass on hold for post op care. These orders will be 1000mg of Tylenol PO or per tube Q6 hours (or Q12 hours if the patient has hepatic insufficiency), oxycodone 5-10mg Q4 hours PRN pain, and dilaudid 0.25-0.5mg Q2 hours PRN pain >5/10 or pain not controlled with maximal oxycodone dose. The subject will be able to receive increases in pain medications as deemed appropriate by the inpatient treating physicians. They will not have any limitations set on pain medications simply because they are involved in the study. The subject will then proceed with surgery as planned. No alterations to intraoperative medications or anesthetic agents will be made based on study participation.

The subject will return to the PACU after extubation. If the subject had to remain intubated, he or she will be withdrawn from the study as he or she cannot complete pain scores while sedated. The study team member administering the preoperative dose will have provided a postoperative order sheet in the inpatient chart signed by an MD on the study team with postoperative pain orders for the nurses in PACU, so that all subjects will start with the same amount of medications available. This order will be written for 2mg morphine IV q2 hours PRN pain. The PACU can increase the dose of postoperative pain medications based on patient need and MD approval as per the usual PACU protocol without restriction based on a subject's study participation. Subjects will remain in the PACU per the usual protocol until the required level of alertness and clinical stability are reached for transfer. The VAS score obtained after surgery will be completed two hours after emergence. This is an approximate time: the post op VAS can be obtained sooner than two hours if the subject is alert and awake. If should not be obtained before one hour after anesthesia emergence. Thus it can be obtained one to two hours after the subject has awokened.

Subjects will be given BID medications per the study protocol and VAS scores will be obtained prior to medication administration. The doses will be scheduled at 7AM and at 7PM. The investigational pharmacist will have delivered the medication dose in a properly labeled container to the 6200 inpatient floor prior to each dose. Note that subjects must have completed surgery by 5PM in order to receive the 7PM dose after their surgery. Otherwise, this dose is to be skipped and the next dose administered will be at 7AM the next day. VAS score will still be obtained two hours post operatively and will count as the 7PM VAS score (see above). A midday VAS score at 12PM will be obtained, pending the availability of the study team. All VAS scores will be obtained with subject privacy optimized, including drawing the curtain in subject room to separate the sides of the room from any potential roommate. Also, the research team member will not vocalize a subject's status as a study patient. VAS scores will be obtained at rest, with cough and following a swallowing gesture. Scores are captured by providing the subject with a pen and asking the subject to mark the location of their pain on a scale of 0-10 during each phase of the VAS. The scale is a validated tool that measures 10cm in size and is marked "no pain" at 0 and "worst pain" at 10. The subject marks their pain level on the scale and the study team member will measure with a ruler and record the resulting number in the study database.

Subjects will fill out a discharge survey before they are discharged or at the completion of their participation to rate their satisfaction with their inpatient pain control. This survey will be a hard copy labeled with study ID and the data will be entered into the study database. All hard copy data will be stored in a locked cabinet accessible only to the study team. At the end of the study, all hard copy data will be properly destroyed.

Subjects will have 24/7 access to members of the study team should questions or concerns arise while they are actively participating in the study as well as up to 30 days after completion of the study.

3.2 Primary Study Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 3, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

3.3 Secondary Study Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) subject's baseline pain tolerance, and (d) hospital length of stay.

(a) Subject satisfaction with pain control will be captured in a survey administered at POD 3 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner. Two of the survey questions will mirror those on the HCAPHS surveys, listed as followed (see attached "post-treatment questionnaire"):

1. How often was your pain well controlled?
 - 0) Never
 - 1) Sometimes
 - 2) Usually
 - 3) Always
2. How often did the hospital staff do everything they could to help you with your pain?
 - 0) Never
 - 1) Sometimes
 - 2) Usually
 - 3) Always
3. How satisfied are you with your overall pain control?
 - 0) Very dissatisfied

- 1) Somewhat dissatisfied
- 2) Neutral
- 3) Somewhat satisfied
- 4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during your inpatient stay?

A point system is created with the sum of the numeric values assigned to questions 1-3 on a scale of 0 to 10, with a score of 0-3 indicates overall dissatisfaction, 4 indicates neutrality, and 5-10 suggests overall satisfaction. This will be analyzed as an ordinal variable.

