A Pilot Study at a Single-Institution of Pregabalin in the Management of Mucositis Pain in Patients undergoing Chemoradiation Therapy to the Head and Neck.

Principal Investigator: Erin McMenamin, MSN, CRNP
Regulatory Sponsor: Alexander Lin, MD
Department of Radiation Oncology
Hospital of the University of Pennsylvania
Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
Philadelphia, PA 19104
215-662-2428

Statistician: Rosie Mick, MS

Funding Source: Sigma Theta Tau
Penn Radiation Oncology

Study Product: Pregabalin (Lyrica)

Protocol Number: IRB 819266; UPCC 43313

Version: 04/21/2016

CONFIDENTIAL

Table of Contents

LIST OF ABBREVIATIONS

CRT – concurrent chemotherapy and radiation therapy
MP – mucositis pain
MTS – mouth and throat soreness
OMQ – oral mucositis questionnaire
OMTS – overall mouth and throat soreness
QOL – quality of life
RIM – radiation induced mucositis
RT – radiation therapy
PI – Principal Investigator
CRF – case report form
IRB – Institutional Review Board
CTSRMC – Clinical Trials Scientific Review and Monitoring Committee
DSMC – Data Safety and Monitoring Committee
DOCM – Department of Compliance and Monitoring

Study Summary

Title	A Pilot Study at a Single-Institution of Pregabalin in the Management of Mucositis Pain in Patients undergoing Chemoradiation Therapy to the Head and Neck.
Short Title	Lyrica Study
Protocol Number	IRB 819266; UPCC 43313
Phase	Pilot
Methodology	Prospective, randomized
Study Duration	18 months
Study Center(s)	Single-center
Objectives	To assess the efficacy of Pregabalin in the management of mucositis pain in patients receiving radiotherapy to the head and neck.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Adult patients undergoing photon or proton radiation therapy and concurrent platinum-based chemotherapy for head and neck cancer.
Study Product, Dose, Route, Regimen	Pregabalin (Lyrica) oral administration with dose of 150mg twice daily vs. placebo
Duration of administration	Approximately 10-12 weeks
Reference therapy	n/a
Statistical Methodology	This is a 2 arm *double blind* randomized pilot trial to generate preliminary data on the cumulative opioid dose for head and neck cancer patients treated with either placebo (the control arm) or Lyrica (pregabalin). Ten patients will be enrolled on each arm for a study total of 20 patients. The primary objective is to generate preliminary data on the cumulative opioid dose over the 11 week observation period for head and neck cancer patients treated with either placebo (the control arm) or Lyrica. For each arm, the mean and standard deviation of the cumulative opioid dose will be computed. In addition, the number of patients who drop out prior to the end of the 11 week observation period will be noted. The mean and SD of the cumulative opioid dose and the number of incomplete dropouts, will inform the design of a future randomized trial to test the hypothesis that Lyrica will significantly decrease the cumulative opioid dose over the 11 week observation period. No inferential analyses are intended in this study.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on

Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Patients undergoing radiation therapy (RT) for malignancies of the head and neck almost invariably develop painful oral mucositis, which may result in decreased oral intake, weight loss, and treatment interruptions [1, 2]. Altered fractionation and concomitant chemotherapy are now commonly utilized, as they have demonstrated improved outcomes, but are complicated by increased toxicity, including mucositis [3-6].

It is now clear that a successful outcome with RT is critically dependent on the ability to manage and support a patient's acute symptoms without necessitating treatment interruptions. This time dependence has been shown to be offset by increasing the total radiation dose suggesting that this may reflect the impact of tumor cell repopulation [7].

From a clinical perspective, symptomatic mucositis accounts for a large proportion of radiotherapy treatment interruptions [8, 9]. Studies have also demonstrated that mucositis pain (MP) is a significant reason for increased rated of hospitalization and treatment costs. These retrospective findings have recently been confirmed in a prospective study [10]. These findings underscore the importance of developing more effective strategies to manage symptomatic mucositis. While ongoing efforts continue to study the biology of radiation mucositis in hopes of developing effective selective mucosal radiation protectants, no effective agents exist for clinical management [11, 12]. In fact, a disproportionate amount of effort has been devoted towards the development of agents that prevent or reduce the pathogenesis of radiation induced mucositis (RIM) rather than optimizing current symptomatic management paradigms.

The current standard of care for management of MP associated with RIM is topical analgesics and oral pain medications including opioids when necessary [13]. While effective at managing pain, the use of morphine and its derivatives is associated with multiple side effects, including depression, sedation, nausea, vomiting, constipation, itching, potential addition, and respiratory depression. Additionally, certain pain types are less responsive to opioid analgesia, requiring increasingly higher doses and additional side effects. Neuropathic pain, for example, is one pain type where opioid use is typically recommended only as a second-line agent [14].

It appears that MP may be similar to neuropathic pain in both its character and response to intervention. Many patients describe MP as a burning or stinging sensation, similar to the neuropathic pain of herpes zoster. Despite a unique pathogenesis, interventions traditionally used for neuropathic pain have been tried and have found limited success. A Danish study of head and neck cancer patients undergoing radiation therapy experiencing MP were refractory to non-opioid analgesics randomized patients to opioids versus a tricyclic antidepressant. Of the 19 patients randomized to receive the antidepressant, 8 were able to complete the treatment course without requiring opioids [15].

Gabapentin is an agent approved for treatment of neuropathic pain, which has been used at this institution in the prevention and management of mucositis pain. Retrospective analysis suggests a possible decreased need for opioids in managing mucositis pain in patients undergoing radiation therapy to the head and neck [16]. A prospective study is currently underway to look at the affect of Gabapentin on quality of life in patient undergoing concurrent chemoradiation (CRT) to the head and neck.

Pregabalin has been effectively used to treat multiple neuropathic pain syndromes including fibromyalgia, post herpetic neuralgia and neuropathic pain associated with diabetic neuropathy [17]. The mechanism of action appears to be similar to Gabapentin, in that it also binds to the α2-δ subunit of voltage sensitive calcium channel channels in the CNS. We hypothesize that pregabalin may reduce or eliminate the need for opioid pain

medication in patients receiving RT to the head and neck. This could have significant implications in reducing the risk of adverse side-effects traditionally associated with opioids with a resultant increase in quality of life of these patients. Ultimately, this could result in improved outcomes due to better tolerance of the more morbid treatments, including altered fractionation and concurrent chemotherapy.

1.1.2 Quality of Life Assessment: QLQ-C30

The first generation of the EORTC quality of life questionnaire (QLQ) was developed by 1987. It was designed to be: Cancer-specific; Multidimensional in structure; Appropriate for self-administration; Applicable across a range of cultural settings; Suitable for use with additional site- or treatment-specific modules. The QLQ-C30 (version 1) incorporated five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease. Subsequent versions were built upon the same basic principles, culminating in the 'core' 30-item EORTC QLQ-C30 (version 3.0) questionnaire, representing over 20 years of continuous development, refinement and validation. Development and validation of the QLQ-C30 has been published. A Scoring Manual is available for the QLQ-C30, and the Reference Values Manual provides values based upon international data sets from many countries. The development continues [22].

