PROTOCOL TITLE:

A Randomized, Open-Label Study to Assess the Pain, Toxicity and Quality of Life Effects of Adding Venlafaxine to the Pain Management Regimen for Patients Treated with Chemoradiation for Head and Neck Cancer

PROTOCOL NUMBER:

I 61117

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VERSION NUMBER:

3

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Confidentiality Statement

Table of Contents

1.0 Objectives

1.1 The primary objective is to assess the pain-reduction effects of adding venlafaxine to a regimen of gabapentin and methadone to control pain during and after chemoradiation.

1.2 The secondary objective is to assess the effect of venlafaxine of the rate of toxicities possibly or probably related to the pain control regimen.

1.3 Tertiary objectives include the effect of Venlafaxine on other quality of life scores, patient nutrition, hydration status, and opioid requirements during and after CRT.

1.4 Our hypothesis is that the addition of Venlafaxine to Gabapentin and Methadone will decrease pain, improve quality of life, and reduce opioid requirements in patients undergoing CRT for head and neck cancer.

2.0 Background

2.1 Squamous cell head and neck cancer is diagnosed in approximately 50,000 Americans annually, and at least 60% of these patients present with locally advanced, non-metastatic disease. Most fatalities result from uncontrolled local and/or regional disease. The standard of care currently for these patients is concurrent chemotherapy and radiation which can be an extremely toxic treatment regimen for patients. The treatment lasts approximately 7 weeks and can lead to severe mucositis and irritation to the structures of the pharynx and larynx which imparts severe pain and pain-related dysphagia on these patients. Extreme pain and dysphagia very frequently leads to anorexia and dehydration to the point of patients requiring placement of PEG tubes, of which approximately 10% require the PEG tube to remain in place long-term.(1, 2) Standard treatment at Roswell Park Cancer Institute for pain, dysphagia, and mucositis during and after treatment had been to use escalating Lortab elixir and transdermal fentanyl patches in these patients. From our clinical experience, virtually all patients require pain medication during CRT and it has been our practice to initiate a pain regimen early in treatment. Experiences with patients seen in the pain clinic provided insight into the use of a combination of gabapentin, oxycodone and methadone, additionally with a regimen centered on escalating gabapentin. With doses titrated up to 3600mg/day, gabapentin has demonstrated improvement of pain, mood, sleep and quality of life in patients with diabetic peripheral neuropathy.(3) In 2008, Sharp H, et al., at the NCI and in collaboration with Singh AK (PI of this study and NCI study) showed that gabapentin can be effective for painful mucosal neuropathy with near resolution of symptoms in head and neck cancer patients.(4) In 2010, Bar Ad et al. of the Radiation Oncology department at the University of Pennsylvania published a review of the use of gabapentin in cancer-related pain syndromes and in combination with opioid analgesics.

The analysis suggested effectiveness of gabapentin in improving the pain control in patients with neuropathic cancer pain, already treated with opiates. Moreover, gabapentin appeared promising in reducing the need for high total doses of opioids and avoiding unplanned treatment interruptions for patients with head and neck malignancies treated with radiotherapy or concurrent chemoradiotherapy (5, 6) Prophylactic use of gabapentin at the start of CRT has been shown to delay PEG tube use and leads to sooner removal of PEG tubes, a finding attributed to better swallowing function secondary to improved pain control (7). Recent data presented at the ASTRO Multidisciplinary Head and Neck Cancer Symposium, demonstrated that prophylactic gabapentin reduced unintentional weight loss during CRT (8). From these analyses and our clinical experience, our practice is to initiate gabapentin at the start of CRT. Furthermore, the combination of gabapentin and morphine has been shown to effect better pain relief at lower doses of each drug when compared with gabapentin or morphine alone in patients with painful diabetic neuropathy or post-herpetic neuralgia. The combination of both drugs was associated with a beneficial effect on pain-related interference with daily activity, mood, sleep and quality of life.(9)

2.2 To this end, Singh AK (PI of this study) initiated clinical trial I 262314 which compared the safety and efficacy of two pain regimens: 1) escalating gabapentin with escalating Lortab elixir and transdermal fentanyl patches as needed and 2) low dose gabapentin with methadone and oxycodone as needed. Preliminary data has suggested potential benefits to both escalating gabapentin and methadone as a breakthrough medication. Consistent with previous literature, the use of gabapentin appears to reduce the proportion of patients who require opioids, delays the onset of opioid initiation, and improves patient-reported overall health and pain scores, with the most significant effects seen in the arm with escalating gabapentin. Additionally, there is evidence that methadone reduced pain and had an overall broader improvement in patient-reported mucositis scores. Enrollment is closed for this study, therefore in an effort to further optimize the therapeutic benefit of low-abuse-potential and non-opioid medications for improving pain control and quality of life, we are aiming to investigate the potential benefits of venlafaxine.

2.3 Historically, antidepressants, particularly tricyclic antidepressants (TCAs), have been used for their proven treatment efficacy of neuropathic pain. (10-12) TCAs, however, have an unfavorable side effect profile in part due to their significant anticholinergic effects with associated cardiotoxicity, thus limiting their use in the modern era. As an alternative with a more favorable side-effect profile, serotonin and norepinephrine reuptake inhibitors (SNRIs) have demonstrated similar efficacy to TCAs for neuropathic conditions.(13) In 2002, Tasmuth et. al. reported on the use of venlafaxine for the treatment of neuropathic pain following breast cancer treatment. In this randomized placebo controlled trial, venlafaxine was found to improve patient-reported daily pain relief and maximum reported neuropathic pain.(14) In 2004,

Rowbotham et al. reported on venlafaxine for painful diabetic neuropathy in a multicenter, double-blind, placebo-controlled trial. At a dose of 150-225mg, venlafaxine significantly reduced pain intensity by week 6 compared to placebo.(15) Furthermore, Simpson identified an additive benefit of venlafaxine to maximum-tolerated gabapentin for pain control and quality of life in patients with painful diabetic neuropathy. This study demonstrated the combination of 150mg/day of venlafaxine with up to 3600mg/day of gabapentin improved pain relief, mood disturbance and quality of life compared to gabapentin-alone. It was also noted the combination of medications was well tolerated.(16) The aim of this study is to evaluate the potential benefit of this combination of venlafaxine and gabapentin, specifically in patients undergoing chemoradiation for head and neck cancer.