(b) VAS pain scores will be assessed 1-2 hours after surgery and then three times a day on POD 1-3 or until day of discharge, whichever comes sooner. Two of these scores will occur prior to study drug administration. A standardized photo-copy of the VAS form will be given to subjects with verbal instruction to first "mark on the line the point that you feel represents your current pain level when you're resting." This is followed by asking the subject to gesture swallowing and "mark another point on the line that represents your pain level when you swallow." Lastly, the subject will be asked to cough and to "mark the final point on the line that represents your pain when you cough." The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from "no pain" on the left to "extreme pain" on the right (see "VAS form"). The distance in millimeters from the left of the line to the center of the patient's three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.

(c) The subject's belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit (see "pre-treatment questionnaire"). This includes the following questions:

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?
 - 0) Very ineffective
 - 1) Somewhat ineffective
 - 2) Somewhat effective
 - 3) Very effective
2. In the past, how has your pain tolerance been?
 - 0) Very poor
 - 1) Somewhat poor
 - 2) Somewhat tolerant
 - 3) Very tolerant
3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition?
 - 1) Yes I do
 - 2) No I do not

The results of these questions will be reported separately in the final analyses.

(d) Hospital length of stay will be calculated for each subject.

3.4 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into “drug-related”, “likely drug-related”, and “unlikely drug-related.” Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Subjects undergoing definitive mucosal head and neck tumor resection including oral cavity, oropharynx, larynx, and hypopharynx
- At least 1 night of planned inpatient stay

4.2 Exclusion Criteria

- Incapable of giving informed consent
- Age < 18
- GFR < 30
- Allergy to gabapentin
- Baseline gabapentin use
- Chronic opioid use for over 6 months

4.3 Subject Recruitment and Screening

Subjects will be recruited in the outpatient head and neck clinic prior to their planned surgeries by designated study team members. Potentially eligible patients will be identified by study team members prior to their scheduled appointments via the outpatient medical records system. Eligible subjects will be approached after their scheduled appointment in a private setting and the study outline explained to the patient. Written informed consent will be obtained from those patients who wish to participate. Patients may choose to think about study participation but will need to decide and provide written consent prior to the day of surgery, either at their subsequent preoperative anesthesia clinic appointment or medical oncology/radiation oncology appointments. Study team members will be properly trained in the informed consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study prior to the expected completion if they develop hypersensitivity reactions to the study drug, are unable to swallow all study drugs in the study period, or choose to withdrawal for other reasons. Subjects without a feeding tube who are unable, or unwilling, to swallow medications after surgery will not be given a feeding tube to remain in the study. A 20% dropout rate was anticipated and accounted for in the sample size calculation. Subjects will be able to withdraw on a continual basis throughout their participation. Withdraw can be requested either by the subject or by any team member if medical significant adverse reactions are observed. All withdraws will be reviewed by the principle investigator. No subject will be denied the ability to withdraw. The withdraw process will begin immediately when deemed necessary or when desired by the subject, and documentation of the reason and time of withdraw will be performed.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be excluded in the final data analysis. The reasons for withdrawal will be recorded and reported separately in the study data outcomes.

5 Study Drug

5.1 Description

300mg of liquid gabapentin or an equal volume of placebo will be pre-packaged by the investigational pharmacist in a labeled medication cup. An unblinded study team member in charge of the randomization process will indicate to the pharmacy which subjects are to receive what medication. The blinded study team members will not know which medication cup contains placebo or gabapentin.

5.2 Treatment Regimen

Subjects will receive either placebo or gabapentin 300 mg PO the preoperative holding area an hour before their procedure is scheduled to begin. This first dose will designate the day of their procedure as POD 0. If the procedure ends late in the evening, and the subject is not able to receive the second POD 0 dose by 7 PM, then this second POD 0 dose will be skipped. The subject must be completed with surgery and awake enough to give a VAS score. Thus any subject not done with the procedure by 5 PM will not receive a 7PM dose on POD 0. Participants will then receive either placebo or 300 mg of gabapentin BID POD 1- POD 3. Dosing will end either on POD 3 after the PM dose or on day of discharge after the AM dose, whichever comes first.