1.1.3 Brief Pain Inventory (BPI) (Short Form)

According to research done by Daut, Cleeland and Flanery, The Wisconsin Brief Pain Questionnaire (BPQ) is evaluated with regard to both reliability and validity. Data from patients with cancer at 4 primary sites and from patients with rheumatoid arthritis suggest that the BPQ is sufficiently reliable and valid for research purposes [25]. For validity, the percentage of patients taking pain medications increased with higher pain ratings. This correspondence between increased medication use and higher pain ratings was significant for both narcotic ($x = 28.17$, $df = 3$, $P < 0.002$) and non-narcotic ($x = 23.75$, ~/f= 3, 1, < 0.002) pain relievers. Thus, the BPQ appears to possess adequate reliability and validity for use in research. The fact that the BPQ may be self-administered makes it especially suitable for research. The data indicate that equally reliable information is obtained by self-administration as by a more expensive and time-consuming interview. We will be administering the Brief Pain Inventory (BPI) in this trial. The BPI is based on the BPQ and is the short form version of this assessment.

1.1.4 Oral Mucositis Daily Questionnaire

According to Elting et al (2008) who used the Oral Mucositis Daily Questionnaire (OMDQ) in their research on reliability of measurements designed to quantify Oral Mucositis: Contrary to previous reports, the risk of mucositis was virtually identical in the 126 patients with oral cavity or oropharynx tumors (99% overall; 85% grade 3-4) compared with 65 patients with tumors of the larynx or hypopharynx (98% overall; 77% grade 3-4). The mean QOL score decreased significantly during RT, from 85.1 at baseline to 69.0 at Week 6, corresponding with the peak of mucositis severity. The mean functional status score decreased by 33% from 18.3 at baseline to 12.3 at Week 6. The impact of mucositis on QOL was proportional to its severity, although even a score of 1 or 2 (mild or moderate) was associated with a significant reduction in QOL (from 93.6 at baseline to 74.7 at Week 6). Despite increases in analgesic use from 34% at baseline to 80% at Week 6, mean mucositis scores exceeded 2.5 at Week 6. [24]

1.2 Investigational Agent

1.2.1 Description

Pregabalin is described chemically as (S)-3-(amino methyl)-5-methylhexanoic acid. The molecular formula is C8H17NO2 and the molecular weight is 159.23.

Pregabalin is a white to off-white, crystalline solid with a pKa1 of 4.2 and a pKa2 of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

Pregabalin capsules are administered orally and are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

Pregabalin oral solution, 20 mg/mL, is administered orally and is supplied as a clear, colorless solution contained in a 16 fluid ounce white HDPE bottle with a polyethylene-lined closure. The oral solution contains 20 mg/mL of pregabalin, along with methylparaben, propylparaben, monobasic sodium phosphate anhydrous, dibasic sodium phosphate anhydrous, sucralose, artificial strawberry #11545 and purified water as inactive ingredients.

Study staff will have access to both capsule and liquid versions of both pregabalin and the placebo version of the medication. Subjects will be able to alternate between capsules and liquid throughout the study based on their medical need. The liquid formulation of Lyrica or placebo will be issued to patients that are required to be NPO (Nil pro os – nothing by mouth) per speech pathology. Patients reporting the inability to swallow pills will also be issued the liquid formulation of the drug.

1.2.2 Clinical Pharmacology

1. Mechanism of Action

Pregabalin binds with high affinity to the α2-δ site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the α2-δ subunit may be involved in pregabalin's antinociceptive and anti-seizure effects in animal models.

In vitro, pregabalin reduces the calcium-dependent release of several neurotransmitters including glutamate, norepinephrine and substance P [18], possibly by modulation of calcium channel function. While pregabalin is a structural derivative of the inhibitory neurotransmitter gammaaminobutyric acid (GABA), it does not bind directly to GABA-A, GABA-B, or benzodiazepine receptors, does not augment GABA-A responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenalin reuptake.

2. Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours. In this study we will monitor patient's laboratory results for safety. Patients with GFR of 30-60ml/min (as determined by laboratory evaluation one week after chemotherapy and hydration) will have drug dose reduced to 75 mg, twice daily for the remainder of the study. Patients with a GFR < 30 will be removed from the study (also listed as exclusion criteria).

1.2.2.2.1 Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C-max) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data. The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C-max of approximately 25% to 30% and an increase in T-max to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

1.2.2.2.2 Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radio labeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (Senantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr).[17]

1.2.3 Safety Concerns [17]

1. Angioedema

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Pregabalin should be discontinued in patients with these symptoms.

Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

2. Hypersensitivity

There have been post-marketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin immediately in patients with these symptoms.

3. Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued, taper the drug gradually over a minimum of 1 week.

4. Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs) including pregabalin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Inform patients, their caregivers, and families that pregabalin and other AEDs increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Subjects will be directed to report behaviors or thoughts of concern immediately to healthcare providers.

5. Peripheral Edema

Pregabalin treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.5% of pregabalin patients and 0.2% placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

6. Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

In the pregabalin controlled trials, dizziness was experienced by 31% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin treated patients compared to 7% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated

patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients.

7. Weight Gain

Pregabalin treatment may cause weight gain. In pregabalin controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.3%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema. Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA1C).

8. Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Subjects will be directed to taper pregabalin gradually over a minimum of 1 week rather than discontinuing the drug abruptly. Please see section 5.2 for more information on taper.

9. Tumorigenic Potential

In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

10. Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician/NP if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.

11. Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 1.5% of patients on pregabalin and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

12. Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 × 103/μL, compared to 11 × 103/μL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 × 103/μL. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than 20 x 103/ μL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

Labs including blood counts, electrolytes, and kidney/liver function are completed by medical oncology every 1-2 weeks as standard of care for patients undergoing chemotherapy. The study team will use these laboratory results to monitor Adverse Events and subject safety. If platelet count qualifies as a Grade 3 toxicity as outlined in Appendix D, subjects will be discontinued from study drug. In the case of a grade 3 toxicity, this protocol will taper patients at a faster rate than usually recommended due to the risks associated with the thrombocytopenia (outlined in section 5.2).

13. PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3–6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse reactions of second or third degree AV block. Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

1.3 Clinical Data to Date

Multiple studies demonstrate the safety and efficacy of pregabalin for neuropathic pain related to diabetic neuropathy, post herpetic neuropathy, spinal trauma, post-operative pain, restless leg syndrome, cervicobrachialgia, lumbosciatalgia, and neuropathic cancer pain [19]. One prospective single-arm study of 28 children who were given pregabalin for chemotherapy associated neuropathic pain demonstrated long-lasting pain relief in 86% of patients, with minimal side effects [20].