2.4 Clinical Studies

- The European Association for Palliative Care concluded from investigating multiple studies that controlled-release oxycodone is comparable to instant-release oxycodone, morphine and hydromorphone in management of moderate to severe cancer pain. The studies also indicated that side effects appear to be lesser than those associated with morphine and that it is a valid alternative to morphine and a first-line treatment for cancer pain. As a result, the European Association for Palliative Care recommended that oral oxycodone could be taken as a second-line alternative to oral morphine for cancer pain.(17)
- MD Anderson Cancer Center (MDACC) performed a systematic review of randomized controlled trials (RCTs) of opioids for cancer pain that showed fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine.(18)
- The International Association for the Study of Pain as well as the Canadian Pain Society considers venlafaxine as first line treatment for neuropathic pain. (19, 20)

3.0 Inclusion and Exclusion Criteria

Individuals will be screened on presentation to the radiation medicine clinic for evaluation of radiotherapy.

3.1 Inclusion Criteria

To be included in this study, patients must meet the following criteria:

- Patients who are eligible for chemoradiation therapy of the head and neck.
- Patients must have adequate renal function to undergo platinum based chemotherapy. This will mean a baseline Cr no greater than 1.5 times the upper limit of normal.
- Have a pathologic diagnosis of squamous cell carcinoma of the head and neck region.
- Age $\geq$ 18 years of age.
- Have an ECOG Performance Status of $\leq$ 2.

- Ability to swallow and/or retain oral or per tube medication.
- Patients of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Patient or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

3.2 Exclusion Criteria

Patients will be excluded from this study for the following:

- Patients who have previously been treated with surgery or radiation for head and neck cancer and/or are being treated for recurrent head and neck cancer.
- Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- Any patients prescribed medications for chronic and/or long term pain and/or neuropathy will be excluded, including patients under treatment of a pain specialist or substance-abuse programs. Acute post-op medications are allowed if the patient has discontinued them prior to initiating study.
- Any patients prescribed a Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAOIs), dextromethorphan, triptan, tryptophan supplements, IV methylene blue, linezolid or any other medication that may increase risk of serotonin syndrome, as deemed by the Investigator's opinion.
- Any patients with suspected or known, current or recent (within last 5 years) use of cocaine, amphetamines, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), or any other drug of abuse that may increase risk of serotonin syndrome, as deemed by the Investigator's opinion.
- Any patients with history of suicide-related events, or those exhibiting a significant degree of suicidal ideation.
- Patients with acute narrow-angle glaucoma.
- Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant or nursing female patients.
- Unwilling or unable to follow protocol requirements.
- Any condition which in the Investigator's opinion deems the patient an unsuitable candidate to receive study drug.
- Received an investigational agent within 30 days prior to enrollment.
- Patients on dialysis or with transplanted organs.
- Patients already enrolled on other studies of systemic pain control agents.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

3.4 Member of the following special population will be excluded:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM:
INCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Efficacy and Quality of Life Analysis of Venlafaxine for Patients Treated with Concurrent Chemoradiation for Head and Neck Cancer

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients who are eligible for chemoradiation therapy of the head and neck.	
☐	☐	☐	2. Patients must have adequate renal function to undergo platinum based chemotherapy. This will mean a baseline Cr no greater than 1.5 times the upper limit of normal.	
☐	☐	☐	3. Have a pathologic diagnosis of squamous cell carcinoma of the head and neck region.	
☐	☐	☐	4. Age ≥ 18 years of age.	
☐	☐	☐	5. Have an ECOG Performance Status of ≤ 2.	
☐	☐	☐	6. Ability to swallow and/or retain oral or per tube medication.	
☐	☐	☐	7. Patients of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	8. Patient or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM:
EXCLUSION CRITERIA

Participant Name: _____

Medical Record No.:_____

Title: Efficacy and Quality of Life Analysis of Venlafaxine for Patients Treated with Concurrent Chemoradiation for Head and Neck Cancer

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients who have previously been treated with surgery or radiation for head and neck cancer and/or are being treated for recurrent head and neck cancer.	
☐	☐	☐	2. Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.	
☐	☐	☐	3. Any patients prescribed medications for chronic and/or long term pain and/or neuropathy will be excluded, including patients under treatment of a pain specialist or substance-abuse programs. Acute post-op medications are allowed if the patient has discontinued them prior to initiating study.	
☐	☐	☐	4. Any patients prescribed a Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAOIs), dextromethorphan, triptan, tryptophan supplements, IV methylene blue, linezolid or any other medication that may increase risk of serotonin syndrome, as deemed by the Investigator's opinion.	
☐	☐	☐	5. Any patients with suspected or known, current or recent (within last 5 years) use of cocaine, amphetamines, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), or any other drug of abuse that may increase risk of serotonin syndrome, as deemed by the Investigator's opinion.	
☐	☐	☐	6. Any patients with history of suicide-related events, or those exhibiting a significant degree of suicidal ideation.	
☐	☐	☐	7. Patients with acute narrow-angle glaucoma.	
☐	☐	☐	8. Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	9. Pregnant or nursing female patients.	
☐	☐	☐	10. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	11. Any condition which in the Investigator's opinion deems the patient an unsuitable candidate to receive study drug.	
☐	☐	☐	12. Received an investigational agent within 30 days prior to enrollment.	
☐	☐	☐	13. Patients on dialysis or with transplanted organs.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	14. Patients already enrolled on other studies of systemic pain control agents.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

4.0 Local and Study-Wide Number of Subjects

4.1 A maximum of 60 patients at Roswell Park will be enrolled. Accrual is expected to take up to 2 years.

5.0 Local and Study-Wide Recruitment Methods

5.1 Potential subjects will be recruited at the first consultation with radiation medicine. Patients will be screened by their healthcare provider in clinic.

5.2 The source of subjects will be the population of patients with head and neck squamous cell carcinoma, who are evaluated in the radiation medicine clinic at a single institution.

5.3 No particular materials will be used to recruit subjects. Patients will be presented with details of the study during a routine consultation for radiotherapy in the radiation medicine clinic.

5.4 Patients will not receive any form of payment for participation in the study.

6.0 Multi-Site Research

NA

7.0 Study Timelines

7.1 Accrual is expected to take 2 years. Data collection will be complete about 4 years after the study opens.

7.2 Patients may remain on study and continue to receive treatment for pain for up to 24 months following CRT.

8.0 Study Endpoints

8.1 Primary Endpoint:

Patient pain levels will be quantified using the Pain Scale from the EORTC Head and Neck Cancer Module (EORTC QLQ-H&N35). Responses will be collected repeatedly during the evaluation period, as described in Section 11. The primary statistical endpoint is the change in H&N35 Pain Scale score between the baseline and week 7 assessments.