5.3 Method for Assigning Subjects to Treatment Groups

After a subject consents to study, the unblinded data manager will randomize the subject into active or placebo group and assign a subject study number. The subject study number will be used to identify which are to receive which medication.

5.4 Preparation and Administration of Study Drug

The Investigational Pharmacist will mix and prepare the study medications necessary for each subject. A pharmacist will deliver the medication to the floor and a designated study team member will administer it. Please see section 5.7 below for mixing and packaging details. Contact information for the pharmacy for this project is pharmacist Kathryn Vehe at 314-795-7286.

Inpatient pharmacists will be responsible for delivering the medication to the floor prior to the AM dose and to the PM dose, as well as will deliver the medication to the pre-op holding area prior to a subject's procedure. Formal training for all study team members who will be administering the study drug or obtaining the VAS pain scores is required prior to subject interaction.

5.5 Subject Compliance Monitoring

The study team members will directly administer each study medication dosage during the study period and record adherence to study protocol. If a dose is missed during this period, the subject will remain in the study through the completion of the protocol. The decision to include data from subjects with missed doses will be made at the discretion of the principle investigator and statistician at the conclusion of the study. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

5.6 Prior and Concomitant Therapy

Every subject will have standard postoperative narcotic medications made available:

- IV Dilaudid 0.25-0.5mg q2h PRN pain greater than 5/10 not improved by oral or per tube medications
- PO/PT oxycodone 5-10mg q4h PRN pain

- PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, and 1000mg q12h in cirrhotic patients

These medications can be up-titrated as needed at the discretion of the physicians managing the patient's care as part of the routine postoperative management.

5.7 Packaging

- Study medications will be in liquid form. Gabapentin comes as a standard liquid form of 250mg/5ml. 6ml of either gabapentin or placebo will be packaged into a brown 20ml plastic cup with a sealed aluminum top. Each cup will have the subject name and study ID on it. The pharmacy will be made aware of all upcoming study subjects and will prepare the medications approximately 24 hours prior to administration, and will store these at 4 degrees Celsius.
- Individual doses will be delivered before each scheduled dose by an investigational pharmacist to the inpatient floor.

5.8 Blinding of Study Drug

The study team members administering the medications will be blinded towards whether a subject receives the study drug or the placebo. The data manager who does not participate in data collection or have direct subject interaction, as well as the pharmacist preparing the medication cups, will be unblinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Investigational pharmacists will be responsible for medication delivery prior to each planned dose. They will be alerted to upcoming procedures that involve study Subjects. They will be responsible for directly delivering the medication to the study team members prior to administration both on the inpatient floor and in the preoperative holding area. Any damaged or unusable study drug in a given shipment will be documented in the study files and discarded.

5.9.2 Storage

Medications will be stored by the investigational pharmacy in a designated, locked area at 4 degrees Celsius.

5.9.3 Dispensing of Study Drug

The study team members administering the medications will receive the medication from the investigational pharmacist. They will then administer the medication and record the time of administration and the subject identification number in the subject's study flow sheet ("Gaba project subject study flow chart" attached).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medications consumed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Medication cups and packaging will be discarded in the red biohazard containers in accordance with hospital policy and documented in the study files.

6 Study Procedures

The study procedures are outlined below and represented in the attached "Gaba project subject study flow chart".

Clinic Visit

- Consent.
- Pre-treatment questionnaire.
- Randomization group will be assigned by the study data manager after she is notified of subject agreement to participate.

Day of Surgery

- One dose of study drug will be administered preoperatively according to subject's randomization group.
- Standard pain medications orders will be provided. These will be up-titrated as needed per discretion of service residents and attending physicians.
 - IV Dilaudid 0.25-0.5mg q2 PRN pain > 5/10 not controlled on PO/PT medications
 - PO/PT oxycodone 5-10mg q4h PRN
 - PO/PT acetaminophen 1000mg q6h for pain in non-cirrhotic patients, 100mg q12h in cirrhotic patients
- One VAS score will be obtained 1-2 hours postoperatively.
- One postoperative dose of study drug will be administered if subjects arrived to inpatient floor prior to 7 PM.