Gabapentin, which has a similar chemical structure and appears to have a similar mechanism of action related to binding of the α2-δ subunit of voltage sensitive calcium channel channels, has been used previously at this institution with retrospective analysis suggesting a possible decreased need for opioids in managing mucositis pain in patients undergoing radiation therapy to the head and neck [16].

1.4 Dose Rationale and Risk/Benefits

The recommended dose of pregabalin ranges from 150 mg/day to 600 mg/day divided into twice or three times daily doses. Increasing dose above 300 mg/day appears to correlate with increasing side effects including dizziness, somnolence, blurry vision, peripheral edema, and constipation. It appears that incremental benefits in neuropathic pain are smaller at the higher dose levels.

2 Study Objectives

Primary Objective
To assess the effectiveness of pregabalin in decreasing the cumulative dose of opioid used in the management of mucositis pain related to radiation therapy to the head and neck.

Secondary Objectives
To assess for quality of life and level of mucositis pain among subjects treated with pregabalin in conjunction with radiation therapy to the head and neck.

To compare the effects of pregabalin in decreasing the need for and degree of opioid use, quality of life, and level of mucositis pain in these patients.

3 Study Design

3.1 General Design

This will be a Pilot study - single institution, two-arm, randomized, double blind study. Eligible study subjects will be enrolled among those being treated for mucosal head and neck squamous cell cancer receiving definitive or post-operative radiation therapy (photons or protons) and concurrent platinum-based chemotherapy in the Department of Radiation Oncology at the University of Pennsylvania. All study subjects will receive pregabalin or matching placebo starting the 1st day of radiation therapy and stopping upon resolution of acute mucositis pain following completion of therapy, approximately one month after the completion of radiation therapy. If it is not feasible to start pregabalin or matching placebo on the 1st day of radiation treatments, patients may start pregabalin or matching placebo anytime following the 1st day of radiation treatment up through the end of the 2nd week of radiation treatment, so long as the patients still meet all eligibility criteria in Sections 4.2 and 4.3.

ENROLLMENT	Concurrent Chemo	RANDOMIZE[a]	<u>Arm 1[b]</u> pregabalin target dose 300mg/day starting concurrent with RT <u>Arm 2[b]</u> Placebo starting concurrent with RT

a) Patients will be randomized prior to starting pregabalin or matching placebo on 1st day of radiation treatment. Patients may also start pregabalin or matching placebo anytime following the 1st day of radiation treatment up through the end of the 2nd week of radiation treatment, so long as all eligibility criteria in Sections 4.2 and 4.3 are still met.
b) See section 5.2 for details of treatment regimen

Follow-up – approximately 1 month post completion of radiation treatments for all study subjects

3.2 Duration of Subject Participation

The subject participation will start with the recruitment and informed consent process in the time period prior to starting RT and will extend until initial follow-up one approximately (1) month after completion of RT. It is anticipated that total participation will be for three or four months.

3.3 Sequence and Duration of Trial Stages

We anticipate this trial to accrue approximately 2-4 subjects per month. This would result in a total duration of approximately 6-11 months for complete accrual. Patient treatment will last approximately 7 weeks, with an approximate one month follow-up on study. This would result in a total duration of approximately 9-14 months completion of the entire trial including accrual and follow-up.

3.4 Primary Study Endpoints

Total opioid use as recorded at weekly on-treatment visits and follow-up visit. Patients will keep a diary of opioid use at home during the week. The diary will be collected by the staff and recorded at the weekly visit.

3.5 Secondary Study Endpoints

QOL as self-reported at baseline, weekly on-treatment visits, and at follow-up visit.

Radiation induced mucositis (RIM) pain as self-reported at weekly on-treatment visits and at one month follow-up visit using the validated mouth and throat soreness score and overall mouth and throat soreness score as well as the short form Brief Pain Inventory (BPI).

3.6 Primary Safety Endpoints

Toxicity will be physician/NP reported at weekly on-treatment visits and at follow-up visit, and will be scored according to NCI CTCAE v4.02 [21]

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Patients with a histologically confirmed diagnosis of mucosal head and neck squamous cell cancer receiving definitive or post-operative radiation therapy (photons or protons) and concurrent platinum-based chemotherapy at the University of Pennsylvania.
2. Age at least 18 years old.
3. Treatment entails significant risk for symptomatic mucositis likely to require opioid analgesia, as per the discretion of treating physician/NP.
4. Subjects are capable of giving informed consent.
   There are no exceptions to exclusion. The DSMC will not approve exceptions.

4.2 Exclusion Criteria

1. History of hypersensitivity to pregabalin or gabapentin.
2. History of seizure or currently taking anti-epileptic medication.
3. Creatinine clearance < 30 mL/min by Cockcroft-Gault estimate.

$$CLCr = \frac{[140 - \text{age(years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

4. Has another painful condition requiring chronic use of opioid analgesic, gabapentin, or pregabalin.
5. History of serious mood disorder or attempted suicide as determined by patient's history and physical and by using the Depression Screening (Appendix H). Subjects with a score of greater than 10 or those answering #5 with scores greater than a "0" will be deemed ineligible to be enrolled on study .
6. History of angioedema.
7. New York Heart Association class III or IV heart failure.
8. Platelets < 150 mg/dL or history of thrombocytopenia.
9. The patient has any uncontrolled intercurrent illness including but not limited to psychiatric illness/social situations that would limit compliance or interfere with their ability to participate.

4.3 Subject Recruitment and Screening

Subjects will be recruited by physician/NPs or other health care professionals in the Department of Radiation Oncology clinical practices of the University of Pennsylvania. No inducements or coercion will be used.

Employees or students of the University of Pennsylvania will be eligible to enroll on this study provided all inclusion criteria are met and no exclusion criteria are identified. For these potential study subjects, additional safeguards to ensure that they are not subjected to potential coercion or undue influence will include a clear discussion that their study participation will not otherwise influence their standing at the University of Pennsylvania and that an alternative to study participation is to not participate and to receive otherwise standard treatment as recommended by their physician/NP. Additional effort will be undertaken to ensure that the handling of PHI (patient health information) for such study subjects will comply with HIPAA guidelines as outlined below.

4.3.1 Vulnerable Populations

Children, pregnant women, fetuses, neonates or prisoners are not included in this research study. Women of childbearing potential must be non-pregnant and non-lactating and willing to exercise an effective form of birth control during radiation therapy (e.g. oral contraceptive, IUD, condoms or other barrier methods etc.). Before receiving chemoradiation, female patients must have a negative pregnancy test. Hysterectomy or menopause must be clinically documented.

Early Withdrawal of Subjects

When to Withdraw Subjects

1. At the subject's request.
2. Determination by the investigator that it is no longer safe for the subject to continue therapy.
3. The presence of CTCAE Grade 4-5 toxicity possibly, probably or definitely related to the study drug.