EORTC QLQ-H&N35 is a 35 item questionnaire designed to assess health-related QoL in head and neck cancer patients. It includes seven scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality) and 11 single items (problems with teeth, problems opening the mouth, dry mouth, sticky saliva, cough, feeling ill, pain killers, nutritional supplements, feeding tube, weight loss and weight gain). Items 1-30 are scored on a four-point Likert scale (1 ‘not at all’; 2 ‘a little’; 3 ‘quite a bit’; 4 ‘very much’). Items 31-35 use a ‘yes’ (2) and ‘no’ (1) response format. Higher scores correspond to lower quality of life.

8.2 Secondary Endpoint:

The toxicity of the pain regimen will be assessed using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

8.3 Tertiary Endpoints:

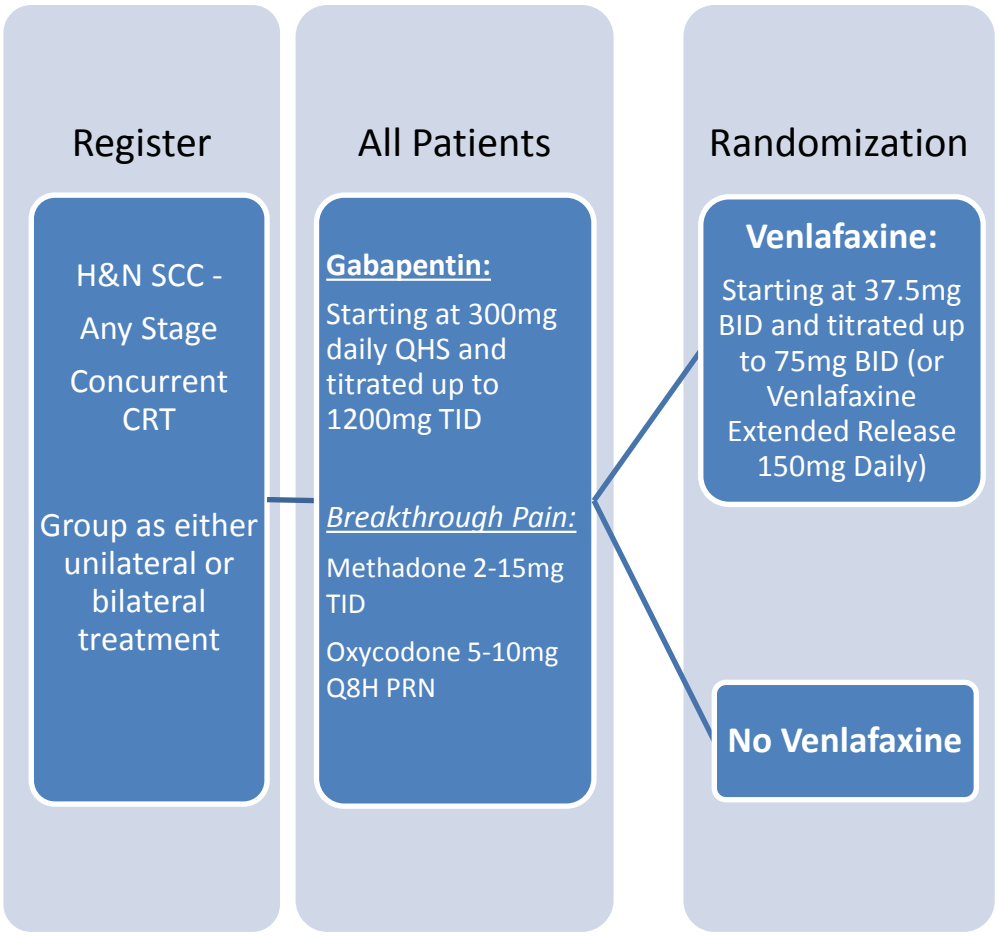
EORTC QLQ-C30 responses will also be collected to describe the patient's global health, physical function, and symptoms. The Oral Mucositis Daily Questionnaire will be used to describe the short and long term effects of radiation on quality of lift. Additional assessments will consider patient nutrition, hydration status, and opioid requirements during and after CRT.

9.0 Design

9.1 The pain-reduction effects of adding venlafaxine to a regimen of gabapentin and methadone to control pain during and after chemoradiation will be assessed in a randomized, two arm, open-label, single institution study. The treatment regimens for the two arms are described in Section 10. Inclusion and exclusion criteria are detailed in Section 3.

9.2 No interim analysis is planned.

9.3 Patients will be randomized 1:1 to the two study arms in stratified, permuted blocks of six patients each. The randomization will be stratified by location of the radiation treatment (unilateral or bilateral). The randomization list will be provided by the study biostatistician.



On Treatment Visits (OTVs) & Follow-Ups: Oral Mucositis Daily Questionnaire (OMDQ), EORTC Quality of Life Survey (QLQ-C30 and H&N35), record weight loss, assess need for regimen or dose escalation, document treatment interruptions.

10.0 Treatment

10.1 **ARM 1** will receive scheduled Gabapentin that will be titrated starting at 300 mg daily QHS by 300 mg TID increase per week, for up to 1200 mg TID, as tolerated. All patients will receive gabapentin regardless of initial pain and in the absence of pain, as is our clinical practice in order to reduce or delay subsequent opiate requirement. Uncontrolled, and subsequent refractory pain, will be treated with Methadone 2 mg TID initially to be titrated as needed up to 15 mg TID for analgesia. Oxycodone 5 - 10 mg Q8H prn will be available for subsequent breakthrough pain. No other opioid or medication for neuropathic pain will be allowed on protocol. Patient compliance will be assessed at weekly on-treatment visits.