Post-Operative Day (POD) 1-3

- TID VAS scores will be obtained, two of which will be prior to drug administrations.
- BID study drug administration will be conducted according to subject's randomization groups.

POD 3 or Day of Discharge

- Post-treatment pain satisfaction questionnaire will be conducted either after the AM dosing on POD 3 or on date of discharge, whichever comes sooner.

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations were performed based on prior studies with gabapentin use in otolaryngology patients undergoing thyroidectomy²¹. A study by Al-Mujadi et al in a population of patients undergoing elective thyroidectomy reported that total morphine consumption in the placebo group in the first 24 hours post surgery required a mean of 29.5mg of morphine with a standard deviation of 9.9mg. Assuming that this magnitude of effect variability will hold true in this project population, it is estimated that 46 subjects per group (total n=92) will be needed to detect with an 80% power at the 2-sided alpha level of 0.05 a difference of 20% or greater in average morphine dose (effect size d=0.6) between the placebo and gabapentin groups. Assuming a 20% drop out rate, 116 subjects will be enrolled in this study. The volume of eligible subjects for this study is predicted to meet the calculated sample size within two years of study start time. A review of surgical procedures meeting inclusion criteria performed over a sample three month time frame ranged from 12 to 17 procedures a month.

7.2 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for

potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

7.3 Subject Population(s) for Analysis

Protocol-compliant subjects who received all study drugs up to the conduction of post-treatment questionnaire will be included for analysis. Subjects with missed medication doses will go on to complete the protocol, and per the discretion of the principle investigator and statistician may or may not be included in the data analysis. Data integrity will be maintained such that subjects who are excluded for missed doses will be consistent among cases.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Adverse Event Reporting Period

The study period during which adverse events must be reported will be the period from the day of surgery to the end of the study treatment follow-up. For this study, the study follow-up is defined as 30 days following the last administration of study drug. Subjects will be provided with contact information for the study member that is in charge of adverse event follow up (Melanie Townsend, PI). They will be instructed to contact this person with questions related to the study, adverse events or side effects experienced.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.2 Recording of Adverse Events

At each interaction with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. Specific side effects that will be elicited at each interaction include nausea, vomiting, dizziness and sedation.

The clinical course of any adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study drug or study participation will be recorded and reported immediately to the IRB.

8.3 Unblinding Procedures

For this study only the data manager and pharmacy will be unblinded to the study drug and placebo assignments. Unblinding of the rest of the study investigators will occur after assurance that data collection has completed. If any subject data is intentionally or unintentionally unblinded, the event will be documented in detail in the study documents within 48 hours. Any unblinding that occurs during the study period for an individual participant will result in exclusion of that participant's data from final analysis. Study investigators must report unblinding to the PI within a 24 hour time period and must document the event. Subjects will immediately be made aware of the unblinding and will be withdrawn from completing the protocol.

Stopping Rules

The study will be terminated prematurely if 50% or more of the subjects receiving study drug (gabapentin or placebo) experience significant adverse events as defined above in section 8.1. The study will not be prematurely stopped if subjects experience less significant medication side effects, specifically nausea, vomiting, dizziness and sedation. A review of adverse events will be conducted at 25% and 50% enrollment to ensure that they are properly tracked.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Monitoring). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Assigned study numbers will be used on all hard copy data collection instruments in place of subject name. Source Documents/Case Report Forms.

Source data will be kept primarily in the electronic forms using REDCap for data collection. Paper forms including the original consents, questionnaires, VAS pain score sheets, adverse event reporting forms etc. will be kept in a locked cabinet that only study team members have access to. At the conclusion of the study, after data has been entered into a password protected spread sheet, will be destroyed in the proper manner. The official source document and case report form for this study will be the REDCap database.

All research records will be maintained in the Outcomes Office, 8th floor McMillan for 7 years after study completion per WU record retention policy.

10 Study Monitoring

10.1 Study Monitoring Plan

This study will be monitored in real time for each subject by the PI and study team. At minimum, with 25% accrual goal all adverse events and data collection forms will be reviewed by the PI and discussed among the study team.

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