How to Withdraw Subjects

1. If pregabalin has not been administered, the study subject will proceed to receive the recommended RT.

2. If pregabalin has been administered, the study subject will taper the dose gradually over a minimum of one week at the discretion of the treating physician/NP.

Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be give to the full data set that should to be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study:,

- If the patient withdraws consent, s/he will be given the choice of withdrawing completely meaning no further contact or data collection or giving the research team permission to follow up contact for data collection. It must be a high priority to try to obtain at least survivial data on all subjects. Patients that agree to be followed with be asked to sign to sign the 'Consent to Follow up' form (appendix G).
- If the PI, treating oncologist or physician withdraws the patient for any reason, the patient will be given the same choice as subjects who withdraw consent themselves. Patients agreeing to be followed with also sign the 'Consent to follow up.'
- If the patient is lost to follow up, the research study staff will make three documented attempts to confirm the subject's status. We would only use the contact information provided by the patient to our department as is our Standard of Practice.

5 Study Drug

5.1 Description

Pregabalin is an agent with anti-nociceptive and anti-seizure effects believed to exert its effect through binding to the α2-δ subunit of voltage-gated calcium channels in the central nervous system. It is available as hard-shelled capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin and as oral solution containing 20 mg/mL. The solution is clear and colorless contained in a 16 fluid ounce white HDPE bottle.

5.2 Treatment Regimen

Study subjects will self-administer oral preparation of pregabalin or matching placebo in twice daily dosage. Study subjects may use capsule form or solution, depending on medical necessity.

All study subjects will start taking 75mg of pregabalin nightly starting on the first day of radiation treatments. The dose will be increased to 75mg twice daily on day 3 and subsequently to 150mg twice daily on day 5.

Study subjects randomized to the treatment arm will continue to take 150mg of pregabalin twice daily for the duration of their radiation treatments until approximately their one month follow up visit. Subjects will be instructed at their follow up visit on how to taper the study drug.

Subjects randomized to the placebo arm will receive capsules and/or liquid that looks identical to the treatment arm. Subjects will titrate and taper in a fashion identical to the treatment arm.

At the discretion of the treating physician/NP, the interval between increasing dosage may be prolonged to a maximum of 4 days or the dosage reduced after the goal dose has been reached. Participants reporting excessive sedation or dizziness will be allowed to delay dose escalation. If a patient is not able to reach or maintain the goal dose at any point during the study (such as due to an adverse event at least possibly related to the study drug), the patient may continue on study and will be included in the analyses. The dose reached/dose

reduction will be recorded by the treating physician/NP with annotation of the rationale for the decision to maintain at that dose.

During titration, patients will be assessed daily by designated study staff before or after their daily radiation treatment in order to discuss/report with/to the PI any adverse events associated with the study drug.

Patients will be screened for suicidal ideation by designated study staff at baseline, daily during week 1 titration of the study drug and on a weekly basis during the study period until chemotherapy and radiation therapy are completed. Patients will be screened for depression again at the 1 month inspection visit. All patients will be screened using the Depression Screening assessment (appendix H).

Patients scoring a 10 or higher or reporting anything other than a 0 on question # 5 will meet with a physician/NP and will be:

1. Immediately removed from the study and discontinue the drug using the taper schedule outlined in section 8.1 (renal dose tapering).

2. Urgently referred to the counseling service at the Abramson Cancer Center.

3. Escorted to PEEC (Psychological Emergency Evaluation Center) if a patient reports suicidal thoughts and a plan to commit suicide that they intend to carry out.

Subjects who develop 1) grade 3 or GREATER thrombocytopenia; or 2) experience an unanticipated event (such as those outlined in the pregabalin package insert) will be directed to reduce their dose by 50% starting that day. The subject will then decrease the study drug by 1 pill per day thereafter until complete discontinuation. Patients titrating over the weekends will be directed to call the Radiation Oncologist on call if they experience any new side effects.

Approximately four weeks following completion of radiation treatments, study subjects will taper the pregabalin dose for a minimum of one week before stopping. This taper will follow a reverse schedule of the titration: 75mg twice daily for three days, 75mg once a day for three days, then no medication on the seventh day. The rate of taper may be modified by the PI or treating physician/NP as per the subject's clinical situation and PI or physician/NP's discretion.

Study subjects with persistent mucositis pain responding to pregabalin may continue to take the pregabalin for up to 4 additional weeks on study. After this point, any additional pregabalin administration will be off-study and solely at the discretion of the treating physician/NP. At that time, the cost of the medication will become the responsibility of the patient (or their medical insurance).

5.3 Preparation and Administration of Study Drug

Pregabalin will be dispensed by the HUP investigational pharmacy. Study subjects will self-administer the medication orally following the indicated scheduling.

5.4 Subject Compliance Monitoring

5.4.1 Study subject non-compliance will be defined by any of the following:

1. Failure of the study subject to complete the baseline quality of life questionnaire.

2. Failure of the study subject to take at least 75% of prescribed pregabalin dosage for at least 4 weeks.

3. Failure of the study subject to receive at least 70% of prescribed radiation treatments.

5.4.2 Study subject compliance monitoring will consist of:

1. Documentation that the study subject has completed the baseline quality of life questionnaire.

2. Documentation that the study subject has taken at least 75% of prescribed pregabalin dosage for at least 4 weeks.

3. Documentation that the study subject has received at least 70% of prescribed radiation treatments.

5.5 Prior and Concomitant Therapy

Patients participating in the trial will ***not*** be allowed to use extra virgin olive oil in therapeutic doses and will be discouraged from using NSAIDS during the trial. Patients are encouraged not to take NSAIDS due to the risk of masking a fever associated with aspiration pneumonia. A single dose may be taken on an occasional basis after ensuring they are afebrile. Given the risk of neutropenia, and an increased risk of aspiration pneumonia in this population (secondary to radiation-induced dysphagia), we recommend that patients not take NSAIDS or Tylenol during the course of treatment, as this may mask a fever and delay diagnosis of febrile neutropenia, a condition that requires timely diagnosis and treatment. Please note this is the standard practice for head and neck patients treated in Radiation Oncology at the Hospital of the University of Pennsylvania. We ask patients to refrain from taking NSAIDS for the reasons noted above, however, patients are not allowed to suffer, with consultation from the treating physician/NP, concessions may be made for a single dose to manage symptoms such as a headache. In the event of more severe pain, patients are offered opioids. We would like to stress that our goal is pain management and thus, have, as part of standard practice, many options to offer patients that will not interfere with this study. There are no dietary limitations for extra virgin olive oil. Viscous Lidocaine or steroids can be used, but will be documented as possible confounders in results.