ARM 2 will receive scheduled Gabapentin that will be titrated starting at 300 mg daily QHS by 300 mg TID increase per week, for up to 1200 mg TID, as tolerated. Venlafaxine will also be titrated starting at 37.5mg BID by 37.5mg BID increase per week, up to 75mg BID per day or 150mg daily of Venlafaxine Extended

Release. Patients unable to tolerate Venlafaxine by mouth will be prescribed equivalent daily Venlafaxine of liquid suspension by mouth or through PEG tube as described.(21) (**Appendix A**) or alternatively patients will be given instructions on administering capsule by opening and sprinkling contents onto a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets, per the package insert. Dosing in suspension form is equivalent to immediate release. Uncontrolled and subsequent refractory pain will be treated with Methadone 2 mg TID initially to be titrated as needed up to 15 mg TID for analgesia. Oxycodone 5 - 10 mg Q8H prn will be available for subsequent breakthrough pain. No other opioid or medication for neuropathic pain will be allowed on protocol.

Patients will be monitored and assessed via vital signs, physical exam, weight loss, dysphagia, OMDQ (**Appendix C)**, EORTC (European Organization for Research and Treatment of Cancer) quality-of-life scores. (22) (**Appendix E and F)**, ECOG performance status (**Appendix D)**, and opioid/morphine equianalgesic calculations. Opioid intake will be summated by Oral Morphine.(23-25)

Patients will be seen at least once a week during the 7 weeks of CRT and, at 1 month, 3 months, 6 months, 9 months (only for patients continuing on a pain regimen at the 6 month follow-up visit), and 12 months after the end of chemoradiation therapy. For patients that require prolonged analgesic therapy (i.e., greater than 12 months), long-term follow-up visits may be extended for up to 24 months (as per investigator judgment).

10.2 Agents

- **Gabapentin (Neurontin®):** Elixir containing 50 mg/mL. Taken by mouth or through PEG tube.
- **Methadone:** Elixir containing 10 mg/mL. Taken by mouth or through PEG tube.
- **Oxycodone:** Elixir containing 5 mg/ 5 mL. Taken by mouth or through PEG tube.
- **Venlafaxine (Effexor®):** Tablet containing either 37.5mg or 75mg. Taken by mouth.
- **Venlafaxine Extended Release (Effexor XR®):** Capsule containing 150mg taken by mouth.
    - Alternatively, patients can administer capsule by opening and sprinkling contents onto a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets. Dosing in this form is equivalent to immediate release.

- A third option is the Elixir containing 15mg/mL(21) (**Appendix A**) taken by mouth or through PEG tube. Elixir dosing is equivalent to immediate release.

- See **Appendix B** for oral morphine equivalent dosage.
- Compliance will be assessed in a subjective manner via patient-physician dialogue and electronic quality-of-life screening tools.

10.3 Treatment is intended for an outpatient setting. However, at the investigator's/physician's discretion, the participant may receive treatment as an inpatient, if deemed necessary.

If patients undergo platinum therapy and EITHER have a rise in their creatinine to >2 ORany symptoms of gabapentin toxicity (such as confusion, unsteady gait, somnolence)*(26)* then the CrCl will be calculated and the gabapentin (Neurontin®) dose modified (see Table 1).

Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (CCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females C_{Cr} =(0.85)(140-age)(weight)/[(72)(S_{Cr})]
for males C_{Cr} =(140-age)(weight)/[(72)(S_{Cr})]

where age is in years, weight is in kilograms and SCr is serum creatinine in mg/dL.

Dosage adjustment in patients ≥ 12 years of age with compromised renal function(27) or undergoing hemodialysis is recommended as follows:

Table 1 Gabapentin (Neurontin®) Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)
≥ 60	900 - 3600	300 TID 400 TID 600 TID 800 TID 1200 TID
> 30 - 59	400 – 1400	200 BIB 300 BID 400 BID 500 BID 700 BID
> 15 - 29	200 -700	200 QD 300 QD 400 QD 500 QD 700 QD
15[a]	100 - 300	100 QD 125 QD 150 QD 200 QD 300 QD

[a] For patients with creatinine clearance < 15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

For patients with GFR=10 to 70mL/min, the total daily dose of venlafaxine will be reduced by 50%. In patients diagnosed with hepatic cirrhosis, the starting dose will be reduced by 50%.

10.4 Any patients prescribed medications for chronic and/or long term pain and/or neuropathy will be excluded, including patients under treatment of a

pain specialist or substance-abuse programs. Acute post-op medications are allowed if the patient has discontinued them prior to initiating study.

Concurrent medications also will be reviewed for safety by the study physician and addressed, as the study physician deems appropriate.

Patients may be pretreated for nausea and vomiting with appropriate anti-emetics.

10.5 The following medications will be prohibited from concomitant use: Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAOIs), dextromethorphan, triptan, tryptophan supplements or any other medication that may increase risk of serotonin syndrome, as deemed by the Investigator's opinion. Concomitant use of aforementioned medications may increase the risk of serotonin syndrome. Management of serotonin syndrome would be per standard of care with symptomatic management and/or pharmaceutical antidote (such as cyproheptadine).(28, 29)

10.6 Gabapentin's most common side effects in adult patients include dizziness, fatigue, weight gain, drowsiness, and peripheral edema (swelling of extremities); these mainly occur at higher doses in the elderly. Gabapentin has been associated with an increased risk of suicidal acts or violent deaths. Gabapentin should not be discontinued abruptly after long term use. Abrupt or overly rapid withdrawal may provoke a withdrawal syndrome reminiscent to alcohol or benzodiazepine withdrawal. Gradual reduction over a period of weeks or months helps minimize or prevents the withdrawal syndrome. Informed consent contains additional details.

10.7 Oxycodone and Methadone's common side effects include constipation, fatigue, dizziness, and nausea, and vomiting, dry mouth, anxiety, itching, and sweating. Less common side effects include loss of appetite, nervousness, abdominal pain, diarrhea, urine retention, dyspnea, and hiccups. In high doses, overdoses, or in patients not tolerant to opiates, oxycodone can cause shallow breathing, bradycardia, cold-clammy skin, apnea, hypotension, miosis, circulatory collapse, respiratory arrest, and death. Concomitant use of opiates increases the risk of aforementioned side effects. The risk of experiencing severe withdrawal symptoms is high if a patient has become physically dependent or addicted and discontinues treatment abruptly.(17, 18, 30, 31) Informed consent contains additional details.