6 Study Procedures

6.1 Screening

The informed consent and HIPAA consent form will be reviewed with the patient and the appropriate signatures will be obtained. Prior to receiving first radiation treatment, prospective study subjects will be screened for eligibility by a physician/NP and research coordinator. The eligibility checklist will be completed (see Appendix B). Patients must have a CBC and blood chemistry panel within the preceding 30 days prior to screening for eligibility demonstrating appropriate creatinine clearance and platelet counts and delineated in the exclusion criteria and on the eligibility checklist. Patients may also be consented and screened following the first radiation treatment so long as they will be able to start the Pregabalin or matching placebo before the end of the 2nd week of radiation treatment.

6.2 Baseline

During a routine clinic visit prior to receiving first dose of Pregabalin or matching placebo, the subject will complete the validated quality of life questionnaire (see Appendix C), the validated pain assessment (see Appendix D) and the Depression Screening (see Appendix H). The validated toxicity assessment form (see

Appendix E) will be completed with the subject by a physician/NP or designee in the Department of Radiation Oncology. This assessment will be performed within 4 (four) weeks of initiation of treatments, for example at the time of planning simulation or treatment set-up.

6.3 On Treatment Visits

Subjects will be instructed to begin taking the study drug on the first day of radiation treatment (or if applicable – on a day following the first radiation treatment up through the end of the 2nd week of radiation treatment) . On a weekly basis, the subject will be provided with an adequate supply of study drug and will be given instructions on details of administration in accordance with the assigned study cohort and treatment regimen (see Sections 3.1 and 5.2).
During each routine weekly on treatment visit (or another day weekly while on treatment), the subject will complete the validated oral mucositis questionnaire (OMQ) (see Appendix F), the pain assessment, the Depression Screening and the quality of life questionnaire. In addition, the pain diary and the pill diary will be collected from the patient for the corresponding week. The physician/NP or designee will complete the toxicity assessment form with the subject. If subjects require additional on treatment visits in addition to the routine weekly visit, no study documentation is required unless there is an adverse event, in which case the appropriate procedure will be followed as outlined in Section 8.

During titration, patients will be screened daily by designated study staff before or after their daily radiation treatment in order to discuss/report with/to the PI any potential adverse events associated with the study drug. In addition, during titration patients will be screened for suicidal ideation by designated study staff before or after their daily radiation treatment. All patients will be screened using the Depression Screening assessment (appendix H). For patients scoring a 10 or higher or reporting anything other than a 0 on question # 5, the procedure outlined in Section 5.2 will be followed.

6.4 Follow up Visit

During the routine approximate one-month inspection follow-up visit, the subject will complete the OMQ, pain assessment, the Depression Screening and the quality of life questionnaire. The pain diary will be collected for the corresponding time frame. The physician/NP or designee will complete the toxicity assessment form with the subject. This visit will occur approximately 4 weeks post completion of the final radiation treatment, but may occur no less than 3 and no more than 6 weeks post completion of radiation treatment.

6.5 Schedule of Events

Study Procedures

	Eligibility	Baseline	Weekly during treatment	Follow up (approximately 1 month)
Tests and Laboratory				
History and PE	X			
CBC and blood chemistry panel	X*		X	
Assessments				
Depression Screening Form		X	X	X
Quality of Life Questionnaire		X	X	X
Pain Assessment Form		X	X	X
Toxicity Assessment Form/Adverse Events		X**	X	X
Oral Mucositis Questionnaire (OMQ)			X	X
Pain Diary			X	X
Study Drug				
Study drug dispensing			X***	X****
Pill Diary/Study drug compliance			X	X

***with 30 days prior to eligibility check**
**** must be completed within 4 weeks of start of Pregabalin or matching placebo treatment**
***** starting on first day of radiation treatment (or if applicable – starting any day following the first radiation treatment up through the end of the second week of radiation treatment)**
******as needed to begin study drug taper**

7 Statistical Plan

7.1 Hypothesis

In head and neck cancer patients treated with chemoradiotherapy, we expect that pregabalin will lessen mucositis-related pain which will translate into a reduced cumulative opioid dose and as a result, will improve quality of life.

7.2 Design

This is a 2 arm *double blind* randomized pilot trial to generate preliminary data on the cumulative opioid dose for head and neck cancer patients treated with either placebo (the control arm) or Lyrica (pregabalin). To reduce bias in terms of initiation of opioid treatment and dosage prescribed, neither the patient, the study coordinator, nor the treating physician/nurse practitioner will know whether Lyrica or placebo had been assigned to a patient. The cumulative opioid dose over an 11 week observation period will be recorded. Randomization will eliminate selection bias and balance patient factors between arms. Ten patients will be enrolled on each arm for a study total of 20 patients. Study drug will be taken daily during the approximately 7 weeks of radiotherapy and for 4 additional weeks post-radiotherapy. The primary choice of the opioid drug for this study is oxycodone.

7.3 Objectives

The primary objective is to generate preliminary data on the cumulative opioid dose over the 11 week observation period for head and neck cancer patients treated with either placebo (the control arm) or Lyrica. Secondary objectives are to generate preliminary data on mucositis pain and quality of life.

7.4 Endpoints

Cumulative opioid dose will be computed as the sum of opioid dose x duration in days over the observation period (approximately 7 weeks of treatment and then 1 month post-treatment). Mucositis pain will be measured using two self reported questions found in the Oral Mucositis Questionnaire (OMQ). Quality of life is self reported using an EORTC questionnaire. These outcomes will be scored on day 1 of radiation, then weekly during 7 weeks of radiation and then at 1 month post-radiation.

7.5 Data Analyses

For each arm, the mean and standard deviation of the cumulative opioid dose will be computed. In addition, the number of patients who drop out prior to the end of the 11 week observation period will be noted. For each arm, the mean and standard deviation of the mucositis pain and quality of life scores will be computed at each time point. Descriptive analyses of the mean and SD of the cumulative opioid dose and the number of incomplete dropouts, will inform the design of a future randomized trial to test the hypothesis that Lyrica will significantly decrease the cumulative opioid dose over the 11 week observation period. No inferential analyses are intended in this study.

7.6 Sample Size Justification

There is presently no data for head and neck patients. A total of 20 patients (10 per arm) will be sufficient to generate preliminary data on the primary and secondary endpoints. Study enrollment should be completed in 1 year. Follow-up will continue for an additional 2.5 months.

7.7 Subject Populations for Analysis

We will analyze the all-treated population and any subject enrolled into the study that received at least one dose of study drug. Any patient who was randomized and then withdrew consent prior to receiving study drug will be replaced. The number of patients who drop out prior to the end of the 11 week observation period will be noted but these patients will be included in the analysis population.

8 Safety and Adverse Events

8.1 Definitions

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 should 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

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should 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 should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician/NP, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is clinically significant and not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Renal dose Taper

In view of dose-dependent adverse reactions and since LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 1. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CLCr = \frac{\left[140 - \text{age (years)}\right] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \; (\times\ 0.85 \text{ for female patients})$$

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr ≥60 mL/min). Then refer to Table 1 to determine the corresponding renal adjusted dose.

(For example: A patient initiating LYRICA therapy for postherpetic neuralgia with normal renal function (CLcr ≥60 mL/min), receives a total daily dose of 150 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75 mg/day pregabalin administered in two or three divided doses.)

For patients undergoing hemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment (see Table 1).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function Creatinine Clearance (CLcr) (mL/min)	**Total Pregabalin Daily Dose (mg/day)***				**Dose Regimen**
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg)†					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

In this protocol, patients with a baseline GFR < 30 will be ineligible. Patients with GFR of 30-60ml/min (as determined by laboratory evaluation one week after chemotherapy and hydration) will have drug dose reduced to 75 mg, twice daily for the remainder of the study. Patients with a GFR < 30 will be removed from the study (also listed as exclusion criteria). Potential side effects associated with a quick taper far out weight the side effects of depression.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject (see Section 6.5), the investigator/provider must seek information on toxicity/adverse events (see Section 8.1) by specific questioning and, as appropriate, by examination. Information on all toxicity/adverse events should be recorded immediately in the source document, and also in the appropriate toxicity/adverse event module of the case report form (see Appendix D). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis, if possible.

All adverse events that would constitute toxicity from the study drug occurring during the study period must be recorded. The clinical course of each event should 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 must be followed up to determine the final outcome.

All adverse events that would constitute toxicity from radiation therapy (photons or protons) and/or concurrent platinum-based chemotherapy during the study period will not be recorded. Though radiation therapy (photons or protons) and concurrent platinum-based chemotherapy are required for inclusion in this study, these treatments are not the interventions being examined nor are they included within the study objectives (Section 2).

8.3 Reporting of Serious Adverse Events

8.3.1 IRB Notification by Investigator

Reports of all serious adverse events/adverse events (including follow-up information) that are BOTH unexpected and probably or definitely related to the study must be submitted to the IRB within 10 business days. Exception: If the adverse event involved a death and indicates that participants or others are at increased risk of harm, investigators are required to submit a report to the IRB within 3 days. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.3.2 DSMC Notification by Investigator

All events meeting the DSMC reporting requirements must be entered into the mandatory Velos AE/SAE **form.** Once an event is reported, you must keep the information accurate and current in Velos. If new/updated information is learned about the event, the event should be amended or corrected promptly. Only an investigator may determine the grade, attribution and expectedness.

On-Site subjects (this includes any subjects enrolled at other sites on an in-house study)

1. All grade 3 or higher events (AE or SAE) within 10 business days of knowledge.
2. All unexpected deaths within 24 hours of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects who are off study for more than 30 days from their last study treatment/intervention are not reportable with the following exceptions:
   a) Deaths on in-house gene or cellular-therapies
   b) Deaths on in-house studies utilizing on-campus manufacturing of the study agent(s) or components of the study agent(s)
   c) Deaths on first-in-human studies

8.3.3 FDA Notification by Principal Investigator

The study PI shall notify the FDA by telephone or by e mail transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the PI's original receipt of the information. Since this protocol was granted an IND exemption, this reporting is voluntary.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study PI will submit the adverse event to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study at his/her site. 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 9 Auditing, Monitoring and Inspecting). 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). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. All data requested on the source documents must be recorded. All missing data must be explained. If a space on the source document is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". If a question is found blank after the subject has completed the assessments, the RC will contact the subjects to obtain information. If the answers are not obtainable, the data will be marked as missing.

All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. Please see Appendices B-E for these source documents.

9.3 Case Report Forms

The data from paper source documents will then be entered by study staff into the electronic CRFs in the Velos data system.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices

Certain studies, as identified by the CTSRMC, will be monitored on an on-going basis by the DOCM. Each study will have an individualized monitoring plan developed by the DSMC and the study team. This plan must be approved by the DOCM Director. Once the CTSRMC determines that a study needs prospective monitoring, the DSMC will work with the PI and study team to develop a monitoring plan that will cover

- All of the Regulatory documentation
- Informed Consents
- Eligibility criteria
- Treatment administration and accountability
- Adverse/Serious Adverse Events and toxicities

• Response assessment
• Subject follow-up
• Data completeness
• Source documentation to Case Report Form (CRF)
• Manufacturing (where applicable)

At the conclusion of the monitoring visit, the monitor will spend time with the PI and/or study team to discuss the findings and to provide guidance on resolving deficiencies. A formal letter will be sent to the PI within about five business days. The PI does not have to respond the monitoring letter unless specifically requested to do so by the monitor. Studies that are high risk protocols are audited approximately six months from their first subject accrual and approximately every six month thereafter for the duration of the study. However, this schedule may be changed at the discretion of the DSMC. High enrolling or quick enrolling studies will be audited more frequently as necessary. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three subjects or 10% of the total accrual, whichever is higher, are audited. The Committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies. If an audit is unacceptable due to major deficiencies, representatives from the DOCM acting on behalf of the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DOCM Director will meet to
discuss necessary actions concerning study status.

10.3 Study Exceptions and Deviations

In order to harmonize with the IRB, the DSMC has changed its designations from Deviations and Violations to Exceptions and Deviations

Exception

A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

Deviation

A one time, unintentional action or process that departs from the IRB and DSMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 10 business days and the IRB within 10 business days.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

Sigma Theta Tau
Radiation Oncology department

12.2 Conflict of Interest

All University of Pennsylvania investigators will follow the University conflict of interest policy. No investigators working on this study have a conflict of interest and all investigators will be reporting through FIDES.

12.3 Subject Stipends or Payments

There will be no stipends or payments made to study subjects.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

1. Lalla, R.V. and D.E. Peterson, *Oral mucositis.* Dent Clin North Am, 2005. **49**(1): p. 167-84, ix.
2. Duncan, G.G., et al., *Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis.* Head Neck, 2005. **27**(5): p. 421-8.
3. Bernier, J., et al., *Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer.* N Engl J Med, 2004. **350**(19): p. 1945-52.