10.8 Venlafaxine's common adverse side effects include headache, nausea, sweating, sedation, fatigue, dizziness, dry mouth, night sweats, sexual dysfunction, loss of appetite, and anxiousness. In high doses or overdoses, venlafaxine can prolong QTc, which has been implicated in a case report of fatal arrhythmia following suicide with intentional overdose of venlafaxine.(32) Combining venlafaxine with similarly acting serotonergic drugs and medications increases the risk of serotonin syndrome. It is a weak

inhibitor of CYP2D6 and thus care should be taken with concurrent use of medications known to interact with CYP2D6. In high doses, increases in blood pressure have been reported. As with all antidepressants, there is an increased risk of suicidality in the initial period of recovery for patients with a history of suicide-related events or who have exhibited a significant degree of suicidal ideation prior to commencement of treatment. As with all antidepressants, there is an increased risk of seizures. If the medication is abruptly stopped, a withdrawal syndrome may occur and may consist of dizziness, sensory disturbances, sleep disturbances, agitation or anxiety, tremor or headache. At completion of chemoradiation or study withdrawal, Venlafaxine will be tapered at 75mg per week, or at 37.5mg per if week if symptoms of withdrawal syndrome occur. Informed consent contains additional details.

11.0 Procedures Involved

11.1 Patient Randomization and Registration

Informed consent *MUST* be completed prior to receiving any study related procedures. After consent has been obtained and eligibility is confirmed, patients will be randomized 1:1 to the two treatment arms as described in Section 9. Treatment assignments will be made by the Clinical Research Coordinator.

11.2 Baseline Evaluations

The following will be performed within 12 weeks prior to first dose of study drug:

- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- Medical history (including analgesic history)
- Pre-existing conditions
- Pregnancy test (urine) in females of childbearing potential
- ECOG Performance Status **(Appendix D)**
- Pain Assessment: (0-10 and/or Visual Analog)
- Quality of Life Questionnaires (EORTC QLQ-C30 and H&N35 Survey):**Appendix E** and **Appendix F**
- Concomitant Medications: Any medication that is ongoing within 1 week prior to the first dose of study drug.

11.3 Evaluations Performed at Weekly On-Treatment Visits

The following evaluations will be performed at the scheduled weekly on-treatment (CRT) visits and, as needed per patient request:

- Body weight
- ECOG Performance Status: **Appendix D**
- Pain Assessment: (0-10 and/or Visual Analog)

- Oral Mucositis Daily Questionnaire (OMDQ Survey): To assess mouth and throat soreness: **Appendix C**
  - The 2 diarrhea questions in the OMDQ will therefore be omitted and assumed to be 0 unless noted otherwise.
- Adverse events
- Morphine-Equivalent Narcotic Usage: What type of pain medication are you using, and how much?

11.4 Evaluations Performed at End of Treatment (Week 7)

The following evaluations will be performed at the end of treatment or at time of treatment discontinuation:

- Body weight
- ECOG Performance Status**: Appendix D**
- OMDQ Survey: **Appendix C**
- EORTC QLQ: C30 and H&N35 Surveys: **Appendix E and F**
- Pain Assessment: (0-10 and/or Visual Analog)
- Adverse events
- Morphine-Equivalent Narcotic Usage: What type of pain medication are you using, and how much

11.5 Follow-Up

The following evaluations will be performed at follow-up which will occur 4 weeks (± 1 week) after the last dose of chemoradiation therapy and, at 3 months (± 1 month), 6 months (± 2 month). Study is complete after 6 months once patients stop pain medicine. Study will continue for patients on pain medicine at 9 months (± 2 month) and 12 months (± 3 month) after the initial follow-up visit

- ECOG Performance Status**: Appendix D**
- OMDQ Survey: **Appendix C**
- EORTC QLQ: C30 and H&N35 Surveys: **Appendix E and F**
- Pain Assessment: (0-10 and/or Visual Analog)

Patients who are unable to make follow-up appointment(s) can be followed by phone/video contact for the Quality of Life assessments, OMDQ Survey and Pain Assessment. If a follow up visit is done via phone/ video contact, then only the Quality of Life Questionnaires, OMDQ Survey and Pain Assessment are required.

11.6 Long Term Follow-Up

The following evaluations will be performed at Long Term follow-up which is for patients requiring prolonged analgesic therapy (greater than 12 months). Long-term follow-up visits may be extended for up to 24 months. Long term follow-up evaluations will be scheduled at 6 months intervals (± 3 months) as long as the patient is on a continuing pain treatment regimen

- ECOG Performance Status**: Appendix D**
- OMDQ Survey: **Appendix C**

- EORTC QLQ: C30 and H&N35 Surveys: **Appendix E and F**
- Pain Assessment: (0-10 and/or Visual Analog)

Patients who are unable to make follow-up appointment(s) can be followed by phone/video contact for the Quality of Life assessments, OMDQ Survey and Pain Assessment. If a follow up visit is done via phone/ video contact, then only the Quality of Life Questionnaires, OMDQ Survey and Pain Assessment are required.

11.7 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in Table 2 below.

Table 2 Schedule of Procedures and Observations

Evaluation	Baseline[1]	During CRT Treatment[2]	End of Treatment (Week 7)	Follow-Up[3]	Long Term Follow-Up[4]
Physical Examination (i.e., temperature, heart rate, respiratory rate, blood pressure, weight, & height)	X				
Body weight only		X	X		
Medical History (to include analgesic history)	X				
Pre-Existing Conditions	X				
Pregnancy Test (urine) in females of childbearing potential	X				
ECOG Performance Status	X	X	X	X	X
Pain Assessment: (0-10 and/or Visual Analog)	X	X	X	X	X
Modified OMDQ Survey[5,7]		X	X		
EORTC QLQ-C30 plus H&N35 Survey[7]	X		X	X	X
Adverse Events		X	X		
Concomitant medications (per hospital EMR)	X[6]				
Morphine Milligram Equivalents[8]	X	X			

1. To be performed within 12 weeks prior to first dose of study drug.
2. Patient may start treatment anytime during weeks 1 through 3 of CRT. Patient should be seen at least 4 weeks out of 7 to be evaluable.
3. Follow-up evaluations will occur 4 weeks (± 1 week) after the last dose of chemoradiation therapy and, at 3 months (± 1 month), 6 months (± 2 month). Study is complete after 6 months once patients stop pain medicine. Study will continue for patients on pain medicine at 9 months (± 2 month) and 12 months (± 3 month) after the initial follow-up visit.

Note: Patients who are unable to make follow-up appointment(s) can be followed by phone/video contact for the Quality of Life assessments, OMDQ Survey and Pain Assessment. If a follow up visit is done via phone/ video contact, then only the Quality of Life Questionnaires, OMDQ Survey and Pain Assessment are required.