4. Cooper, J.S., et al., *Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck.* N Engl J Med, 2004. **350**(19): p. 1937-44.
5. Pignon, J.P., et al., *Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients.* Radiother Oncol, 2009. **92**(1): p. 4-14.
6. Fu, K.K., et al., *A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003.* Int J Radiat Oncol Biol Phys, 2000. **48**(1): p. 7-16.
7. Withers, H.R., J.M. Taylor, and B. Maciejewski, *The hazard of accelerated tumor clonogen repopulation during radiotherapy.* Acta Oncol, 1988. **27**(2): p. 131-46.
8. Vera-Llonch, M., et al., *Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma.* Cancer, 2006. **106**(2): p. 329-36.
9. Trotti, A., et al., *Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review.* Radiother Oncol, 2003. **66**(3): p. 253-62.
10. Murphy, B.A., et al., *Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy.* J Pain Symptom Manage, 2009. **38**(4): p. 522-32.
11. Bensinger, W., et al., *NCCN Task Force Report. prevention and management of mucositis in cancer care.* J Natl Compr Canc Netw, 2008. **6 Suppl 1**: p. S1-21; quiz S22-4.
12. Hensley, M.L., et al., *American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants.* J Clin Oncol, 2009. **27**(1): p. 127-45.
13. Worthington, H.V., J.E. Clarkson, and O.B. Eden, *Interventions for preventing oral mucositis for patients with cancer receiving treatment.* Cochrane Database Syst Rev, 2007(4): p. CD000978.
14. Dworkin, R.H., et al., *Pharmacologic management of neuropathic pain: evidence-based recommendations.* Pain, 2007. **132**(3): p. 237-51.
15. Ehrnrooth, E., et al., *Randomized trial of opioids versus tricyclic antidepressants for radiation-induced mucositis pain in head and neck cancer.* Acta Oncol, 2001. **40**(6): p. 745-50.
16. Bar Ad, V., et al., *Gabapentin for the treatment of pain related to radiation-induced mucositis in patients with head and neck tumors treated with intensity-modulated radiation therapy.* Head Neck, 2009. **32**(2): p. 173-177.
17. Pfizer. *LYRICA (pregabalin) Prescribing Information*. 2009 12/2009; Available from: http://media.pfizer.com/files/products/uspi_lyrica.pdf.
18. Taylor, C.P., *Mechanisms of analgesia by gabapentin and pregabalin--calcium channel alpha2-delta [Cavalpha2-delta] ligands.* Pain, 2009. **142**(1-2): p. 13-6.
19. Chiechio, S., et al., *Pregabalin in the treatment of chronic pain: an overview.* Clin Drug Investig, 2009. **29**(3): p. 203-13.
20. Vondracek, P., et al., *Efficacy of pregabalin in neuropathic pain in paediatric oncological patients.* Eur J Paediatr Neurol, 2009. **13**(4): p. 332-6.
21. *NCI CTCAE v4.02*. January 25, 2010]; Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf.
22. Fayers, P., & Bottomley, A. (2002). Quality of life research within the eortc-the eortc qlq-c30. *European Journal of Cancer*, *38*, 125-133.
23. Atkinson, T. M., Rosenfeld, B. D., Sit, L., Mendoza, T. R., Fruscione, M., Lavene, D., Shaw, M., & Li, Y. (2011). Using confirmatory factor analysis to evaluate construct validity of the brief pain inventory (bpi). *Journal of Pain and Symptom Management*, *41*(3), 558-565.
24. Elting, L. S., Keefe, D. M., Sonis, S. T., Garden, A. S., Spijkervet, F. K. L., Barasch, A., Tishler, R. B., & Canty, T. P. (2008). Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy. *Wiley InterScience*,

25. Daut, R. L., Cleeland, C. S., & Flanery, R. C. (1983). Development of the wisconsin brief pain questionnaire to assess pain in cancer and other diseases. *Pain*, *17*, 197-210.

15. Attachments

15.1 Appendix A

Eligibility Checklist

15.2 Appendix B

EORTC Quality of Life Questionnaire

15.3 Appendix C

Brief Pain Inventory

15.4 Appendix D

Toxicity Assessment Form

15.5 Appendix E

Oral Mucositis Questionnaire

15.6 Appendix F

Pain Diary

15.7 Appendix G

Consent to follow up

15.8 Appendix H

Depression Screening

15.9 Appendix I

Pill Diary

15.1 Appendix A Eligibility Checklist

Inclusion Criteria

- ☐ Patient undergoing concurrent chemoradiation therapy for a histological diagnosis of squamous cell carcinoma of the head and neck at the University of Pennsylvania.
- ☐ Age at least 18 years old.
- ☐ Treatment entails significant risk for symptomatic mucositis likely to require opioid analgesia, as per the discretion of treating physician/NP.
- ☐ Subject is capable of giving informed consent.

Exclusion Criteria

- Patients anticipated to receive radiation therapy with Protons
- History of hypersensitivity to pregabalin or gabapentin.
- History of seizure or currently taking anti-epileptic medication.
- Creatinine clearance < 30 mL/min by Cockcroft-Gault estimate.

$$CLCr = \frac{[140 - \text{age(years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

- Has another painful condition requiring chronic use of opioid analgesic, gabapentin, or pregabalin.
- History of serious mood disorder or attempted suicide.
- History of angioedema.
- New York Heart Association class III or IV heart failure.
- Platelets < 150 mg/dL or history of thrombocytopenia.

15.2 Appendix B

Quality of Life Assessment

THE QLQ-C30 VERSION 1.0 WITH FUNCTIONAL / SYMPTOM SCALES INDICATED

	SCALE	NO	YES
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	Physical	1	2
2. Do you have any trouble taking a **long** walk?	Physical	1	2
3. Do you have any trouble take a **short** walk outside of the house?	Physical	1	2
4. Do have to stay in bed or a chair for most of the day?	Physical	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	Physical	1	2
6. Are you limited in any way in doing either your work or doing household jobs?	Role	1	2
7. Are you completely unable to work at a job or to do household jobs?	Role	1	2

During the past week:	SCALE	**Not at all**	**A little**	**Quite a bit**	**Very much**
8. Were you short of breath?	Dyspnea	1	2	3	4
9. Have you had pain?	Pain	1	2	3	4
10. Did you need rest?	Fatigue	1	2	3	4
11. Have you had trouble sleeping?	Insomnia	1	2	3	4
12. Have you felt weak?	Fatigue	1	2	3	4
13. Have you lacked appetite?	Appetite Loss	1	2	3	4
14. Have you felt nauseated?	Nausea and Vomiting	1	2	3	4
15. Have you vomited?	Nausea and Vomiting	1	2	3	4

During the past week:	SCALE	Not at all	A little	Quite a bit	Very much
16. Have you been constipated?	Constipation	1	2	3	4
17. Have you had diarrhea?	Diarrhea	1	2	3	4
18. Were you tired?	Fatigue	1	2	3	4
19. Did pain interfere with you daily activities?	Pain	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	Cognitive	1	2	3	4
21. Did you feel tense?	Emotional	1	2	3	4
22. Did you worry?	Emotional	1	2	3	4
23. Did you feel irritable?	Emotional	1	2	3	4
24. Did you feel depressed?	Emotional	1	2	3	4
25. Have you had difficulty remembering things?	Cognitive	1	2	3	4
26. Has your physical condition or medical treatment interfered with your **family** life?	Social	1	2	3	4
27. Has your physical condition or medical treatment interfered with your **social** activities?	Social	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	Financial Difficulties	1	2	3	4

GLOBAL HEALTH STATUS

29. How would you rate your overall **physical condition** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

15.3 Appendix C Brief Pain Inventory

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

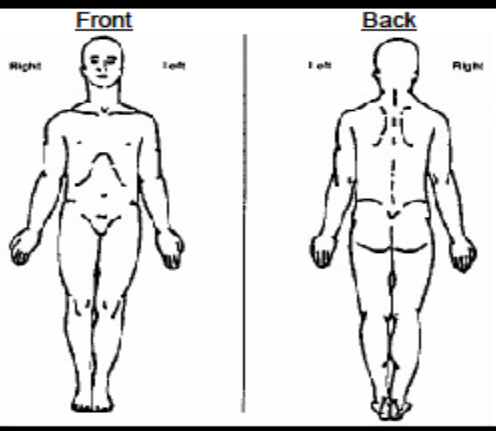
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

15.4 Appendix D

Toxicity Assessment Form

Does the patient have any adverse event that would constitute toxicity?: Y N

If so, please describe:

_____

_____

_____

Grade of adverse event:_____

Common Terminology Criteria for Adverse Events (CTCAE)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Cardiac disorders – P-R interval prolongation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately lifethreatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0- 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Allergic reaction: Hypersensitivity/Angioedema	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death

15.5 Appendix E: Oral Mucositis Questionnaire

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 (Worst Possible) 1 2 3 4 5 6 7 8 9 10 (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 (None) 1 2 3 4 5 6 7 8 9 10 (Worst Possible)

5. During the PAST 24 HOURS, how much **DIARRHEA** did you have? *(Circle one number)*

0	1	2	3	4
No diarrhea	A little diarrhea	Moderate diarrhea	Quite a lot of diarrhea	Severe diarrhea

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

0 (None) 1 2 3 4 5 6 7 8 9 10 (Worst Possible)

7. During the PAST 24 HOURS did you take medication for any of the following: *(Please check all that apply)*

☐ Pain ☐ Diarrhea ☐ Nausea/vomiting ☐ Did not take medication for pain, diarrhea, or nausea/vomiting

8. If you checked "Pain" in question 7, please list the medications you took for *pain* during the PAST 24 HOURS

_____ _____

☐ Did not take medication for pain.

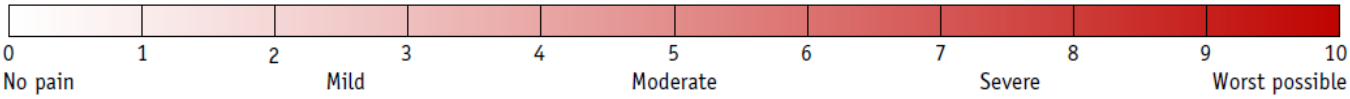
STOP

15.6 Appendix F. Pain Diary

Daily Pain Diary

Use this diary to record details about your pain, including how you treated it and how effective the treatment was. This will help you keep track of what works and what doesn't. Show this to your doctor at your next appointment so your doctor can better understand your pain level and what you're doing about it.

Use this scale to rate the severity of your pain.



Week of:	Time	Where was the pain?	Rate from 0 to 10, and describe	What were you doing when the pain started or increased?	Medicine or supplements: What did you take and how much?	Other therapies you tried (heat, relaxation, meditation, etc.)	One hour later, rate pain again	Any other effects? Comments?	Overall, how was your pain today?
Sunday									
Monday									
Tuesday									
Wednesday									
Thursday									
Friday									
Saturday									

Reference: Adapted from the AGS Foundation for Health in Aging

15.7 Appendix G. Consent to Follow up

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT WITHDRAWAL FROM STUDY/
CONSENT TO FOLLOW UP FORM

PROTOCOL TITLE: A pilot study at a single-institution of pregabalin in the management of mucositis pain in patients undergoing chemoradiation therapy to the head and neck.

PRINCIPAL INVESTIGATOR: Erin McMenamin, MSN, CRNP

REGULATORY SPONSOR: Alexander Lin, MD

EMERGENCY CONTACT: 215-662-4000; 24-HOUR, PLEASE ASK FOR THE RADIATION ONCOLOGIST ON CALL

__Withdrawal of Consent/Consent to Follow for Survival

Although you have withdrawn your consent to participate in the study, we would like to continue to access your medical records to monitor how you are feeling and your overall survival. Your decision will not interfere with your future care, or other services to which are otherwise entitled. If you consent to ongoing follow-up through your medical records, you will no longer be asked to complete any forms or examinations that are required by this study. Your Doctor will continue to provide treatment he/she feels is best for you.

By signing this form, I am allowing the research team to continue to access my medical records to collect data for long-term follow-up.

_____	_____	_____
Name of Subject (Please print)	Signature of Subject	Date
_____	_____	_____
Name of Person Obtaining Consent (Please print)	Signature of Subject	Date

15. 8 Appendix H.

Lyrica Trial – Depression Screening

Patients with a score of 10 or greater overall or those that rate the last question > 0 will be excluded/removed from the study

0 I do not feel sad.
1 I feel sad
2 I am sad all the time and I can't snap out of it.
3 I am so sad and unhappy that I can't stand it.

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel the future is hopeless and that things cannot improve.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

15. 9 Appendix I.

DP **Radiation Therapy Oncology Group**
Pill Diary

PROTOCOL TREATMENT: On the appropriately dated line, please indicate the total dose of drug given. Every day that the patient received drug must be documented.

Year

Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
1	1	1	1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4	4	4	4
5	5	5	5	5	5	5	5	5	5	5	5
6	6	6	6	6	6	6	6	6	6	6	6
7	7	7	7	7	7	7	7	7	7	7	7
8	8	8	8	8	8	8	8	8	8	8	8
9	9	9	9	9	9	9	9	9	9	9	9
10	10	10	10	10	10	10	10	10	10	10	10
11	11	11	11	11	11	11	11	11	11	11	11
12	12	12	12	12	12	12	12	12	12	12	12
13	13	13	13	13	13	13	13	13	13	13	13
14	14	14	14	14	14	14	14	14	14	14	14
15	15	15	15	15	15	15	15	15	15	15	15
16	16	16	16	16	16	16	16	16	16	16	16
17	17	17	17	17	17	17	17	17	17	17	17
18	18	18	18	18	18	18	18	18	18	18	18
19	19	19	19	19	19	19	19	19	19	19	19
20	20	20	20	20	20	20	20	20	20	20	20
21	21	21	21	21	21	21	21	21	21	21	21
22	22	22	22	22	22	22	22	22	22	22	22
23	23	23	23	23	23	23	23	23	23	23	23
24	24	24	24	24	24	24	24	24	24	24	24
25	25	25	25	25	25	25	25	25	25	25	25
26	26	26	26	26	26	26	26	26	26	26	26
27	27	27	27	27	27	27	27	27	27	27	27
28	28	28	28	28	28	28	28	28	28	28	28
29	29	29	29	29	29	29	29	29	29	29	29
30		30	30	30	30	30	30	30	30	30	30
31		31		31		31	31		31		31

Comments: _____

Signature:_____ Date:_____-_____-_____

*Please consider this page as a worksheet. You may give a copy to the pt./family member to record daily doses.