4. For patients requiring prolonged analgesic therapy (greater than 12 months). Long-term follow up visits may be extended for up to 24 months. Long term follow-up evaluations will be scheduled at 6 month intervals (± 3 months) as long as the patient is on a continuing pain treatment regimen. Note: Patients who are unable to make follow-up appointment(s) can be followed by phone/video contact for the Quality of Life assessments, OMDQ Survey and Pain Assessment. If a follow up visit is done via phone/ video contact, then only the Quality of Life Questionnaires, OMDQ Survey and Pain Assessment are required.
5. H&N patients rarely experience diarrhea. The 2 diarrhea questions in the OMDQ will therefore be omitted and assumed to be 0 unless noted otherwise.
6. Medications that are ongoing within 1 week prior to first dose of study drug. The Roswell Park EMR will be the documentation and will not need to be repeated in notes.
7. Captured in REDCAP.
8. Pain Medications will be recorded in REDCAP and converted to Morphine Milligram Equivalents (**Appendix B**).

11.8

Gabapentin is a gamma-aminobutyric acid (GABA) analogue that was originally formulated to treat epilepsy. The drug is known to provide significant pain relief in about a third of people who take it for fibromyalgia or chronic neuropathic pain; however, side effects result in two thirds of people. It is effective in reducing narcotic usage post-operatively and is helpful in neuropathic pain due to cancer.

Oxycodone is a narcotic analgesic generally indicated for relief of moderate to severe pain. It was developed in 1916 in Germany as one of several new semi-synthetic opioids in an attempt to improve on the existing opioids. Oxycodone 15 mg taken orally is equivalent to 10 mg IV Morphine and 30 mg PO Hydrocodone, each with 3-5 hours average duration.(18, 30)

Methadone is a synthetic opioid. It is used medically as an analgesic and a maintenance anti-addictive and reductive preparation for use by patients with opioid dependency. However, methadone has gained popularity among physicians for the treatment of other medical problems, such as an analgesic in chronic pain. Due to its activity at the N-Methyl-D-aspartate (NMDA) receptor it may be more effective against neuropathic pain, but, for the same reason, tolerance to the analgesic effects may be lesser compared to other opioids. The greatest benefit in this setting is that methadone can be dosed less frequently than shorter-acting drugs like morphine or hydrocodone. Another factor in the increased usage is the low cost.(17, 18, 31)

Venlafaxine is a Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) used medically for depression, anxiety disorders and pain. Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine uptake. Serotonergic actions are present at low doses, while its noradrenergic actions are progressively enhanced as dose increases. It is theorized the balanced inhibition of presynaptic uptake in both serotonin and norepinephrine is the primary mechanism accounting for pain relief. (34)

12.0 Withdrawal of Subjects

12.1 Reasons for treatment discontinuation and withdrawal from study without patient consent will include the following:

- Death
- Patients with symptomatic deterioration: global deterioration of health status requiring discontinuation of treatment
- Treatment-related toxicity
- Toxicity unrelated to treatment that may prevent the patient from continuing
- Reported or prescribed use of an opioid or neuropathic pain medication not listed in section 10.2
- Investigator judgement

- The Investigator may withdraw a patient if, in his/her judgement, it is in the patient's best interest to do so.

- Noncompliance

12.2 Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All patients who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated or stabilized. The final status of the AE will be reported in the patient's medical records and to the appropriate eCRF.

13.0 Risks to Subjects

13.1 Please see page 16 and 17.

The benefit to the patient in terms of improvement in pain, quality of life, and reduced opioid requirement likely outweigh the risks.

13.2 Venlafaxine is a Category C teratogen. There are no adequate or well controlled studies in human women. Pregnant women are excluded from this study. A urine pregnancy test is required in women of child-bearing potential prior to enrollment.

13.3 There are no known risks to others who are not subjects.

14.0 Potential Benefits to Subjects

14.1 Patients may benefit from this study by potentially having decreased pain, improved quality of life and reduced opioid requirement during chemoradiation treatment.

15.0 Data and Specimen Banking

15.1 NA

16.0 Measurement of Effect

16.1 Schedules for measuring the pain and quality of life outcomes are described in Section 11. Toxicity assessments are described in Section 17.

17.0 Safety Evaluation

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

- **Diagnosis Versus Signs and Symptoms**

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

- **Adverse Events Occurring Secondary to Other Events**

  In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

  However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

- **Abnormal Laboratory Values**

  Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

  If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

  If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia".

  Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

- **Preexisting Medical Conditions (Baseline Conditions)**

  A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens

during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

- **Grading and Relationship to Drug**

The descriptions and grading scales found in the CTEP Version 5 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5 of the CTCAE is identified and located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version5.
The relationship of event to study drug will be documented by the Investigator as follows:
Unrelated: The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
Unlikely: The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
Possible: The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
Probable: The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
Definite: The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

Reporting Adverse Events**: Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received. For this study, venlafaxine is the study drug. All other pain interventions are considered standard of care. Attributions for AE's will only be captured for the venlafaxine arm. Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 17.6** for details on reporting Unanticipated Problems.

17.4 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.5 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 17.3.**

Reporting Unanticipated Problems:

Unanticipated problem reporting will begin at the time of participant consent. An Unanticipated Problem shall be submitted to the CRS Compliance Office as "Reportable New Information" in the Click system within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS Compliance will submit the UP to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance as "Reportable New Information" in the Click system..

17.6 FDA Reporting

NA

18.0 Data Management and Confidentiality

18.1 Waiver of HIPPA Authorization

HIPPA Authorization will not be waived. In order to conduct the research, PHI will be accessed via the EMR in order to accurately document patient information including diagnosis, treatment, and medical history. Medical record numbers, date of birth, date of death, and age will be necessary for the research. Each patient will be consented for this process including consent for investigators to access medical records.

Data will be entered into a secure RedCap Database on the Roswell Park server. This will be accessible only to investigators on the study. For analysis, data will be entered into eClinical, which will only be accessible to authorized individuals (see section 18.2).

Any paper files containing identifiers will not be taken off Roswell Park premises. PHI will not be reused or disclosed to any other person or entity.

18.2 Data collection and storage

Patient data will be kept on the secure Roswell Park RedCap database, and will be accessible only by the PI, co-investigator, and the CRS representative. It will be password protected. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only.

Data entry into the database is to be completed in a timely fashion (within 30 days) after the patient's clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Source Form, which is handled in an expedited fashion.

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs (via the EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

18.3

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.4

- Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.
- Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

19.0 Statistical Plan

19.1 The primary objective of the study is to assess the pain-reduction effects of adding venlafaxine to a regimen of gabapentin and methadone to control pain during and after chemoradiation. Pain will be quantified using EORTC QLQ-H&N35, which is measured repeatedly during the 7-week radiation treatment process, and periodically for as long as the patient receives pain management treatment, up to 24 months after enrollment (see Section 11).

19.2 Analysis Samples

(1) The intent to treatment (ITT) sample includes all enrolled patients, assuming they treated in accordance with the randomized treatment assignment.

(2) The Per-Protocol sample includes enrolled patients who comply with the prescribed pain control regimen during their radiation therapy, and complete the 7-week follow-up EORTC QLQ-H&N35 survey.

19.3 Primary Analysis: The efficacy of venlafaxine will be quantified by comparing the within-patient change in pain scores (EORTC QLQ-C30) between the baseline and week 7 assessments in the ITT sample. The treatment effect will be estimated with a Generalized Linear Mixed model, describing the continuous EORTC QLQ-C30 outcomes as a function of a random patient effect, and fixed effects for treatment assignment, time (7-week vs baseline), the stratification factor, the treatment assignment (venlafaxine vs not) and the treatment/time interaction. This modeling approach also for adjustment of other biologically relevant factors, such as age, gender, and disease severity. The magnitude,

direction and 95% confidence interval for the adjusted interaction term estimate will be used to describe the effect venlafaxine in improving the pain management regimen. An interaction p-value <0.05 will be considered statistically significant.

19.4 Power and Sample Size:

Preliminary data from I-26314 of the end-point measured as pain score in final week of treatment demonstrated an effect size between 11-16% with the addition of gabapentin compared to the standard of care, and a 6% benefit with the addition of methadone compared to gabapentin alone. Tasmuth et al (14) showed a 24% improvement in patient-reported pain relief for venlafaxine versus placebo. Simpson (16) demonstrated a 29% improvement for the addition of venlafaxine to gabapentin.

Power calculations consider the simplified case where the exogenous factors (stratification and biologically relevant covariates) for not meaningful. Then the effect of venlafaxine on the change in pain score can be assessed using a 2x2 repeated measures ANOVA. In both treatment arms, the baseline H&N35 pain scores are expected to have mean=75 and standard deviation between 14 and 20.[32] The corresponding coefficients of variation are between 0.20 and 0.30.

Based on the data from I-26314, the week 7 follow-up Pain Scores in the control arm are expected to have a mean of 63, indicating 15% decline from the baseline mean of 75. Correlation of 0.2 is assumed for the within-patient outcome measurements. The table below shows the maximum week 7 mean in the venlafaxine arm that is detectable with 80% power using a 2-sided $\alpha = 0.05$ F-test for the treatment/time interaction in the model above, under different assumptions about the common coefficient of variation in the outcome.

Coefficient of Variation	Week-7 venlafaxine mean score	% decline from Baseline=75
0.20	50	33%
0.25	47	37%
0.30	44	41%

19.5 Toxicity Outcomes:

Toxicities will be tabulated by treatment arm using the maximum grade observed by patient. Possible differences by treatment will be described using odds ratio and 95% confidence interval estimates derived use Maental Hanzel methods to account for laterality of the radiation treatment.

19.6 Tertiary Outcomes:

The frequency of rescue medication use, morphine equivalent dose, and weekly OMDQ scores between treatments for each group individually and the combined cohort. The effect of venlafaxine on other quality of life outcomes will be quantified using the methods described for the primary outcome.

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

20.1 The Roswell Park Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

21.0 Vulnerable Populations

NA

22.0 Community-Based Participatory Research

22.1 NA

23.0 Sharing of Results with Subjects

23.1 NA- due to the nature of the study, there are no expected incidental findings or tests that would need to be conveyed to patients or primary care physicians.

24.0 Setting

24.1 Patients will be recruited from the Radiation Oncology clinic at Roswell Park, or from the Roswell Park satellite facility. All research procedures will be performed within Roswell Park. .

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 All discussion regarding the study including recruitment, consent process, and follow up visits will be conducted in a quiet, private environment. Any Investigator working with the patient will be introduced and an attempt will be made to ensure that the same Investigator is available to see the patient at the next visit. Subjects will be free to request an alternate provider should they feel more comfortable with someone else.

25.2 All procedures will be thoroughly explained to each patient, both during the consent process, and during the baseline visit and follow ups. Ample opportunity will be provided for questions to be asked and answered. Subjects will be provided with a number to call should they have any further concerns following their visits.

25.3 The Investigators are responsible for retention of the patient log and patient records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The Investigators are also responsible for obtaining patient authorization to access medical records and other applicable study specific information according to the Health Insurance

Portability and Accountability Act regulations (where applicable). Records and personal information will be accessed only through the Roswell Park network on a password protected server.

26.0 Resources Available

26.1 All Investigators on the study have been trained in human subject research as per requirements at Roswell Park. Dr. Singh is currently overseeing several other clinical trials in human subjects. All Investigators that will be working with subjects have experience working with patients in a clinical setting, and are familiar with the resources available at Roswell Park. Specifically, Dr. Singh is the PI for Clinical Trial I 262314, which included the same patient population of head and neck cancer patients undergoing chemoradiotherapy and a similar analgesia regimen with Gabapentin and Methadone.

26.2 Recruitment of new subjects is feasible based on the volume of new patients seen in the radiation medicine clinic on a weekly basis. On average, there are at least 4 new consultations per week, and if all patients are screened, approximately half will be eligible for the study based on need for chemotherapy. Clinical Trial I 262314 accrued 60 patients in 18 months, which has similar inclusion criteria as the current study. Therefore, we anticipate completion of accrual to be within 24 months.

Time devoted to conducting and completing the research will include subject recruitment, consent process, fielding patient phone calls, and arranging follow up visits. Each visit with a patient will require approximately 30 minutes of devoted time from the Investigator. Additional time will be spent ensuring patient compliance, entering data into the electronic system, and analyzing data.

The facilities at Roswell Park include a medical oncology clinic, radiation oncology clinic, chemotherapy infusion clinic, and various support staff for patients. This includes a social work department as well as psychologists who will be available to meet with patients should the need arise.

All persons assisting with the research will be fully informed regarding research procedures and protocols prior to starting work on the study. A clinical research coordinator assigned to the study will be available to assist with ensuring compliance with all protocol requirements.

27.0 Prior Approvals

NA

28.0 Compensation for Research-Related Injury

NA

29.0 Economic Burden to Subjects

29.1 All medications will be covered by insurance. There should therefore be no additional costs to patients who have insurance.

30.0 Consent Process

30.1 Informed consent will take place in the radiation medicine clinic at Roswell Park. The Investigator (or IRB approved designee) is responsible for obtaining written consent from each patient or the patient's legally authorized representative in accordance with "SOP: Informed Consent Process for Research (HRP-090)" using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the patient, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The patient should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the patient and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the patient file. At any stage, the patient may withdraw from the study and such a decision will not affect any further treatment options.

Non-English Speaking Subjects

- The population of potential subjects may include those that speak languages other than English. During screening for the study, the patient will be asked their preferred language. If a non-native English speaker is enrolled, translator services will be required at the first visit, during the consent process, and during each follow up evaluation. The translator will be medically qualified and fluent in both English and the patient's primary language. The consent for itself will be in English, however, a translator will be present to read and explain the consent to the subject in the subject's native language. In addition to scheduled visits, phone translators will always be available should the subjects have questions.

Subjects who are not yet adults (infants, children, teenagers)

- Subjects less than 18 years of age will not be enrolled in the study.

Cognitively Impaired Adults

- Subjects with cognitive impairment will not be enrolled in the study.

Adults Unable to Consent

- Adults unable to consent will not be enrolled in the study.

31.0 Process to Document Consent in Writing

31.1 Written documentation of consent will be completed in accordance with "SOP: Written Documentation of Consent (HRP-091)."

32.0 Drugs or Devices

- Drugs will not be supplied by the study.

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34.0 APPENDICES/SUPPLEMENTS

Appendix A Oral Suspension Recipe(21)

Drug name:	Venlafaxine	**Dosage Form:**	Suspension
Concentration:	15 mg/ml	**Shelf Life:**	28 days
Route:	Oral	**Storage:**	Refrigerate or room temp
Volume:	100 ml	**Auxiliary Labeling:**	Shake Well

Ingredients	QS	Quantity	Units
Venlafaxine 75 mg extended release tablets		20	tablets
Ora-Plus/Ora-Sweet	Y	50/50	mLs

Directions:

1. Crush tablets in a mortar and pestle and triturate to a fine powder.
2. Combine 50 mLs of each Ora-Plus & Ora-Sweet.
3. Add vehicle and mix well to form a viscous, but smooth and uniform paste.
4. Continue adding vehicle in geometric portions, mixing well.
5. Transfer to graduate.
6. Rinse mortar and pestle with vehicle and transfer to graduate.
7. QS to final volume with vehicle. Stir well.

Notes: may substitute simple syrup for Ora-Plus/Ora-Sweet

Appendix B Oral Morphine Equivalence Ratios(35)

Drug	Dose (mg)	Duration (h)*
Morphine	20–30	2–4
Codeine	200	3–4
Hydrocodone	30	4–6
Oxycodone	20	3–4
Hydromorphone	7.5	3–4
Meperidine	300	2–4
Methadone	20	4–8
Fentanyl (transdermal)	1 µg/h transdermally ≈ morphine 2 mg/24 h orally	48–72

Table 4

Recommended Dose Conversion

Transdermal Fentanyl	Morphine*	
	IM	Oral
25 µg/h	20 mg/d	60 mg/d
50 µg/h	40 mg/d	120 mg/d
75 µg/h	60 mg/d	180 mg/d
100 µg/h	80 mg/d	240 mg/d

Equianalgesic Potency Conversion
TABLE A

Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	NA	20
Hydrocodone	NA	30-45
Oxymorphone	1	10
Meperidine	75	300
Codeine	130	200

Appendix C Oral Mucositis Daily Questionnaire (OMDQ)

ROMC-TR100	Site No.	Investigator Number	Patient Number	Patient Initials	
DAILY QUESTIONNAIRE				Month	Day

1. How would you rate your **OVERALL HEALTH** during the PAST 24 HOURS? *(Please circle the most appropriate number.)*

0	1	2	3	4	5	6	7	8	9	10
Worst Possible	←									→ Perfect Health

2. During the PAST 24 HOURS, how much **MOUTH AND THROAT SORENESS** did you have? *(Circle one number)*

0	1	2	3	4
No soreness	A little soreness	Moderate soreness	Quite a lot of soreness	Extreme soreness

3. During the PAST 24 HOURS, how much did **MOUTH AND THROAT SORENESS** limit you in each of the following activities?

	Not limited	Limited a little	Limited some	Limited a lot	Unable to do
a. Swallowing	0	1	2	3	4
b. Drinking	0	1	2	3	4
c. Eating	0	1	2	3	4
d. Talking	0	1	2	3	4
e. Sleeping	0	1	2	3	4

4. On a scale from 0 to 10, how would you rate your **OVERALL MOUTH AND THROAT SORENESS** during the PAST 24 HOURS? *(Please circle the most appropriate number.)*

0	1	2	3	4	5	6	7	8	9	10
None	←									→ Worst Possible

Appendix D ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix E EORTC QLQ-C30 Questionnaire

	Not at All	A Little	Quite A Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite A Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

	Not at All	A Little	Quite A Bit	Very Much
16. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
17. Do you have any trouble taking a long walk?	1	2	3	4

18. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
19. Do you need to stay in bed or a chair during the day?	1	2	3	4
20. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite A Bit**	**Very Much**
21. Were you limited in doing either your work or other daily activities?	1	2	3	4
22. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
23. Were you short of breath?	1	2	3	4
24. Have you had pain?	1	2	3	4
25. Did you need to rest?	1	2	3	4
26. Have you had trouble sleeping?	1	2	3	4
27. Have you felt weak?	1	2	3	4
28. Have you lacked appetite?	1	2	3	4
29. Have you felt nauseated?	1	2	3	4
30. Have you vomited?	1	2	3	4

Appendix F EORTC QLQ-H&N35 Questionnaire

During the past week:	Not at All	A Little	Quite A Bit	Very Much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

During the past week:	Not at All	A Little	Quite A Bit	Very Much

49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	**No**	**Yes**
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?		

Scoring for the EORTC QLQ-C30 and HN35 modules: Global Health Status (QoL), Functional Scales, and Symptom Scales are scored from combining items. The methodology and process is outlined on the EORTC website: http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf