Date of Protocol: 01/26/2024

Official Title of Study: Transdermal Buprenorphine for the Treatment of Radiation-Induced Mucositis Pain in Head and Neck Cancer Patients: A Pilot Study

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MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

Transdermal Buprenorphine for the Treatment of Radiation-Induced Mucositis Pain in Head and Neck Cancer Patients: A Pilot Study

Short Title:

Buprenorphine-Mucositis Pain- HN Study

Stuart Wong, MD (Study PI)
Aditya Shreenivas, MD (Co-PI)

Current Version Number and Date
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PROTOCOL SUMMARY

Title	**Transdermal Buprenorphine for the Treatment of Radiation-Induced Mucositis Pain in Head and Neck Cancer Patients: A Pilot Study**
Principal Investigator	Stuart Wong, MD (Study PI)
Clinical Trial Phase	Phase II
Study Population	Stage I–IV by AJCC staging system 8th edition head and neck squamous cell carcinoma (HNSCC) patients, candidate for curative intent or adjuvant radiation therapy
Primary Objectives	To investigate the efficacy of using FDA-approved doses of transdermal (TD) buprenorphine in combination with oral tramadol to provide adequate pain control in radiation induced mucositis.
Secondary Objectives	1. Assess compliance of the study drug regimen. 2. Assess use of off-protocol pain medications during treatment and follow-up period. 3. Compare average weekly pain scores calculated by the oral mucositis (OM) pain app with the average pain scores recorded by the BPI short form. 4. Correlate average weekly pain scores with physical activity as documented on symptoms and functional assessment tools like MDASI-HN. 5. Assess use of nonopiod supportive care medications (i.e., laxatives, antiemetics and oral anesthetics) in conjunction with the study drug combination during treatment and follow-up period. 6. Assess gastrointestinal and cognitive side effect profile of study drug combination and its impact on cognition and quality of life. 7. Evaluate safety of the study drug combination.
Primary Endpoint	Establish efficacy of study regimen by showing that at least 33% of patients will achieve at least 30 percent decrease in visual analog scale (VAS) pain score of BPI questionnaire from baseline to the end of week 9 of treatment and follow-up period.
Secondary Endpoint	1. Monitor compliance of study drug regimen through the OM Pain App and medication diary. 2. Identify study participants that require off protocol opioids for pain control despite being on highest dose of study drug combination. 3. Correlate cumulative mean weekly pain scores calculated by the pain app with the average weekly pain scores recorded by the BPI short form. 4. Correlate average weekly OM Pain App scores and average weekly pain scores calculated from BPI short form and the MD

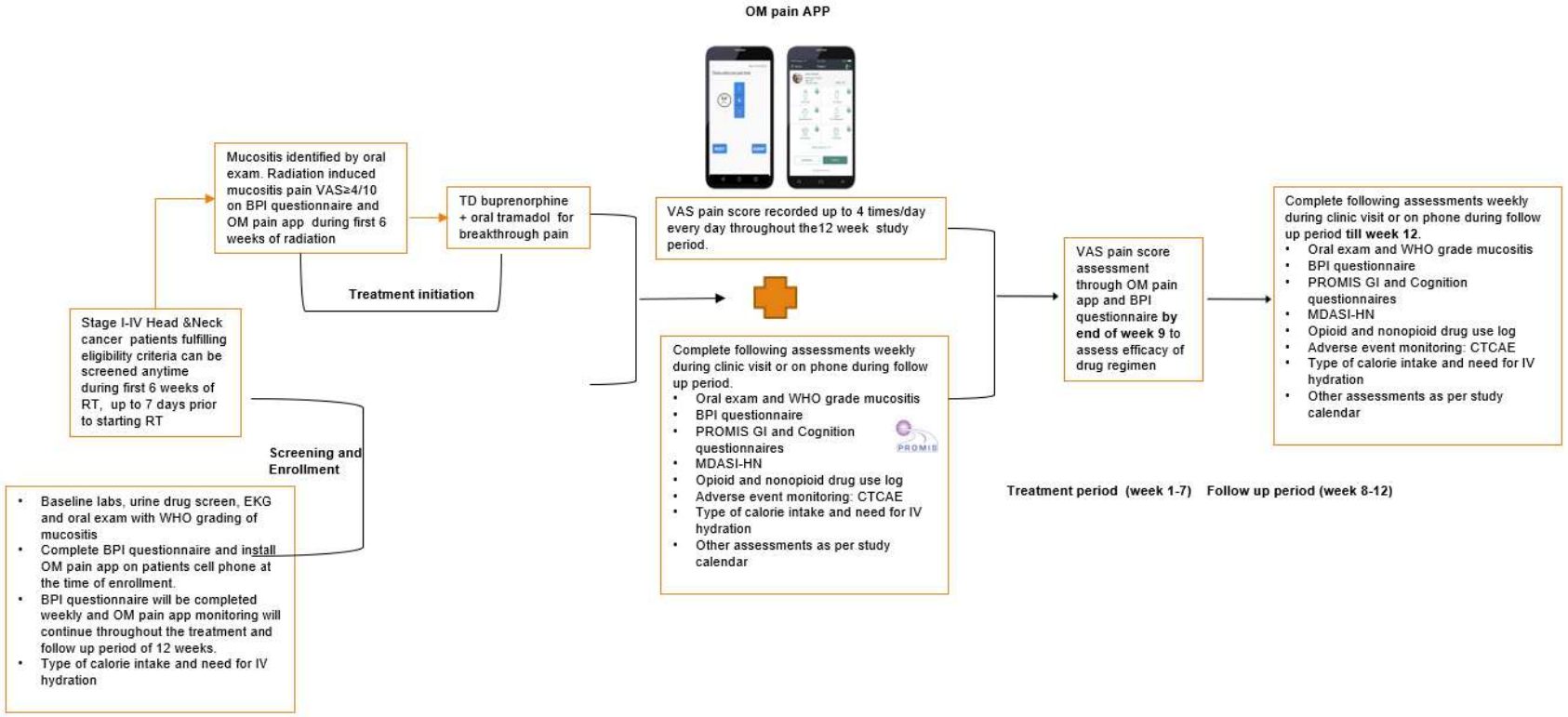
<table>
<tr><td></td><td>Anderson Symptom Inventory - Head & Neck (MDASI-HN), which is a head and neck symptom and function evaluation tool.
5. Maintain a weekly log of use of other nonopiod medication, such as laxatives, antiemetics, and oral anesthetics in conjunction with the study drug combination during treatment and follow-up period through weekly questionnaires.
6. Assess incidence and severity of gastrointestinal and cognitive adverse events measured by weekly PROMIS® (GI and cognition) questionnaires to better characterize the side effect profile of the drug regimen and its impact on quality of life.
7. Safety: Assess incidence and severity of adverse events associated with study drug combination, using the CTCAE version 5.</td></tr>
<tr><td>Main Inclusion Criteria</td><td>1. Age >18 years.
2. Histologically confirmed malignancies of Head and Neck involving Stage I-IV by AJCC staging system 8th edition (oral cavity, oropharynx, nasal or paranasal sinuses, hypopharynx and larynx etc.) including both squamous and non squamous cell histology’s (salivary gland carcinomas and carcinomas of unknown primary will be included)
3. Undergoing a course of either definitive radiation (dose of at least 50 Gy to the head and neck region) with or without chemotherapy or adjuvant radiation (at least 50 Gy to the head and neck region) with or without chemotherapy (patients with a history of prior definitive course of radiation will be allowed).
4. ECOG Performance status ≤ 2.
5. Concurrent enrollment on an interventional trial is allowed.
6. English speaking and literate.
7. Patients will be allowed to take radiotherapy mix, viscous lidocaine or magic mouthwash-like agents that do not contain opioids. Tylenol® allowed for fever.
8. Adequate organ function: Minor dose adjustments for tramadol are required in cases of severe liver and renal impairment so we would only include patients with adequate organ function outlined in table below. No dose adjustment for renal or hepatic impairment is required for TD buprenorphine. Some other parameters like hemoglobin, platelets, and WBC are required for administration of standard-of-care chemotherapy, such as cisplatin along with radiation in treatment of HNSCC. They are not required for administration of buprenorphine or tramadol.

<table>
<tr><th colspan="2">Organ Function Table</th></tr>
<tr><td colspan="2">Adequate hepatic function:</td></tr>
<tr><td>total bilirubin</td><td>< 2 mg/dL</td></tr>
<tr><td>AST(SGOT)/ALT</td><td>< 5 times institutional upper limit</td></tr>
<tr><td colspan="2">Adequate renal function:</td></tr>
</table>
</td></tr>
</table>

	creatinine clearance: > 30 mL/min/1.73 m2 for patients with creatinine levels above institutional normal
Main Exclusion Criteria	1. Physical exam demonstrating pre-existing mucositis from prior radiotherapy treatments or other causes. 2. Pre-existing oral infection or ongoing toxicity from prior radiotherapy.History of opioid abuse disorder, confirmed by medial history or subject disclosure. positive urine drug screen at screening visit. Exceptions will be made for subjects with current prescriptions post-surgery or other medical intervention. Previous history of allergic reaction to buprenorphine and tramadol. 3. Patients with multiple distant metastasis. (Patients with resectable oligometastasis will be allowed). 4. Current or recent use of short or long acting mixed opioid agonists/antagonists or other opioid antagonists. (Treatment with more than 2 doses of short acting oral or intravenous opioids like Oxycodone, morphine or hydromorphone within 24 hours of screening). Patients on treatment with long-acting opioids like fentanyl patch, methadone, oxycodone extended release, morphine extended release within 72 hours of screening would be excluded.Patients presenting with any other cause of pain not related to radiation-induced mucositis or head and neck cancer VAS >4/10 on BPI questionnaire (question 3: worst pain in last 24 hours) on the day of enrollment requiring opioid medications for pain control. 5. Prolonged QTc greater than 450 milliseconds in males and greater than 470 milliseconds in females at the time of enrollment. 6. Patients receiving induction chemotherapy prior to or after radiation/chemoradiation; such as patients with nasopharyngeal carcinoma. 7. Patients with a history of abdominal surgery within 60 days of registration or acute gastrointestinal conditions, such as colitis and appendicitis within four weeks of registration. 8. Conditions that may compromise the blood-brain barrier permeability. The blood-brain barrier may become leaky in select neurological diseases, such as amyotrophic lateral sclerosis, epilepsy, brain trauma, and brain edema. 9. Patients with a history of myocardial infarction ≤ 6 months prior to registration. 10. Patients with a history of significant respiratory depression; acute or severe bronchial asthma; known or suspected gastrointestinal obstruction, including paralytic ileus.

Study Design	Single-arm prospective clinical trial to determine the efficacy of transdermal buprenorphine and oral tramadol drug combination in alleviating radiation-induced mucositis pain in head and neck cancer patients during treatment and the follow-up period.
Study Agent	Transdermal buprenorphine with oral tramadol.
Number of Subjects	20
Estimated Time to Complete Enrollment:	Approximately 12 months.

STUDY SCHEMA



STUDY CALENDAR

Procedure	Screening [1]	Weeks During Chemoradiation (± 3 days)							Weeks follow-up period [2] (± 3 days)				
Study Day/Visit Day		**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Informed consent	X												
Baseline medical conditions	X												
WHO grade mucositis#	X	X	X	X	X	X	X	X		X			X
Oral exam for presence of other causes of mucositis (oral candidiasis, infections, trauma), etc.	X	X	X	X	X	X	X	X		X			X
Urine drug screen	X												
CBC with differential	X	X	X	X	X	X	X	X		X			X
CMP [3]	X	X	X	X	X	X	X	X		X			X
Opioid use and nonopiod drug use log [4]		X	X	X	X	X	X	X	X	X	X	X	X
OM Pain App assessment [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pain app compliance questionnaire		X	X	X	X	X	X	X		X			X
Monitor WI PDMP website for opioid use	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/stage of disease	X												
Weight	X	X	X	X	X	X	X	X		X			X
Performance status/ECOG	X							X		X			X
PROMIS® GI and cognition scoring [6]		X	X	X	X	X	X	X	X	X	X	X	X
BPI(Brief Pain Inventory) score	X	X	X	X	X	X	X	X	X	X	X	X	X
MDASI-HN [6]		X	X	X	X	X	X	X	X	X	X	X	X
Review device usage and proper reporting [6]		X	X	X	X	X	X	X		X			X

Procedure	Screening [1]	Weeks During Chemoradiation (± 3 days)							Weeks follow-up period [2] (± 3 days)				
Study Day/Visit Day		**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
EKG[7]	X							X					X
Digital image collection of oral cavity to evaluate mucositis [8]	X				X					X			X
Record type of caloric intake (normal, soft, liquid, parental/enteral)	X	X	X	X	X	X	X	X		X			X
Report use of IV fluids for hydration	X	X	X	X	X	X	X	X		X			X
Adverse event recording (CTCAE v5)		X	X	X	X	X	X	X		X			X
Pregnancy test (HCG) for WOCB	X												

*week 1 starts with the first week of radiation therapy and is continuous without adjustment.
WHO mucositis score will be recorded by the investigators during weekly clinic visits

1. Patients found to be eligible for the study can be screened and enrolled anytime during first six weeks of radiation therapy. VAS pain scores will be recorded weekly using BPI questionnaires and daily using the pain app from the day of enrollment, as outlined in study calendar. Treatment with study regimen, collection of PROMIS®, MDASI, CTCAE and other assessments like opioid drug use log, as outlined in the study calendar will start once the patient develops mucositis and has VAS ≥4/10 pain score on the OM Pain App and BPI questionnaire (question 3: your pain at its worst in last 24 hours). Patients usually develop mucositis by the third or fourth week of radiation therapy so we anticipate treatment would begin by fourth week in most patients, but it may start sooner if the patient develops mucositis and has VAS≥ 4/10 pain. If a patient presents with radiation-induced mucositis pain on the day of enrollment, then, all study procedures, including PROMIS®, MDASI-HN, and CTCAE will be completed that day. Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window of two days. Clinician follow-up will be scheduled weekly (1–7) and then on weeks 9 and 12.
2. If a subject is off the study drug regimen or the subject withdraws, then they will be followed as per follow-up requirements.
3. Serum chemistry values will include ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect) creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, glucose,. Serum chemistry results obtained from unscheduled visits should be entered into the electronic database. Additional serum

chemistry testing should be done as clinically indicated.

4. Record of opioid pain medications,laxatives, and antiemetic use from the patient's drug diary will be copied by investigators on weekly clinic visits. This will commence after starting treatment. a) Patients will document pain and supportive medication use data daily in their diariesbut that information will be verified and recorded by investigator/research coordinator during weekly clinic visits in the electronic medical record(EMR). This data is currently being collected in a section of pain app. Patients average weekly VAS pain scores (question 3 of BPI questionnaire) will also be documented in EMR during weekly clinic visits as per standard of care and can be used for study purposes.
5. The Oral Mucositis (OM) Pain App will be evaluated by the study team on a daily basis through a real-time pain assessment tool in the mobile app. Patients can start using the OM Pain App before starting therapy to familiarize themselves with the instrument. b) Pain app readings will be recorded up to four times/day. The daily pain data will be analyzed by the UWM research team on a weekly basis.
6. All questionnaires/forms can be recorded on weekly in-person visits from weeks 1–7 then completed weekly through in-person/ telephone interviews by CTO staff from week 8–12. Other assessments can also be done over phone during week 8, 10 and 11. Window period of +/-3 days will be allowed for data collection.
7. EKG will be done at screening and then on week 7 and 12 if the patient is on treatment with Buprenorphine patch.
8. Digital photos will be taken to document mucositis on the day of enrollment, treatment initiation, then during week 9 and week 12 clinic visits.

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BPI	Brief Pain Inventory
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CDK	cyclin-dependent kinases
CQ	chloroquine
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T cell
CTO	Clinical Trials Office
DFS	disease-free survival
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	data and safety monitoring plan
ER	estrogen receptor
FDA	Food and Drug Administration
GCP	good clinical practice
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HGB	hemoglobin
HNSCC	head and neck squamous cell carcinoma
IP	investigational product
IRB	Institutional Review Board
LDH	lactate dehydrogenase

MDASI-HN	MD Anderson Symptom Inventory - Head & Neck Cancer
MCWCC	Medical College of Wisconsin Cancer Center
MTD	maximum-tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	disease progression
PK	pharmacokinetics
PSGL-1	P-selectin glycoprotein ligand-1
PR	partial response
PROMIS	Patient-Reported Outcomes Measurement
RBC	red blood cell (count)
ROS	reactive oxygen species
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SRC	Scientific Review Committee
ULN	upper limit of normal
UP	unanticipated problem
UPIRSO	unanticipated problems involving risks to subjects or others
WHO	World Health Organization

TABLE OF CONTENTS

1 BACKGROUND

1.1 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the eighth most common cancer in the United States with more than 53,600 new cases diagnosed annually.(1) Early-stage or locally advanced head and neck cancer patients are typically treated by a multimodality approach including surgery, radiation and chemotherapy. Mucositis-related pain and dysphagia are two of the most common primary toxicities associated with head and neck radiation. Around 80–100% of head and neck cancer patients being treated with radiation therapy suffer from oral mucositis pain. Severe mucositis (WHO grades 3 and 4) occurs in 25% of patients when standard fractionated radiation (once-daily dose) is used as a single modality. The incidence of severe mucositis can be as high as 50%–75% when radiation is used in conjunction with concurrent radio-sensitizing chemotherapy. (2, 3)

1.2 Opioid Management of Mucositis-Related Pain

Mucositis is the most common and feared side effect for head and neck cancer patients undergoing definitive radiation or chemoradiation. It is commonly clinically evident by the third week of therapy, or after approximately 30 Gy of radiation has been delivered. It may develop earlier when concomitant chemotherapy is being given or if an altered fractionation schedule is used.(4) The vast majority of patients require treatment with strong pain relief medications like morphine, fentanyl, and oxycodone as they experience moderate-to-severe mucositis-related pain. Exposure to strong opioids during radiation therapy may sometimes lead to long-term opioid dependence and adverse effects.(5, 6) Opioid naïve patients are apprehensive about using this class of drugs because of fear of habit-forming properties and drug-related side effects. As a result, this causes reduced pain medication compliance and may also contribute to poor pain control.(7, 8)

1.3 Rationale for Using Buprenorphine and Tramadol to Manage Radiation-Induced Mucositis Pain

Buprenorphine is a potent pain medication with a more favorable side effect profile and lower habit-forming potential compared to other opioids.(9, 10) It is a derivative of the thebaine, which has mixed opioid agonistic activities (agonistic effect on μ opioid and the OR L1 receptors but the antagonistic effect on kappa and delta opioid receptors).(11) Transdermal buprenorphine, with its active polymeric matrix, is superior to some of the other long-acting opioids in terms of therapeutic efficacy and compliance. Unlike other opioids, it has a ceiling effect, which means its effects increase until the person takes a certain amount; then, these effects level off, which limits euphoria, confusion, and respiratory depression.(12) Earlier studies have shown that buprenorphine suppresses opioid withdrawal and craving, and reduces illicit opioid use.(13) Furthermore, it can safely be administered with no dose adjustments in patients suffering from chronic kidney disease or those who develop chemotherapy-related acute renal failure. This unique characteristic of buprenorphine makes it a good option for mucositis-related pain control in HNSCC patients being treated with commonly used cisplatin-based chemotherapy, which is often associated with acute kidney injury.(14) With appropriate education, patients may perceive buprenorphine to be less addictive than other opioids and its use may be more acceptable. As a result, this may contribute to better pain control and compliance during treatment. Tramadol is a short-acting, weak opioid, which works by both monoaminergic and opioid mechanisms and has

synergistic activity with other long-acting opioids.(15) It is associated with lower incidence of cardiorespiratory depression and reduced dependence compared to strong opioids.

It can be used to treat breakthrough pain in combination with long-acting TD buprenorphine. Furthermore, it has been safely used in combination with both fentanyl and buprenorphine patches in earlier studies to alleviate cancer related pain.(9, 16) European studies have shown that buprenorphine patches used at higher doses (>35 µg/hour) in combination with Tylenol® or tramadol for breakthrough pain can provide adequate analgesia in cancer patients and is associated with fewer adverse effects compared to other opioids.(9) However, there is a paucity of similar studies with FDA-approved doses (5 µg to 20 µg/hour) of buprenorphine patches in the United States. In fact, to our knowledge, there are no active or completed studies of FDA-approved doses of buprenorphine in the treatment of mucositis in head and neck cancer. The goal of this study is to show efficacy of using FDA-approved doses of buprenorphine patches with oral tramadol in providing adequate pain relief in patients suffering from moderate to severe radiation-induced mucositis pain. This is an innovative and timely study question as several head and neck cancer patients continue to suffer from opioid addiction and opioid-related toxicities.

1.4 Safety data on studies using this drug combination.

Multiple studies have utilized a combination of transdermal buprenorphine and oral tramadol for cancer-related pain.(17-19). In a study by Pace et al., a group of 52 cancer patients with chronic pain were randomized 1:1 between two groups. Twenty-six patients were treated with a titratable dose of TD buprenorphine (35 µg/hour) with oral tramadol (200 mg/day) for breakthrough pain and 26 patients were treated with 60 mg/day of oral morphine. Final analysis of this study revealed that buprenorphine-based regimen was more effective in providing pain relief and was better tolerated than oral morphine. The incidence and severity of side effects were significantly lower in the buprenorphine arm compared to the morphine arm. Overall, common side effects reported in the buprenorphine arm of 26 patients were vertigo (12%), drowsiness (12%), headache (12%), constipation (8%), confusion (4%), and nausea (12%). No serious adverse event was observed.(9) In another 40-patient study of cancer patients, oral tramadol was safely used in combination with TD buprenorphine. Side effects, including nausea, buprenorphine patch insertion site pruritus and erythema, constipation, and headache were observed but were for the most part self-limiting.(18) Overall, there is some evidence in the literature to prove the safety of buprenorphine and tramadol drug combination regimen in cancer patients. However, there are no large randomized trials with this combination. Details on the dose justification of the study drug regimen are included in Section 5.2.

1.5 Symptom and Functional Assessments

Several validated metrics are available to measure treatment-related symptoms. We plan to use some of these patient-reported outcome measures and symptom and functional assessment tools in our study. We also plan to use a novel smartphone-based pain app to evaluate and monitor radiation-induced mucositis pain.

1.5.1 MD Anderson Symptom Inventory

U.S. and European phase I through IV trials have used and validated the MD Anderson Symptom Inventory (MDASI). This tool can be used in clinical and research settings. The Visual Analog Scale (0–10) measures symptom severity and interference with daily activities.(20-22) The 13-core MDASI symptom items are based on an extensive evaluation related to cancer and cancer-

treatment symptoms. MDASI symptoms include pain, fatigue, and appetite changes that the head and neck cancer population typically experiences. Patients easily complete it as a self-report tool in five minutes. Alternatively, research staff may assist patients in completing it in the clinic or by telephone with an interactive voice response system.

The instrument was developed in a manner that allows individuals to add items relevant to specific cancers and cancer treatments to patient-completed modules. The head and neck module (MDASI-HN) (21) was created with focus group input. These groups comprised head and neck cancer patients; surgical, medical, dental, and radiation oncology specialists; and symptom researchers. This instrument includes 12 to 14 head- and neck-specific items, including at least five that do not appear in the Functional Assessment of Cancer Therapy for Patients with Head and Neck Cancer (FACT-HN) — another commonly used quality of life tool. The coefficient alpha, a measure primarily used as a means of describing the reliability of multiitem scales, is highly reliable with the MDASI-HN. It was validated in a cohort of more than 200 patients in multiple studies.(3, 23) It was validated in several languages. In our trial, we plan to use the MDASI-HN tool to study the impact of radiation-induced mucositis pain on head- and neck-related symptoms and physical activity.

1.5.2 Brief Pain Inventory

The Brief Pain Inventory (BPI) asks patients to rate their pain for the last week on a 0 to 10 scale at its “worst,” “least,” “average” and “now.” The scales are presented on a 10-cm line with each number equidistant from the next. Each scale is bounded by the words “no pain” at the 0 end and “pain as bad as you can imagine” at the other. Patients are also asked to rate how pain interferes with several quality of life domains, including activity, walking, mood, sleep, work and relations with others. These scales are bounded by “does not interfere” at the 0 end and “interferes completely” at the other. Patients also are asked to estimate pain relief related to their pain treatment (by percentage), to locate areas of pain on a human figure and to estimate pain cause (cancer disease, cancer treatment, or non-cancer). The patient can complete the BPI in approximately five minutes, and the assessment is available in 12 languages.

BPI validity and reliability issues have been examined in detail.(24) In clinical trials where pain reduction (or prevention) represents primary or secondary outcome measures, professionals frequently use the BPI due to its ease of translation and brief administration. As a pain assessment tool, it is the FDA standard. The typical standard deviation for the item “worst pain” in most cancer populations is 2.4. Therefore, the finding of a one-point difference in the “worst pain” item at different times or between two comparative groups is considered significant. We plan to use the Brief Pain Inventory to assess and quantify radiation-induced mucositis pain.

1.5.3 MDASI and BPI Limitations and Rationale for the Smartphone Pain App

While the above-mentioned pain assessment tools measure oral mucositis pain, they only provide pain severity snapshots. In a head and neck cancer clinical trial, mucositis pain questionnaires are typically administered only once or twice per week. Other pain assessment tools require the patient to rate pain by memory recall of pain severity, thereby introducing a variable prone to inaccuracy.(22) Patients with severe oral mucositis experience unrelenting pain. It is often characterized by wide fluctuations with pain peaks occurring with swallowing saliva, eating, talking, and with waning analgesic medication effects. The limitation of most pain assessment tools in failing to capture fluctuating pain is well recognized. Momentary self-reporting of chronic pain with an electronic diary has been shown to overcome this limitation without undue burden.

Pain questionnaires also fail to capture patterns of pain unique to the head and neck cancer population, such as pain related to the timing of radiation (early in the week versus later in the week versus weekend). Pain, occurring at night and interfering with sleep, is likewise not accounted for in typical pain surveys for mucositis.

The difficulty of measuring radiation-induced oral mucositis pain under optimal conditions of a clinical trial is put into perspective by pointing out that in the non-research setting oncologists do not routinely use any assessment tools for measuring mucositis pain. This may be in part due to the shortcomings of the available tools described above. More likely, however, it is due to logistical restrictions — the availability of trained personnel to administer surveys, time constraints of the doctors' office schedules and the difficulty of documenting paper surveys and integrating them into the electronic medical record. Instead, most commonly, patients simply are asked to verbally report an assessment of their pain, such as worst pain level or average level of pain. The head and neck cancer patient population is predisposed to specific problems that further limit the ability to assess pain, such as the ability to articulate and accurately describe pain, language and physical communication barriers, cultural influences, as well as fear of the appearance of drug-seeking or difficult behavior.

To address the difficulty of accurately monitoring patients' mucositis pain, we developed a new method for assessing radiation-induced oral mucositis pain by adopting widely available cell phone technology.

1.5.4 Oral Mucositis (OM) Pain App

Under the auspices of an existing protocol approved by the Medical College of Wisconsin Institutional Review Board (NCT02727062), we are planning to use the OM Pain App in our study. The OM Pain App is a smartphone application that was designed to permit patients to key in pain severity, using a visual analog 0–10 scale (VAS). The app is programed with an alarm to prompt the patient to record pain severity at prescribed intervals daily and through spontaneous patient input. Deidentified data collected on each patient's smartphone will be backed up wirelessly to cloud storage where the data can be analyzed remotely or viewed on the device. The software can generate a time-weighted measure of pain, total area under the pain curve (AUC), a summary measure that integrates serial assessments of a patient's pain over the duration of the study. The OM Pain App may be a significant improvement over the current standard of care, which is essentially nonexistent. The validated OM Pain App has the potential to significantly improve the management of pain in head and neck cancer patients. As noted, at the Medical College of Wisconsin, we developed an oral mucositis pain app (OM Pain App) and implemented a clinical trial (NCT02727062) to accurately assess pain requirements of head and neck cancer patients undergoing radiation. Preliminary data from 16 patients currently enrolled in the pain app study shows feasibility of using this application for real-time pain assessments. We are currently analyzing this data and hope to report these findings very soon. This app has potential applicability to other types of cancers in which treatment-associated pain is encountered.

1.5.5 Outcome Measure Tools to Identify Gastrointestinal, Cognitive Side Effects of the Study Regimen.

Radiation-induced mucositis pain treated with strong opioids often leads to gastrointestinal and cognitive side effects, which limit drug adherence and affect the quality of life of patients. A study by Pace et al. showed that buprenorphine is associated with lesser gastrointestinal side effects compared to other conventional opioids.(9) However, to our knowledge the gastrointestinal and

cognitive side effect profile of transdermal buprenorphine has not been studied extensively in patients being treated for mucositis pain in head and neck cancer patients. We plan to use a highly intuitive patient-reported outcome measurement information system tool called PROMIS® to assess the side effect profile of the study drug regimen. All scales of PROMIS® have been validated in cancer patients. PROMIS® is a set of person-centered outcome measures that evaluates and monitors physical, mental, and social health in adults and children. It is very sensitive, easy to use and available in multiple languages. Patients can also take assessments at home or through paper forms in clinic. Thus, there is less disruption to clinic flow with this methodology. We plan to use PROMIS® questionnaires to evaluate cognitive and gastrointestinal side effect profiles of the drug regimen and collect data to make appropriate and timely symptom-related interventions. Both PROMIS® GI and PROMIS® Cognition scores have been validated in multiple studies. (25, 26). We plan to use PROMIS® scores to evaluate the gastrointestinal and cognitive side effects of the study regimen and its impact on the quality of life of patients.

2. HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

We hypothesize that the use of long-acting transdermal buprenorphine (FDA-approved dose from 5 mcg to 20 mcg/week) in conjunction with oral tramadol (50 mg to 400 mg/day) as needed for breakthrough pain will lead to a significant reduction in mucositis-related pain in locally advanced head and neck cancer patients being treated with radiation therapy by the end of treatment and the follow-up period of nine weeks.

2.1 Primary Objectives

To investigate the efficacy of using FDA-approved doses of TD buprenorphine in combination with oral tramadol to provide adequate pain control in radiation-induced mucositis.

2.2 Secondary Objectives

1. Assess compliance of the study drug regimen.
2. Assess use of off-protocol pain medications during treatment and follow-up period.
3. Compare the average weekly pain scores calculated by the pain app with the average pain scores recorded on the BPI short form.
4. Correlate average weekly pain scores with physical activity as documented on symptom and functional assessment tools, such as the MDASI-HN.
5. Assess the use of nonopiod supportive care medications (i.e., laxatives, antiemetics, and oral anesthetics) in conjunction with the study drug combination during treatment and follow-up period.
6. Assess gastrointestinal and cognitive side effect profiles of the study drug combination and their impact on cognition and quality of life.
7. Evaluate safety of the study drug combination.

2.4 Primary Endpoint

Establish the efficacy of the study regimen by showing that at least 33% of the patients will achieve at least a 30 percent decrease in the VAS pain score on the BPI questionnaire (question 3: worst pain in last 24 hours) from baseline to the end of week 9 of treatment and the follow-up period. Earlier studies have shown that the VAS pain score(≥4/10) on the day of

treatment initiation may be used as the baseline in this setting and a 30% or higher reduction in the baseline pain score is a sign of a meaningful drug response.(27-29)

2.5 Secondary Endpoint(s)

1. Monitor compliance of the study drug regimen through the OM Pain App and medication diary.
2. Identify study participants who require off-protocol opioids for pain control despite being on the highest dose of the study drug combination.
3. Correlate the cumulative mean weekly pain scores calculated by the pain app with the average weekly pain scores recorded on the BPI short form.
4. Correlate the average weekly OM Pain App scores and average weekly pain scores calculated from BPI short form with head and neck symptom and functional evaluation tool MDASI-HN. The cumulative average area under the curve (AUC) weekly pain scores are expected to be inversely proportion to MDASI-HN average weekly AUC physical activity scores.
5. Maintain a weekly log of the use of other nonopiod medication, such as laxatives, antiemetics, and oral anesthetics in conjunction with the study drug combination during the treatment and follow-up period through weekly questionnaires. The average weekly use of laxatives and antiemetics is expected to decrease by the end of the follow-up period.
6. Assess the incidence and severity of gastrointestinal and cognitive side effects of the study drug regimen and their impact on the quality of life as measured by weekly PROMIS® (GI and cognition) questionnaires.
7. Safety: Assess incidence and severity of other adverse events associated with study drug combination, using the CTCAE version 5.

2.6 Rationale for Outcome Measures Selection

A. Primary objectives: We plan to use the average daily and weekly pain scores determined by the OM Pain App and the average weekly pain scores determined by the BPI short form to assess the efficacy of the study drug combination. Cancer and cancer therapy-related pain estimates vary widely and there is a lack of standardization of pain assessment tools in this area. Studies have shown that real-time assessment of patient-reported pain outcomes improves provider awareness and leads to better management of pain. Further, real-time assessment is very important for the head and neck cancer patient population as these patients are predisposed to specific problems, such as difficulty in articulating and accurately describing pain due to severe mucositis. These issues can be resolved with real-time assessment of pain by a smartphone-based application. To our knowledge, app-based pain assessment of buprenorphine has never been studied on head and neck cancer patients suffering from radiation-induced mucositis pain. Our goal will be to use the VAS-based pain assessment tools on the OM Pain App and BPI short form to evaluate the pain response of the buprenorphine and tramadol combination regimen.

Painful mucositis usually manifests by the third to fourth week of starting radiation and continues four to five weeks after the termination of therapy. Therefore, we decided to follow patients up to 12 weeks after they begin radiation therapy.(4, 17, 30) Mild-intensity mucositis pain can be effectively managed with low-potency pain medications like Tylenol®, NSAIDS, and oral lidocaine. Thus, we plan to initiate treatment with the tramadol

and buprenorphine combination once the patient develops mucositis and a VAS pain score $\geq$ 4/10. Earlier pain management studies in radiation-induced mucositis have acknowledged that the pain curve follows a nonlinear pattern during radiation therapy and starts to peak by the fourth to fifth week of radiation therapy. It then plateaus and later drops to a lower level after initiation of long-acting effective pain medications, such as fentanyl or oxycodone. Hence, it is reasonable to use the pain score on the day of treatment initiation as our baseline pain score. (27, 29, 31)

B. Secondary Objectives: Adherence to the prescribed dose and frequency of pain medications is vital to symptom management of radiation-induced mucositis pain. Poor adherence is often associated with worse symptom control and inaccurate assessment of the potency of pain medications. Greater clinical support and research are needed to overcome the challenges of fragmentation in care from clinic to home, with specific attention to adherence and symptom management. We plan to use our pain app to make accurate and real-time assessments of compliance and efficacy of the pain regimen. We will also assess the use of off-protocol pain medications during study period.

We plan to study the impact of radiation-induced mucositis pain on head- and neck-related symptoms and physical activity. This data will be further characterized and evaluated by the MDASI-HN symptom and function tool. Use of other medication like laxatives and antiemetics in conjunction with the study drug combination during treatment can be used as surrogate markers of gastrointestinal side effects associated with the drug regimen. We plan to record these values on a weekly basis and expect its use to decrease by the end of follow-up period. To study the gastrointestinal and cognitive side effect profile of transdermal buprenorphine and tramadol regimen, we plan to use a highly intuitive patient-reported outcome measurement information system tool called PROMIS®. All PROMIS® scales have been validated in cancer patients. We plan to use PROMIS® questionnaires to evaluate the cognitive and gastrointestinal side effect profile of the drug regimen and its impact on quality of life of patients. Incidence and severity of adverse events associated with the study drug regimen, such as constipation, sedation, respiratory depression, and others will also be evaluated, using the CTCAE version 5. We will collect this data to make appropriate and timely symptom-related interventions.

3 STUDY DESIGN

3.1 General Description

This is a single-arm, interventional, supportive care clinical trial for head and neck cancer patients evaluating the role of a TD buprenorphine and tramadol combination in alleviating radiation-induced mucositis pain. This will generate preliminary data to test the feasibility and efficacy of the study drug regimen. The study will also test the clinical usefulness of the smartphone pain app in recording and reporting radiation-induced mucositis pain. Additionally, it will also evaluate the role of symptom and function assessment tools, such as MDASI-HN and PROMIS® in identifying adverse effects related to the study regimen in the setting of chemoradiation therapy.

3.2 Study Procedures

Patients found to be eligible for the study can be screened and enrolled anytime during the first six weeks of radiation therapy. VAS pain scores will be recorded weekly using the BPI questionnaires. They will also be recorded daily, using the pain app from the day of enrollment as outlined in study calendar. Treatment with the study regimen, collection of data from the PROMIS®, MDASI, CTCAE evaluation, and other assessments, such as the opioid drug use log as outlined in study calendar will start once patient develops mucositis and has VAS >4/10 pain score on the OM Pain App and the BPI questionnaire (question 3: your pain at its worst in last 24 hours). Patients usually develop mucositis by the third to fourth week of radiation therapy so we anticipate treatment would begin by fourth week in most patients, but it can start sooner if the patient develops mucositis and has VAS≥4/10 pain. If a patient presents with radiation-induced mucositis pain on the day of enrollment, then, all study procedures, including administering the PROMIS® and MDASI-HN questionnaires, in addition to CTCAE evaluation, will be completed on that day. Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window of two days. Clinician follow-up will be scheduled weekly (weeks 1–7) and then on weeks 9 and 12. Data can also be collected over phone during the follow-up period (weeks 8–12 from the start of radiation therapy). If a subject stops radiation therapy within the first 7 weeks, weekly visits will continue as scheduled if he/she is on treatment.

3.3 Study Completion

The study is expected to complete its accrual goal in 12 months. The study will reach study completion approximately 18 months from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

Investigators must follow all MCW IRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering a patient for the trial per institutional recruitment methods).
- Screening: the period after the consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibility criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first-day treatment with study drug regimen while undergoing radiation
- Off treatment: last day of treatment with study drug regimen
- On follow-up: from the last day of treatment to the end of the follow-up period.
- Off study: follow-up period completed, with no additional data gathered.

- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off the study by the local principal investigator.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent but are not subsequently assigned to the study intervention or enrolled in the study. MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

A written signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Screening Procedures

Refer to the study calendar of events for details. Patients found to be eligible for the study will be screened and enrolled anytime during first six weeks of radiation therapy. EKG, lab, urine drug screen, medical history and other assessments as per study calendar will be collected on the day of enrollment. This day, patients will complete the BPI questionnaire and the OM Pain App will be installed on their cell phones. Those who do not have a smartphone will be provided with a wifi enabled device with OM Pain App installed on it. Going forward, BPI questionnaire will be completed during weekly clinic visits and daily OM Pain App data monitoring will continue throughout the rest of the treatment and follow up period of 12 weeks. Treatment with the study drug regimen will commence once the patient develops mucositis and has a VAS pain score ≥4/10 on the BPI and pain app. Additional data from PROMIS®, MDASI-HN, opioid and nonopiod drug use log, CTCAE evaluation, calorie requirements, the need for IV hydration, and other assessments will also be recorded as per study calendar.

Based on earlier studies and our clinical practice, we anticipate that most patients will develop moderate intensity pain and require an opioid-based pain regimen by the third to fourth week of radiation therapy.(4, 30) As we will be using the pain score on the day of treatment initiation and not the date of enrollment as our baseline, we don't expect that timing of initiation of drug regimen would have a significant impact on our results.

4.5 Registration Process

Recruitment

Potential study participants will be identified by routine care in the MCW Cancer Center clinics.

Subjects will sign the informed consent form in the cancer center clinics. A team approach will be used whereby physician sub-investigators will discuss and describe the clinical trial with study candidates. The study coordinator will obtain the informed consent from participants and perform study registration. For women of childbearing potential, a negative pregnancy test must be obtained within 24 hours prior to starting radiation therapy. Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window of two days.

4.6 Study Procedures: On the Day of Enrollment

Screening Assessments

- Record WHO mucositis grade.
- Brief Pain Inventory.
- ECOG/Zubrod Performance Status.
- Oral cavity digital image collection to evaluate mucositis will be done on the day of enrollment, treatment initiation, end of week 9 and then week 12.
- Physical examination (demonstrating no pre-existing mucositis).
- Record mucositis due to other causes (oral candidiasis, infections, trauma, etc.).
- OM pain data monitoring (VAS included in pain app).
- Review bloodwork, including CBC and CMP during clinic visits.
- Record type of calorie intake (normal, liquid, soft, parental/enteral).
- Report use of IV fluids for hydration.
- EKG.
- Urine drug screen.
- Pregnancy test for women of childbearing age.

4.7 Training for the Intervention

Study investigators and/or study coordinator will train subjects for use of devices (OM Pain App) and study procedures during treatment.

Study procedures as per study calendar will continue until treatment with the study drug regimen is started.

4.8 Study Procedures: After starting study drug regimen(Weeks 1–7)

These procedures must be completed weekly during the study. These will be recorded once the patient starts the drug regimen when radiation-induced mucositis pain VAS is greater than 4/10 on the BPI and pain app. The following procedures, such as MDASI and PROMIS® questionnaire administration, and adverse event evaluation, using CTCAE, will also be completed if the patient presents with radiation-induced mucositis pain (VAS≥4/10) on the day of enrollment.

- Record WHO mucositis grade.
- Brief Pain Inventory.
- ECOG/Zubrod Performance status.

- MD Anderson Symptom Inventory.
- PROMIS® cognition and GI questionnaires.
- Oral cavity digital image collection to evaluate mucositis will be done on the day of treatment initiation, the end of week 9, and then week 12.
- Record mucositis due to other causes (oral candidiasis, infections, trauma, etc.).
- Record adverse events, using CTCAE v.5.0.
- Record type of calorie intake (normal, liquid, soft, parental/enteral).
- Report use of IV fluids for hydration.
- OM Pain App data monitoring (VAS included in pain app).
- Review OM Pain App device usage and proper reporting.
- Review opioid log and record use of oral anesthetics, laxatives, and antiemetics at home. This data is currently being collected in a section of pain app. Patients average weekly VAS pain scores (question 3 of BPI questionnaire) because of radiation induced mucositis will also be documented in EMR during weekly clinic visits as per standard of care.

- Monitor opioid usage through WIPDMP,
- Review bloodwork, including CBC and CMP.
- EKG will be performed at screening, week 7 and 12 for patients on buprenorphine patch

If a subject stops radiation therapy prior to week 7, visits will remain on the same schedule, Subjects will need to come in for a weekly visit(s).

4.9 Study Procedures: Follow-up Period (Week 8–12 from start of radiation therapy)

End-of-Treatment Procedures

To be completed by the CRC between week 8 to week 12. Refer to the study calendar for details.

- Record WHO mucositis grade.
- Brief Pain Inventory.
- ECOG/Zubrod Performance status.
- Evaluate and record potential other causes of mucositis (oral candidiasis, aphthous ulcer, infections, trauma, etc.).
- PROMIS® GI and cognition questionnaires recorded over phone or in person weekly.
- MD Anderson Symptom Inventory recorded over the phone or in person weekly.
- Oral cavity digital image collection to evaluate mucositis will be done on the day of treatment initiation, the end of week 9, and then week 12.
- Physical examination (demonstrating no pre-existing mucositis).

- Record adverse events, using CTCAE v.5.0.
- Record type of calorie intake (normal, liquid, soft, parental/enteral).
- Report IV fluids for hydration.
- Review OM Pain App device usage and proper reporting.
- OM pain data monitoring (VAS included in pain app). Data from week 9 will be used for primary endpoint analysis.
- Review bloodwork, including CBC and CMP.
- Review opioid log and record use of oral anesthetics, laxatives, and antiemetics at home. This data is currently being collected in a section of pain app. Patients average weekly VAS pain scores (question 3 of BPI questionnaire) because of radiation induced mucositis will also be documented in EMR during weekly clinic visits as per standard of care.
- Monitor opioid usage through WIPDMP.
- EKG will be performed at screening, week 7 and 12 for patients on buprenorphine patch

4.10 Eligibility Confirmation

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the MCW PI can only provide guidance or clarification on eligibility. Any eligibility questions should be directed to Dr. Wong at swong@mcw.edu.

Study Population Locally advanced (stage I to IV) head and neck cancer patients being treated with either definitive or adjuvant radiation with or without chemotherapy who fulfill all eligibility criteria will be enrolled in this study. Patients deemed eligible for the study will be screened and enrolled in the study; treatment with study regimen will start once mucositis-related pain measured by VAS ≥4/10 anytime during first six weeks of radiation therapy.

Inclusion Criteria

1. Age > 18 years.
2. Histologically confirmed malignancies of Head and Neck Stage I-IV by American Joint committee on cancer (AJCC) staging criteria 8th edition involving(oral cavity, oropharynx, nasal or paranasal sinuses, hypopharynx and larynx etc.) including both squamous and non-squamous cell histology's (salivary gland carcinomas and carcinomas of unknown primary will be included)
3. Undergoing a course of either definitive radiation (dose of at least 50 Gy to the head and neck region) with or without chemotherapy or adjuvant radiation (at least 50 Gy to the head and neck region) with or without chemotherapy. (Patients with a history of prior definitive course of radiation will be allowed).
4. ECOG Performance status ≤ 2.
5. Concurrent enrollment on interventional trial is allowed.
6. English speaking and literate.
7. Patients will be allowed to take radiotherapy mix, viscous lidocaine or magic mouthwash-like agents that do not contain opioids. Tylenol® is allowed for fever or mild pain before starting drug regimen. It can be used for fever anytime during the study. Use of Tylenol for non-radiation mucositis related pain may be allowed in rare circumstances at investigators discretion.
8. Adequate organ function: Minor dose adjustments for tramadol are required in severe liver and renal impairment so we would only include patients with adequate organ function outlined in the table below. No dose adjustment for renal or hepatic impairment is required for TD buprenorphine. Some other parameters like hemoglobin, platelets and WBC are required for administration of standard of care chemotherapy like cisplatin along with radiation in treatment of HNSCC. They are not required for administration of buprenorphine or tramadol.

Organ Function Table	
Adequate hepatic function:	
total bilirubin	< 2 mg/dL
AST(SGOT)/ALT	< 5 times institutional upper limit
Adequate renal function:	

Organ Function Table	
creatinine clearance	> 30 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

9. Pregnancy: It is known that standard-of-care treatments of HNSCC radiation therapy and chemotherapy have detrimental effects on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.
   Female patients must meet one of the following:
   - Postmenopausal for at least one year before the screening visit, or
   - Surgically sterile, or
   - If they are of childbearing potential, agree to practice two effective methods of contraception from the time of signing of the informed consent form through three months after the last dose of study drug, AND
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or
   - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable contraception methods.)

   Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
   - Practice effective barrier contraception during the entire study treatment period and through 90 days after the last study drug dose, OR
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
   - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)
10. Ability to understand a written informed consent document, and the willingness to sign it.
11. Ability to operate and key in information on OM Pain App (a smartphone application).

Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Physical exam demonstrating pre-existing mucositis from prior radiotherapy treatments or other causes.
2. Pre-existing oral infection or ongoing toxicity from prior radiotherapy.
3. History of opioid abuse disorder, confirmed by medial history or subject disclosure. positive urine drug screen at screening visit. Exceptions will be made for subjects with current prescriptions post-surgery or other medical intervention.

4. Patients with multiple distant metastasis (patients with resectable oligometastasis will be allowed).
5. Current or recent use of short acting mixed opioid agonists/antagonists or other opioid antagonists. (Treatment with more than 2 doses of short acting oral or intravenous opioids like Oxycodone, morphine or hydromorphone within 24 hours of screening). Patients on treatment with long-acting opioids like fentanyl patch, methadone, oxycodone extended release, morphine extended release within 72 hours of screening would be excluded.
6. Prolonged QTc greater than 450 milliseconds in males and greater than 470 milliseconds in females at the time of enrollment
7. Patients on systemic therapy (chemotherapy or immunotherapy) for another cancer subtype.
8. Patients receiving induction chemotherapy prior to or after radiation/chemoradiation, such as patients with nasopharyngeal carcinoma.
9. Patients with a history of abdominal surgery within 60 days of registration, acute gastrointestinal conditions like colitis and appendicitis within four weeks of screening.
10. Patients with conditions that may compromise the blood-brain barrier permeability. The blood-brain barrier may become leaky in select neurological diseases, such as amyotrophic lateral sclerosis, epilepsy, brain trauma, and edema.
11. Patients presenting with any other cause of pain not related to radiation-induced mucositis or head and neck cancer, VAS >4/10 on BPI questionnaire (question 3: worst pain in last 24 hours) on the day of enrollment requiring opioid medications for pain control
12. Patients with a history of myocardial infarction ≤ 6 months prior to registration.
13. Patients with a history of significant respiratory depression; acute or severe bronchial asthma; known or suspected gastrointestinal obstruction, including paralytic ileus.
14. History of serious or severe hypersensitivity reaction to buprenorphine, tramadol or any of its excipients.
15. Use of the following drugs will not be permitted after initiation of study drug regimen: capsaicin, NSAIDS, tetrahydrocannabinol, and cannabinoids. Refer to Section 7 for details on contraindication of drug regimen. Patients will be allowed to participate in the study if they have been using antidepressants like SSRI'S, other antipsychotics and antiseizure medications for at least 4 weeks prior to enrollment on the study. Chronic use of these agents will not affect our primary endpoint of assessing impact of study regimen of Buprenorphine and Tramadol on alleviating acute radiation induced mucositis pain. As per package insert of buprenorphine and tramadol concomitant use of the above-mentioned agents with study pain regimen is not contraindicated. However, clinicians are advised to exercise caution as there have been some rare incidences of serotonin release syndrome (SRS) with concurrent administration of SSRI's and Tramadol. Buprenorphine is also not contraindicated but should be used with caution in patients with h/o seizure disorders. Study regimen can be stopped if SRS or any other adverse event occurs as a consequence of this combination. Periodic EKG's will also be performed to monitor for QTc prolongation.
16. Pregnant and lactating women are excluded from this study because chemotherapy and radiation given for the treatment of HNSCC have a potential for teratogenic or abortifacient effects. Additionally, buprenorphine is classified as category C for use during pregnancy, which means that the risk of adverse effects on the fetus cannot be ruled out. Buprenorphine does cross the placenta, and the use of opioids during pregnancy may result in neonatal withdrawals soon after birth. Symptoms of this may include irritability, apnea, increased tone, tremor, convulsions, or respiratory depression

in the neonate. The onset of withdrawal in a neonate whose mother has taken buprenorphine during the pregnancy could be anywhere from the first day of life to the eighth day of life.

17. Patients with history of seizure disorder as oral tramadol may reduce seizure threshold.
18. Patient with history of opioid use disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition describes opioid use disorder as a problematic pattern of opioid use leading to problems or distress, with at least two of the following occurring within a 12-month period: 1.Taking larger amounts or taking drugs over a longer period than intended. 2. Persistent desire or unsuccessful efforts to cut down or control opioid use. 3. Spending a great deal of time obtaining or using the opioid or recovering from its effects. 4. Craving, or a strong desire or urge to use opioids 5. Problems fulfilling obligations at work, school or home. 6. Continued opioid use despite having recurring social or interpersonal problems. 7. Giving up or reducing activities because of opioid use Using opioids in physically hazardous situations. 8.Continued opioid use despite ongoing physical or psychological problem likely to have been caused or worsened by opioids.9Tolerance (i.e., need for increased amounts or diminished effect with continued use of the same amount) 10. Experiencing withdrawal (opioid withdrawal syndrome) or taking opioids (or a closely related substance) to relieve or avoid withdrawal symptoms.

"I have reviewed all inclusion/exclusion criteria and confirm the subject is eligible."	
CRC Name and Initials	**Date**
Enrolling Investigator Name (print)	
Enrolling Investigator Signature	**Date**

4.11 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. The subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol, and AEs/SAEs will continue to be reported according to this protocol.

In the absence of treatment delays due to adverse events, study treatment/intervention may continue until:

- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- An inter-current illness that prevents further treatment administration.
- The subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
- The clinical need for concomitant therapy that is not permitted in the study.
- Subjects who sign the informed consent form, enroll, and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow their IRB of record's SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal, with no study follow-up.
- Selective consent withdrawal from the interventional portion of the study but agree to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance, or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.12 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered, **AND**
    - A letter (Appendix 2) to the participant's last known mailing address goes unanswered, **AND**
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore® (Follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the study team, the subject should be considered in follow-up again.

4.13 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® tracks accrual throughout the study.
- If the study must be suspended, OnCore® is updated to "suspended" status.
- When the accrual number is reached, OnCore® notifies staff of study closure.

4.14 End-of-Study Definition

A participant is considered to have completed the study if he or she completed all phases of the study, including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

4.15 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study PI, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the investigational new drug (IND) sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB), and the sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 TREATMENT PLAN

5.1 Study Intervention

The main objective of this study is to provide preliminary evidence that the FDA-approved dose of transdermal buprenorphine in conjunction with oral tramadol can provide adequate analgesia of radiation-induced mucositis pain during treatment and the follow-up period in head and neck

cancer patients. There is no clear consensus definition of adequate pain relief in this setting. For the purpose of our trial, we have defined adequate analgesia as VAS ≤ 3/10 for 72 hours. Inadequate analgesia is defined as VAS>3/10 for 72 hours and unbearable pain as VAS>3/10 for 96 hours based on some prior studies and titratability requirements of a TD buprenorphine dose. (16, 17). Patients found to be eligible for the study can be screened and enrolled anytime during first six weeks of radiation therapy. Pain app data monitoring, BPI, base line labs, and medical history as outlined in study calendar will be collected on the day of enrollment. Treatment with study regimen, collection of PROMIS®, MDASI, and other assessment data, as outlined in the study calendar will start once the patient develops mucositis and has a VAS ≥4/10 pain score on the OM Pain App and BPI questionnaire (question 3: your pain at its worst in last 24 hours). Patients usually develop mucositis by the third to fourth of radiation therapy. Therefore, we anticipate treatment would begin by the fourth week in most patients, but it can start sooner if the patient develops mucositis and has VAS≥4/10 pain. If a patient presents with radiation-induced mucositis pain on the day of enrollment, then all study procedures, including administration of the PROMIS® and MDASI will be completed that day.

The OM Pain App will be installed on their smartphone. Subjects who do not have a smartphone will be provided with a wifi-enabled device with a pre-installed OM Pain App. Treatment with the study regimen will commence once at least grade 1 radiation-related mucositis is observed and mucositis-related pain measured by the visual analog scale (VAS) on BPI questionnaire ≥ (4/10) anytime during radiation therapy. Pain scores will be evaluated according to the visual analog scale (VAS), with 0 indicating no pain, 10 indicating the worst pain, 1–3 indicating mild pain, 4–6 indicating moderate pain, and scores ≥7 indicating severe pain. Investigators in earlier studies on radiation-induced mucositis pain have used Tylenol®, NSAIDS, and viscous lidocaine to manage mild pain and initiated long-acting pain medications like buprenorphine and fentanyl patch to treat moderate to severe pain. For the study purposes, we decided to start the treatment regimen once radiation mucositis pain > 4/10 VAS pain score on the BPI and pain app. The study drug combination, including transdermal buprenorphine 5 mcg to 20 mcg/week with oral tramadol 50 mg to 400 mg/day as needed for breakthrough pain (details in Table 2), will be provided to the study population. Drug will be dispensed by investigators after verifying opioid use information on WIPDMP. Radiation-induced mucositis begins to heal approximately two weeks after the last dose of stomatotoxic chemotherapy or radiation therapy.(30, 32) We will assess a percentage decrease in pain score by the end of week 9 of treatment to show a drug response. This way, we will try to avoid any bias of the normal healing process on pain alleviation. Based on our clinical practice experience and earlier studies, most HN patients will continue to have moderate to severe mucositis pain until 12 weeks of the follow-up period. Thus, we decided to monitor these patients for 12 weeks in our study.(32) Moreover, it would be easier to focus on the side effect profile of the study drug combination after completion of radiation therapy, as both chemotherapy and radiation may confound adverse event assessment of study drug regimen.

We will quantify and evaluate mucositis-related pain through the serial VAS-based pain app and BPI short form during a 12-week period (including first seven weeks of radiation and five weeks of the follow-up period). Real-time pain assessments will be done through the OM Pain App. The pain app will record pain readings up to four times daily. Pain scores will also be recorded through BPI short form questionnaires. The clinical research coordinator or investigator will also record symptom severity and functional assessments through the MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) questionnaires. PROMIS® gastrointestinal and cognitive questionnaires will be used to evaluate gastrointestinal and cognitive side effects of the study regimen. These assessments will be completed during weekly clinic visits as per study calendar.

Study assessments can also be completed virtually through a video/telephone visit during the post-treatment follow-up period (weeks 8–12). Dose titration of pain medications as per study protocol will be made over the telephone by investigators or sub-investigators. Patients will leave a MyChart message on EPIC (electronic medical record) if their pain remains uncontrolled on the prescribed dose of pain medications. These changes will be documented as a telephone encounter in the patient's EMR.

We expect that adequate pain control will be achieved with a titratable dose of the (buprenorphine and tramadol) study regimen throughout the treatment and follow-up period of 12 weeks, using the above-mentioned pain assessment tools. We are planning to use a smartphone application (oral mucositis pain app) designed to permit patients to key in pain severity, using a visual analog 0–10 scale in a real-time setting. Deidentified data collected on each patient's smartphone will be backed up wirelessly to secure cloud storage where the data can be analyzed remotely. The software can generate a time-weighted measure of pain, total area under the pain curve (AUC). It also monitors drug compliance and use of rescue pain medications. Head and neck cancer patients being treated with radiation with or without chemotherapy endure maximum radiation-related toxicities during first seven weeks of treatment. During this period, the pain curve often follows an unpredictable nonlinear pattern; hence, it is difficult to predict peaks and troughs of the pain curve of an individual during radiation. We will study the radiation-induced mucositis pain curve patterns during the therapy and follow-up period. We hypothesize that at least 33% of patients being treated with the drug regimen will have a 30% decrease from the highest baseline mean weekly AUC pain score by end of week 9. Earlier studies have shown that a 30% drop in mean AUC pain score from baseline value was significant and suggestive of drug efficacy.(28, 33).

As noted earlier, radiation-induced mucositis begins to heal approximately two weeks after the last dose of stomatotoxic chemotherapy or radiation therapy.(30, 32) Hence, we will assess a percentage drop in pain score by the end of week 9 of treatment to show a drug response. This way we will be able to avoid any bias of the normal healing process on pain alleviation. Studies have also shown that painful mucositis continues four to five weeks after the termination of radiation therapy. Thus, we plan to continue the study drug regimen up to 12 weeks. (17) (32) Recording of data will cease after 12 weeks, at which time mucositis-related pain symptoms substantially abate in many individuals. Details on buprenorphine and tramadol dose determination and titration are included in Section 5.2 of this protocol. Post-marketing data of buprenorphine, other opioid studies, and clinical experience have shown that around 20 percent of the patients receiving transdermal buprenorphine may have inadequate pain control and require rescue off-protocol pain medications despite being on the highest titratable dose of buprenorphine. Therefore, we have allowed the use of oxycodone in situations where pain is uncontrolled on highest titratable doses of the drug regimen and plan to monitor the use off-protocol pain oxycodone in our study.(17, 34)

Details for the use and logistics of the OM Pain App, as well as the measure of the patient's compliance to the use of the pain app are detailed below. This study will not interfere with or cause adjustments to the standard-of-care treatments each patient will receive as determined by their multidisciplinary team of cancer doctors. To this end, basic treatment descriptions and standards are briefly described as a reference to ensure proper patient selection and to verify that patients observed on the trial will be somewhat homogeneous from a treatment perspective. A short description of possible supportive treatments that could be needed during treatment is also included. All study interventions and treatments will be administered on an outpatient basis.

5.2 Dose Determination for Buprenorphine and Tramadol

Based on our clinical experience and earlier studies barring exceptions, the typical MEDD dose of standard-of-care regimens, such as oxycodone, morphine and fentanyl patch used in the treatment of radiation-induced mucositis can range from 20 to 90 mg. Buprenorphine is a potent opioid substitute but there is no consensus at equipotency ratio for morphine to transdermal buprenorphine. Some authors have reported that it lies somewhere between 75:1 to 100:1.(34) This makes finding the appropriate morphine equivalent daily dose (MEDD) for buprenorphine in controlling mucositis-related pain a challenging task. For our study, we used 75:1 equipotency ratio to calculate our morphine equivalent daily dose (**Table 1**). As transdermal buprenorphine is a long-acting medication, we plan to allow tramadol 50 mg (total daily dose) as needed for breakthrough pain up to 400 mg/day (total daily dose), which roughly translates to 5 mg to 40 mg MEDD. Steady-state plasma buprenorphine concentration levels are achieved by day 3, during the first application of buprenorphine. Therefore, it can be titrated after a minimum of 72 hours. We hope to evaluate the possibility of using tramadol to facilitate dose adjustment of buprenorphine. With the buprenorphine and tramadol combination, we hope to provide MEDD to patients which is comparable to other standard-of-care opioids. There is no clear consensus definition of adequate and inadequate pain relief in this setting. However, it is well known that a VAS pain score of ≤ 3/10 is considered mild intensity pain in multiple settings. Based on some earlier studies and the titratability of TD buprenorphine dose, we have defined adequate analgesia as VAS ≤ 3/10 for 72 hours, inadequate analgesia as VAS>3/10 for 72 hours, and unbearable pain as VAS>3/10 for 96 hours.(16, 17) If patients have unbearable pain (VAS > 3/10 x 96 hours) despite being on highest dose of the buprenorphine patch and tramadol, then, we will switch from tramadol to oxycodone for breakthrough pain and continue treatment with buprenorphine. We will titrate this combination as needed for pain control until study completion. Some authors have also shown the benefit and safety of using immediate-release oxycodone in conjunction with transdermal buprenorphine for moderate to severe pain.(35) If the pain is still uncontrolled >3/10 for 72 hours, even after using oxycodone 90 mg/day with buprenorphine 20 µg/hour, then, the patient will be taken off the study regimen. However, data monitoring will continue. Patients suffering intolerable side effects (severe constipation, vomiting, headache, pruritis, sedation, or respiratory depression, etc.) or those who wish to switch to standard-of-care oxycodone due to ineffective pain control or unclear reasons at any time during the study will be taken off study regimen. However, data monitoring through the pain app and questionnaires will continue. The dose titration schedule is illustrated in **Table 2**.

5.3 Morphine Daily Dose Equivalent of TD Buprenorphine

Table 1:

Buprenorphine patch	Morphine equivalent daily dose
5 mcg/hr	9 mg
10 mcg/hr	18 mg
15 mcg/hr	27 mg
20 mcg/hr	36 mg

5.4 Drug Regimen Titration Schedule

Table 2 Drug Titration Schedule

Drug: Buprenorphine with tramadol for breakthrough pain (**First seven weeks of study) T = 0–7 weeks**;

Start TD buprenorphine 5 µg/hour along with oral tramadol 50 mg to 150 mg (total dose over 24 hours) as needed for breakthrough pain when mucositis related pain is ≥4/10 on VAS measured on OM Pain App and BPI. Further dose adjustments will be made through pain app.

- If VAS is >3/10 for 72 hours on tramadol 150 mg (total dose over 24 hours) and buprenorphine 5 µg/hour, then, increase tramadol to 250 mg (total dose over 24 hours).
- If VAS is >3/10 for 72 hours, even with tramadol 250 mg (total dose over 24 hours) and buprenorphine 5 µg/hour, then, increase dose of buprenorphine to 10 µg/hour.
- If the pain persists VAS>3/10 for 72 hours on tramadol 250 mg (total dose over 24 hours) and 10 µg/hour, then, increase the dose of tramadol to 350 mg (total dose over 24 hours).
- If VAS pain is >3/10 x 72 hours with both tramadol 350 mg (total dose over 24 hours) and buprenorphine 10 µg/hour, then, increase dose of buprenorphine to 15 µg/hour.
- If VAS pain >3/10 x 72 hours on tramadol 350 mg (total dose over 24 hours) and 15 µg/hour of buprenorphine, then, increase the dose of tramadol to 400 mg (total dose over 24 hours) and buprenorphine to 20 µg/hour.
- If the pain persists and is unbearable at >3/10 for 96 hours, despite being on highest dose of both drugs, then, replace tramadol with oxycodone at the clinician's discretion up to 90 mg (total dose over 24-hour period) for pain relief.
- If VAS is ≤3/10 maintained for 72 hours, then, we can start tapering off total daily tramadol dose by 50 mg every day, but not change the buprenorphine dose during the first seven weeks of treatment, as mucosal injury from ongoing radiation may increase pain later.

(Post-radiation period) T = 8–12 weeks: if necessary, increase dose of buprenorphine up to 20 mcg along with tramadol up to 400 mg/day as per titration schedule used in the first seven weeks until VAS is ≤3/10. If pain is well controlled (VAS ≤3/10 x 72 hours), start weekly tapering of buprenorphine by 5 mcg and tramadol by 50 mg daily.

Special Circumstances

If pain is uncontrolled with VAS >3/10 x 72 hours on 90 mg oxycodone (total dose over 24-hour period) and 20 µg/hour of buprenorphine, then, buprenorphine patch can be taken off and other stronger pain medications can be started at clinician's discretion. If the patient is admitted and requires IV pain medication for pain control, then, the study drug regimen will be held, and data monitoring will stop for that time. The patient can be discharged on the study regimen (tramadol and buprenorphine) or a combination of oxycodone and buprenorphine patch or any other combination at clinician's discretion, and data monitoring will resume.

5.5 Availability

Both tramadol and buprenorphine are FDA approved and commercially available

5.6 Usage of Concurrent/Concomitant Medications

Use of all the medications mentioned below are allowed

- Antidiarrheal like loperamide and Lomotil (atropine and diphenoxylate).
- Antiemetics like prochlorperazine, steroids or serotonin antagonists may be used if clinically indicated.
- Antihistamines.
- Topical steroid creams.
- Anticoagulants.
- Viscous lidocaine.
- NSAIDS before starting study regimen.
- Tylenol® before starting study drug regimen or any time for fever.

CYP3A4 inhibitors and inducers: Buprenorphine is mainly a substrate of CYP3A4, and the manufacturers and others advise caution in its concurrent use with CYP3A4 inhibitors (e.g., cimetidine, clarithromycin, erythromycin, itraconazole, ketoconazole, protease inhibitors), because it may cause decreased clearance of buprenorphine, which could lead to an increase in buprenorphine plasma concentrations and result in increased or prolonged opioid effects. If coadministration with TD buprenorphine is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved. Similarly, CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) could reduce buprenorphine levels. These agents should be avoided during treatment with study regimen. If coadministration or discontinuation of a CYP3A4 inducer with TD buprenorphine is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.

Anticholinergics: Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation. Monitor patients for signs of urinary retention or reduced gastric motility when TD buprenorphine is used concurrently with anticholinergic drugs.

5.7 Prohibited Medications

Alcohol, and use of other opioids, such as fentanyl or morphine or hydromorphone will not be allowed with study drug regimen. CNS depressants, such as benzodiazepines, antidepressants, antipsychotics should be used with caution as concurrent use of these agents with any opioids including buprenorphine can increase the risk of respiratory depression, profound sedation and in rare cases even coma and death.

5.8 Monitoring Subject Compliance

Study drug can be dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt through WIPDMP website.

5.9 OM Pain App

5.9.1 Device Description/Overview

The Oral Mucositis (OM) Pain App is a smartphone application that was designed to permit patients to key in pain severity using a visual analog 0–10 scale. The app is programed with an alarm to prompt the patient to record pain severity at prescribed intervals daily and through spontaneous patient input. Time intervals for prompted pain queries can be customized, when, for instance, patients work a night shift or have specific sleep/wake cycle preferences.

Deidentified data collected on each patient's smartphone will be transferred wirelessly to cloud storage. Data transmitted wirelessly will use HTTP secure (HTTPS) sessions and JSON/XML protocols, such as the security used in online banking. Security measures and only deidentified data will be transmitted. Study participants will be encouraged not to update the smartphone operating system during the conduct of the study. Study PIs and/or study coordinator will perform OM Pain App software updates on smartphones.

Analysis of data collected from smartphones will be performed from cloud-stored data on deidentified sources only. This would be done in collaboration with our co-investigators at University of Wisconsin Milwaukee (UWM). The raw pain scores will be used to generate a time-weighted measure of pain called total area under the pain curve (AUC). Average weekly pain scores will also be calculated. This is a summary measure that integrates serial assessments of a patient's pain over the duration of the study. Architecture of the pain app is illustrated in figures 1 and 2.

5.9.2 Device Distribution to Subjects

The OM Pain App will be installed on the smartphone of each participant. If during the conduct of the study, a smartphone is lost, stolen, or broken, the subject will not be responsible for the cost of the device.

The study is designed for Android platform. However, an iOS app will be developed for the iPhone and will also be tested during this project. See figures 1 and 2 for further illustration and description of architecture, framework, and IT network for mobile platforms.

Deidentified data will be transmitted by wifi to a cloud storage server. Patients who do not have a smartphone will be issued a device with the OM Pain App installed on it at the initiation of their participation in the study. These phones will not have an active cellular phone service; but will have active wifi. Syncing of data from the phone will occur by hardwire connection (during initial testing) or by wifi (later during software testing). The device will be collected from participants at the end of the study period.

5.9.3 Daily Intervention

If enrolled, patients can start using the app up to one week prior to radiation therapy for training and practice. Formal data monitoring would only start once patients start study drug regimen. As noted,subjects will receive a preprogrammed alarm four times a day from their smartphones prompting them to directly enter OM pain levels on the device. Patients may submit as many pain entries as they wish beyond the four minimum levels. The software also allows patients to document self-administration of breakthrough pain medication. This event will prompt immediate entry of a pain level and an automatic pain assessment one-half hour later. Because symptoms of mucositis do not commence typically until the third week of radiation therapy, and no sooner than week 2, we don't expect to start data recording earlier than that. Recording of data will cease five weeks (week 12) after the end of radiation therapy at which time mucositis symptoms typically start to resolve and pain symptoms substantially abate (see the schema).

5.9.4 Avoiding Bias: A viewable graphic summary of pain scores will be a functionality of the app but will be disabled in this study to avoid bias of care provider or participant. For the feasibility phase, patients and providers will be blinded to the pain scores and symptoms will be managed with supportive treatments during routine weekly provider visits and symptom-initiated clinical visits.

5.9.5 Monitoring Compliance: The study coordinator will download data and check the equipment weekly for proper functioning and compliance. Patients will be interviewed weekly to assure the device is functioning correctly and that data are being recorded. Compliance with the device use will be assessed by the percent adherence to the device prompted four times daily pain assessment.

Architecture, Framework, and IT Network for Mobile Platforms

Figure 1 Shows the architecture for the proposed iPhone/Android Apps. To ensure data security and confidentiality, web registration was implemented in the Apps for the web server to generate a unique device ID for the purpose of secure information exchange. The Apps will incorporate an intuitive user interface for recording pain severities in order for the patients to engage in the reporting activities. The reported pain data will be uploaded to a secure web server via secure Hypertext Transfer Protocol (HTTPS) to allow for monitoring by the health professionals.

Figure 1.

Figure 2 Shows the general framework for the proposed mobile platforms. The internet-based computing platform consisting of web services, web servers, and database servers will provide web interfaces for professionals and patients as well to monitor the history reports of pain severities.

Figure 2.

Experimental setup: Our web and data servers will run Windows Server 2008 R2, The Apache HTTP Server, the MySQL Database and the PHP Hypertext Preprocessor (PHP). We will use the Google Android and Apple iPhone platforms running on popular devices such as Apple iPhone, Samsung Galaxy and Motorola Moto X. These cover the majority of app-driven cell phones.

5.10 Patient-Reported Outcomes Measurement Information System (PROMIS®)

To study the side effect profile of patients treated with transdermal buprenorphine and tramadol, we will use (PROMIS®) questionnaires. We will use PROMIS® cognition and gastrointestinal side effect assessment questionnaires for our secondary outcome analysis. For example, PROMIS® GI Symptom instrument has 60 items and assesses eight domains: gastroesophageal reflux (13

items), disrupted swallowing (seven items), diarrhea (five items), bowel incontinence/soilage (four items), nausea and vomiting (four items), constipation (nine items), belly pain (six items), and gas /bloating /flatulence (12 items). For the study purposes, we will only be using disrupted swallowing, constipation and nausea/vomiting forms. A higher score denotes more GI symptoms. Similarly, the PROMIS® Applied Cognition short form has four questions. A higher cognition score would denote more cognitive impairment. The recall period for PROMIS® GI Symptom items is around one week. We will be collecting PROMIS® data weekly through an in-person visit or through telephone interviews for up to 12 weeks. We hope to quantify and measure severity of study regimen-related side effects. We also plan to record frequency of antinausea, laxative and oral anesthetic use. We expect that buprenorphine will have manageable GI and cognitive side effect profile. (25, 26) The PROMIS® GI and cognition forms are included in appendix section of this protocol.

5.11 Other Functional, Symptom Assessments

A compliance questionnaire that has been previously used to test an electronic pain diary will be administered periodically by the study coordinator, as per study calendar. The coordinator who is trained in using the WHO mucositis scale will grade mucositis weekly during radiation therapy. The Brief Pain Inventory questionnaire and MDASI-HN will also be administered weekly during radiation therapy and the follow-up period, as per study calendar. These questionnaires can also be administered through a telephone interview by a provider or CRC. All responses in the BPI (24) short form will be recorded, including severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the past week

MDASI consists of 28 question items. Along with the core MDASI's 13 symptom items and six interference items, the MDASI-HN (21) also assesses nine symptoms relevant to head and neck cancer, such as mucus in the mouth and throat, difficulty swallowing or chewing, choking or coughing, difficulty with voice or speech, skin pain/burning/rash, constipation, problems with tasting food, mouth/throat sores and problems with teeth or gums. Copies of the BPI and MDASI forms are included in appendix section of this protocol.

5.12 Opioid and Non-Opioid Drug Use Assessments

Patients and family members will be asked to maintain a drug diary at home to document use of opioids, laxatives, antiemetics, and oral anesthetics. Record of the opioid pain medications, laxatives, and antiemetics from patient drug diary will be copied by the investigators / CRC on weekly clinic visits. Opioid drug use will also be monitored by investigators through Wisconsin Prescription Drug Monitoring Program - WI (PDMP).

6 ADVERSE EVENTS: DEFINITIONS, COLLECTION AND REPORTING REQUIREMENTS

6.1 Definitions
6.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonization [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Adverse events (AEs) may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures.

For the purpose of the study, only the adverse events related to the study intervention will be reported for regulatory oversight (e.g., related to OM Pain App, drug regimen of buprenorphine and tramadol, etc.).

Adverse events related to anticancer therapy will not be reported, as these treatments are considered standard of care and are not the focus of investigation of this trial.

Some patients who are enrolled in a therapeutic clinical trial may also be eligible for the present study. Adverse events related to cancer treatment in these patients will be reported under the umbrella of their active treatment clinical trial.

For this study, adverse events may be defined as follows:

- Loss of device (including theft,). AirWatch will be loaded on each mobile device that is provided to participants. MCW Information Service agrees to provide oversight and assistance to deactivate lost or stolen devices.
- Loss of protected health information.
- Established side effects of tramadol and buprenorphine for example: skin reaction to transdermal patch, central nervous system depression, respiratory compromise or hypercapnia due to drug regimen use, prolonged QTc> 500 ms, new onset seizures, and gastrointestinal side effects not attributable to standard-of-care radiation and chemotherapy. For details, refer to Section 7.

Radiation related Adverse Events

Radiation toxicity data will be used to associate with OM pain data. All acute and late adverse events from radiation therapy will be recorded and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. As noted, a copy of the CTCAE v5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov/). While radiation therapy side effects will be recorded, they will not be reported as adverse events for the purpose of the study, because its purpose is to evaluate the efficacy of the study drug regimen. The radiation therapy will be delivered according to the standard of care and not directed by this protocol.

Chemotherapy Adverse Events

Chemotherapy-related toxicity data will be used to associate with OM pain data. All acute and late adverse events from chemotherapy will be recorded and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Toxicity data will be recorded because cumulative toxicity may have indirect effects on pain perception.

While chemotherapy side effects will be recorded, they will not be reported as adverse events for the purpose of the study, because the purpose of this study is to evaluate the efficacy of buprenorphine and tramadol combination regimen.

The investigator and his or her team will follow the Medical College of Wisconsin policies related to adverse event reporting. This information may be found on the Human Research Protection Program website.

6.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.
- **Life-threatening**. Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- **Pregnancy**
- **Medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

6.1.3 Attribution of an Adverse Event

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:
Related: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Unrelated: *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal

relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments). *The AE is clearly NOT related to the intervention.* The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

6.1.4 Expectedness of an Adverse Event

Study Investigator or treating Physician will be responsible for determining whether an AE is expected or unexpected as indicated in Reference Safety Information within drug information brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described in the reference safety information for the investigational product for the study intervention.

6.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

6.2.1 Collection of Adverse Events

All adverse events (including SAEs) must be recorded in OnCore® and/or an adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator's or treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time of initiation of drug regimen to the end of follow up period. AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.

Please see sections 6.1.1, 6.2.2 and Table 3 to identify the adverse events that need to be reported.

6.2.2 Reporting of Adverse Events and Serious Adverse Events

Please refer to Table 3 below to identify adverse events that meet reporting requirements. All serious adverse events (SAEs) that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported. All SAEs will be followed until satisfactory resolution, or until the investigator deems the event to be chronic. All serious adverse events (SAEs) must also be documented in OnCore®.

Table 3: Adverse Events and Serious Adverse Events Reporting Requirements.

<table>
<tr><th rowspan="3">Attribution</th><th colspan="4">SAE</th><th colspan="3">AE</th></tr>
<tr><th colspan="2">Grade 1, 2 & 3</th><th colspan="2">Grade 4 and 5</th><th>Grade 3</th><th colspan="2">Grade 4</th></tr>
<tr><th>Expected</th><th>Unexpected</th><th>Expected</th><th>Unexpected</th><th>Unexpected</th><th>Expected</th><th>Unexpected</th></tr>
<tr><td>Unrelated
Unlikely</td><td rowspan="2">IRB[1] and DSMC-Routine Review[2]</td><td>IRB[1] and DSMC-Routine Review[2]</td><td rowspan="2">IRB[1]-Routine Review[2]

DSMC[3]-Within 5 calendar days</td><td>IRB[1]-Routine Review[2]

DSMC[3]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Routine Review</td><td rowspan="2">DSMC[3]-Within 5 calendar days</td><td rowspan="2">DSMC[3]-Within 5 calendar days</td></tr>
<tr><td>Possible
Probable
Definite</td><td>IRB[1] and DSMC[3]-Within 5 calendar days</td><td>IRB[1] and DSMC[3]-Within 5 calendar days</td></tr>
</table>

Footnotes

[1] Guidance on adverse event reporting to the IRB will follow the current MCW IRB Policies and Procedures.

[2] For routine reporting, the events will be reported to IRB as part of the annual continuing progress report, and the DSMC will review events entered in OnCore™ at the time of scheduled monitoring.

[3] For expedited DSMC reporting, study coordinator/research nurse must notify the DSMC via email. For AEs, include the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. For SAEs, DSMC will review the SAE report entered into OnCore™.

6.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

6.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study, or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the drug manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a drug manufacturer representative. Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

7 PHARMACEUTICAL INFORMATION

7.1 Buprenorphine

7.7.1 Mechanism of Action

Buprenorphine is a derivative of the thebaine, which has mixed agonistic activities. It exerts an agonistic effect on μ opioid and the OR L1 receptors, but it has antagonistic effect on kappa and delta opioid receptors.(13, 36) It is also a low-molecular weight compound (467 g/mol), has a low melting point, is lipophilic and water soluble, making it an ideal candidate for transdermal administration. (37)

7.1.2 Formulation Used

Transdermal buprenorphine with a polymeric active matrix is superior to some of the other long-acting opioids in terms of therapeutic efficacy and compliance. Continuous and controlled release of drug by passive diffusion through polymeric matrix maintains a constant level of buprenorphine in plasma. This effect gives transdermal buprenorphine an edge over some of the other long-acting opioids, as there is less likelihood of side effects related to periodic plasma drug level surges associated with some of the other opioids. The longer half-life of buprenorphine and its high affinity to the μ-receptor make it longer lasting and up to 100 times more efficacious (per mg) as an analgesic than morphine. For usage as a transdermal patch, buprenorphine is incorporated into an adhesive polymer matrix (acrylate vinyl acetate), from which it is continuously released into the systemic circulation over a period of seven days. Buprenorphine transdermal patch (BTP) is available in three strengths — 5, 10, and 20 mg — with a rate of drug release of 5, 10, and 20 mg/h, respectively. Following removal of the patch, concentrations decrease to about one-half in 12 hours, and then decline more gradually with an apparent half-life of about 26 hours.(38)

Unlike other opioids, it has a ceiling effect, which means its effects increase until the person takes a certain amount; then, these effects level off. This limits euphoria and respiratory depression.

7.1.3 Metabolism

Buprenorphine is metabolized by the liver, via CYP3A4 (also CYP2C8 seems to be involved) isozymes of the cytochrome P450 enzyme system into norbuprenorphine (by N-dealkylation). The glucuronidation of buprenorphine is primarily carried out by UGT1A1 and UGT2B7, and that of norbuprenorphine by UGT1A1 and UGT1A3. These glucuronides are then eliminated mainly through excretion into bile. The elimination half-life of buprenorphine is 20 to 73 hours (mean 37 hours). Due to the mainly hepatic elimination, there is no risk of accumulation in people with renal impairment.(39) One of the major active metabolites of buprenorphine is norbuprenorphine, which, in contrast to buprenorphine itself, is a full agonist of the MOR, DOR, and ORL-1, and a partial agonist at the KOR. However, relative to buprenorphine, norbuprenorphine has extremely little antinociceptive potency (1/50th that of buprenorphine), but markedly depresses respiration (10-fold more than buprenorphine). This may be explained by very poor brain penetration of

norbuprenorphine due to a high affinity of the compound for P-glycoprotein. In contrast to norbuprenorphine, buprenorphine and its glucuronide metabolites are negligibly transported by P-glycoprotein. The glucuronides of buprenorphine and norbuprenorphine are also biologically active and represent major active metabolites of buprenorphine. Buprenorphine-3-glucuronide has affinity for the MOR, DOR, and ORL-, and no affinity for the KOR. It has a small antinociceptive effect and no effect on respiration. Norbuprenorphine-3-glucuronide has no affinity for the MOR or DOR but does bind to the KOR (Ki = 300 nm.) and ORL-1 (Ki = 18 μM). It has a sedative effect but no effect on respiration.(40, 41)

7.1.4 Contraindications

The only true contraindication to buprenorphine use is a hypersensitivity reaction to it. Its use requires caution in patients with respiratory depression, seizure disorder, and gastrointestinal obstruction. It should be avoided in patients with gastrointestinal obstruction and surgical abdomen, such as pancreatitis or appendicitis. Patients with significant respiratory depression, such as severe chronic COPD, asthma, or myasthenia gravis should not be given buprenorphine. Buprenorphine is also not a recommended agent for patients who are currently using full opioid agonists, such as heroin or morphine, because the concurrent use of a full and partial agonist may result in acute withdrawal (see "Monitoring"), thus, defeating the purpose of buprenorphine administration. Concurrent use of benzodiazepines, other CNS depressants and alcohol is prohibited. (42)

7.1.5 Side Effects

Common side effects (>5%) of buprenorphine include nausea, vomiting, constipation, drowsiness, dizziness, headache, and sweating. It may also cause central nervous system depression, respiratory depression, and QT prolongation. Anticholinergic side effects like dry mouth, miosis, orthostatic hypotension, and urinary retention are also seen. Transdermal patches are also associated with contact dermatitis in some individuals. (42) If QTc prolongation of more than 500 ms is noticed, then, buprenorphine should be held until it is less than 470 ms. If respiratory depression is observed, then, remove buprenorphine patch, give oxygen, administer IV naloxone 2 mg stat over 90 secs in the hospital or urgent care setting.

7.1.6 Special Considerations

It is not recommended in pregnant and lactating women, as it is category C medication, and it does pass into breast milk.

HIV:

Since many HAART drugs also affect the liver microsomal enzymes, healthcare workers should closely monitor liver function and drug levels in patients who have buprenorphine prescribed at the same time. In some patients, the dose of buprenorphine may require alteration.

Hepatitis:

Both hepatitis B and C are common comorbid conditions in opioid-dependent patients. Since buprenorphine break down occurs in the liver, these patients should have their liver function and drug levels closely monitored. Clinicians should caution patients with hepatitis that intravenous use of buprenorphine has correlations with liver damage.

Complete and updated information is available in the investigational drug brochure and/or product package insert.

Others: Specific patient populations, such as the elderly, debilitated patients, or those with pre-existing pulmonary disease are at greater risk of respiratory depression with buprenorphine. It should be used with extreme caution in these individuals.

7.1.7 Dose Adjustments: No dose adjustments for liver or renal impairment required for TD buprenorphine. Refer to **Table 3.**

7.1.8 Drug Administration and Handling: Instruct patients to apply it immediately after removal from the individually sealed pouch. Instruct patients not to use TD buprenorphine if the pouch seal is broken or the patch is cut, damaged, or changed in any way. See the instructions for use for step-by-step instructions for applying TD buprenorphine. TD buprenorphine can be applied to any of these sites, including the upper outer arm, upper chest, upper back or the side of the chest. These four sites (each present on both sides of the body) provide eight possible application sites. The patients should be advised as follows: Rotate TD buprenorphine among the eight described skin sites. After TD buprenorphine removal, wait a minimum of 21 days before reapplying to the same skin site. Apply the patch to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Do not apply the TD buprenorphine to irritated skin. If the application site must be cleaned, clean the site with water only. Do not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before applying TD buprenorphine. Incidental exposure of the TD buprenorphine patch to water, such as while bathing or showering is acceptable based on experience during clinical studies. If problems with adhesion of TD buprenorphine occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, the patch may be covered with waterproof or semipermeable adhesive dressings suitable for seven days of wear. If the TD buprenorphine patch falls off during the seven-day dosing interval, dispose of the transdermal system properly and place a new drug patch on at a different skin site. When changing the system, instruct patients to remove TD buprenorphine and dispose of it properly. If the buprenorphine-containing adhesive matrix accidentally contacts the skin, instruct patients or caregivers to wash the area with water and not to use soap, alcohol, or other solvents to remove the adhesive because they may enhance the absorption of the drug.

Disposal Instructions: Patients should refer to the instructions for use for proper disposal of TD buprenorphine. Dispose of used and unused patches by following the instructions on the Patch-Disposal Unit that is packaged with the TD buprenorphine patches. Alternatively, patients can dispose of used patches by folding the adhesive side of the patch to itself, then flushing the patch down the toilet immediately upon removal. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet. Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed.

Rash Related to TD buprenorphine:

Erythema and mild pruritis from TD buprenorphine are common. If localized erythema or rash is observed, then, the site of application of patch should be changed. In rare cases, if severe application site skin reactions with signs of marked inflammation including “burn,” “discharge,” and “vesicles” are noticed, then, the patch should be discontinued. If severe anaphylactic reaction, bronchospasm or angioedema occurs from the study drug regimen then it should be discontinued.

Refer to package insert for details on management of other adverse events
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021306s015s019lbl.pdf

7.2 Tramadol

7.2.1 Mechanism of Action

Tramadol is an atypical synthetic compound that acts as a μ-opioid receptor agonist, serotonin releasing agent norepinephrine reuptake inhibitor, NMDA receptor antagonist (IC50=16.5 μM), 5-HT2C receptor antagonist (EC50=26 nM), (α7)5 nicotinic acetylcholine receptor antagonist, TRPV1 receptor agonist, and M1 and M3 muscarinic acetylcholine receptor antagonist. (43, 44)

7.2.2 Formulation

It is administered orally. Immediate release tablet formulation will be used. Its analgesic effects take about one hour to come into effect and two to four hours to peak after oral administration with an immediate-release formulation. On a dose-by-dose basis, tramadol has about one-tenth the potency of morphine and is approximately equally potent when compared to pethidine and codeine.(45)

7.2.3 Metabolism

Tramadol is extensively metabolized in the liver by O- and N-demethylation and by conjugation reactions to form glucuronides and sulfate metabolites. The O-demethylation of tramadol to its main active metabolite, O-desmethyltramadol (M1), is catalyzed mainly by cytochrome P450 (CYP) 2D6 enzyme. (46)

7.2.4 Contraindications

- Patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids.
- GI obstruction, surgical abdomen like pancreatitis or appendicitis.
- Patients with significant respiratory depression like severe chronic COPD/asthma or myasthenia gravis.
- Patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment.
- It also decreases seizure threshold by antagonizing 5HTc receptors.(47)
- All other opioid contraindications, including intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.

7.2.5 Side Effects

Most common adverse reactions (incidence > 10%) are nausea, constipation, dry mouth, somnolence, dizziness, and vomiting. Complete and updated information is available in the investigational drug brochure and/or product package insert.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022370s000lbl.pdf

7.2.6 Rationale for Using Oral Tramadol with Transdermal Buprenorphine
Tramadol is being used for breakthrough pain as TD buprenorphine is long acting.

7.2.7 Dose adjustments in renal failure
No dose adjustment of tramadol is required for creatinine clearance >30ml/min. Creatinine clearance <30ml/min: restrict maximum daily dose of tramadol immediate release to 200 mg/day.

7.2.8 Dose Adjustment in Liver Failure
No dose adjustment is required in mild to moderate liver failure (Child Pugh class A and B). Restrict dose to 50 mg q12 in severe liver impairment**. Refer to Table 4**

Table 4. Dose Modifications of Buprenorphine and Tramadol

Table 4:		
Organ Impairment	**Buprenorphine Patch**	**Oral Tramadol**
Renal: Creatinine clearance >30ml/min.	No dose adjustment.	No dose adjustment.
Renal: Creatinine clearance <30ml/min.	No dose adjustment.	Restrict maximum daily dose of tramadol immediate release to 200 mg/day.
Mild to moderate liver failure (Child Pugh class A and B).	No dose adjustment.	No dose adjustment.
Severe liver failure (Child Pugh C).	Not studied in severe impairment.	Restrict dose to 50 mg q12 in severe liver impairment.
Cytopenia's (any grade).	No dose adjustment required.	No dose adjustment required.
Other side effects, such as severe nausea, vomiting, headache, respiratory depression, somnolence, dizziness, and constipation.	Dose adjustment at clinician's discretion.	Dose adjustment at clinician's discretion.
Prolonged QTc>500 msec attributable to buprenorphine (other causes ruled out).	Hold buprenorphine patch until QTc comes back to normal range <470 msec	Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Study Endpoints

8.1.1 Primary endpoint: Establish efficacy of study regimen by showing that at least 33% of patients will achieve at least a 30 percent decrease in VAS pain score from baseline to the end of week 9 of treatment and follow-up period. Earlier studies have shown that the VAS pain score (≥4/10) on the day of treatment initiation can be used as baseline in this setting and a 30% or higher reduction in baseline pain score is a sign of meaningful drug response.(27-29)

8.1.2 Secondary endpoint:
1. Monitor compliance of study drug regimen through OM Pain App and medication diary.

2. Identify study participants who require off-protocol opioids for pain control despite being on the highest dose of study drug combination.
3. Correlate cumulative mean weekly pain scores calculated by the pain app with the average weekly pain scores recorded by the BPI short form.
4. Correlate average weekly OM Pain App scores and average weekly pain scores calculated from the BPI short form with head and neck symptoms and function evaluation tool MDASI-HN. The cumulative average area under the curve (AUC) weekly pain scores are expected to be inversely proportion to MDASI-HN average weekly AUC physical activity scores.
5. Maintain a weekly log of use of other nonopiod supportive care medications, such as laxatives, antiemetics, and oral anesthetics, in conjunction with the study drug combination during treatment and follow-up period through weekly questionnaires. Average weekly use of laxatives and antiemetics is expected to decrease by the end of follow up period.
6. Assess incidence and severity of gastrointestinal and cognitive side effects of the study drug regimen and their impact on quality of life, as measured by weekly PROMIS® (GI and cognition) questionnaires.
7. Safety: Assess the incidence and severity of other adverse events associated with the study drug combination using CTCAE version 5.

8.2 Study Design

This is a single-arm prospective clinical trial to determine the safety and feasibility of using transdermal buprenorphine in alleviation of radiation-induced mucositis pain in head and neck cancer patients with 12-week follow-up.

8.3 Study populations

- The enrolled population will consist of all enrolled patients. This population will be used in the CONSORT diagram, and patient disposition summaries.
- The treated population will consist of all enrolled patients who received at least one dose of the study medication. This population will be used for the efficacy and safety analyses.
- The per-protocol population will consist of all treated patients whose treatment followed without major protocol violations. This population will be used for sensitivity analyses.

8.4 Determination of Sample Size and Accrual Rate

Based on earlier studies (48) and the IMMPACT recommendations(28), a 30% or higher decrease in pain score from baseline to the end of the follow-up period is a sign of clinically meaningful efficacy of the drug regimen within a patient. A randomized trial of pregabalin for the treatment of radiotherapy-related pain in head-and-neck cancer patients (33) observed an at least 30% decrease in 33% of placebo-treated patients. This study will use a single-stage design to evaluate the hypothesis that patients treated with buprenorphine will achieve at least a 30% decrease in pain with probability exceeding 33%. Formally, the following hypotheses will be evaluated at a one-sided 5% significance level:

H_0: p (≥30% decrease) = 0.33 versus H_a p (≥30% decrease) > 0.33.

With 18 subjects, the study will have at least 80% power to reject the null hypothesis if the probability of achieving at least 30% decrease in pain with buprenorphine is, in fact, 63%. The hypothesized effect is consistent with the efficacy seen with other active treatments. Specifically,

buprenorphine will be considered an acceptable pain control medication if 10 or more subjects out of the 18 experience at least 30% pain reduction. We will enroll 20 subjects to allow for 10% drop-out rate.

8.5 Feasibility
We will be able to complete protocol development and receive IRB approval in two months. Based on our previous experience, we normally see around 64 stage II–IV HNSCC patients annually who fulfill the eligibility criteria of the study. During 12 months of the potential accrual period, we will be able to contact 25 subjects. Under an assumed 80% consent rate, 19 to 20 subjects will be enrolled into the study. Assuming a 10% dropout rate, we will end up with around 18 patients participating in our study. Since close to 100% patients develop mucositis and develop at least moderate intensity pain requiring opioid medications through radiation therapy, we do not anticipate any screen failures. However, if a screen failure occurs for some reason then we plan to replace those patients to ensure an evaluation of 18 patients. Patients will be followed for 12 weeks. Final interpretation of pain app data, standardized measurement tools and document of results will be done in the last month of the study period. We are confident of completing the accrual in 12 months.

8.6 Data Analysis
Serial measurements of patient-reported pain data will be analyzed throughout the follow-up period to look for inadequate pain control and use of off-protocol breakthrough pain medication use. The pain app data will be analyzed by study coordinators and our collaborators at UWM. Data recording will commence on the day the patient starts taking the drug regimen. We plan to study the daily and weekly pain score patterns during therapy. We will determine the baseline VAS pain score on the day of treatment initiation. Other pain management studies in radiation-induced mucositis acknowledged the fact that the pain curve follows a nonlinear pattern during radiation therapy, but it plateaus and later drops down to a lower level after initiation of long-acting effective pain medications. Hence, it is reasonable to use the pain score on the day of treatment initiation as our baseline pain score. (29, 31) Radiation-induced mucositis begins to heal approximately two weeks after the last dose of stomatotoxic chemotherapy or radiation therapy.(30, 32) We will assess a percentage drop in the pain score by the end of week 9 of treatment to show a drug response. This way, we will try to avoid any bias of the normal healing process on pain alleviation. At least two-week treatment with study drug regimen will be required in order to be considered evaluable for study endpoints. Earlier studies and consensus guidelines have shown that a 30% drop in average weekly pain score by end of the follow-up period is significant. (28). The recording of data will cease after 12 weeks, at which time mucositis-related pain symptoms substantially abate in many individuals. (32)

The primary analysis will compare the proportion of patients achieving a 30% drop in pain scores to the null-hypothesis value of 33% at a one-sided 5% significance level using a binomial test. The number of patients using analgesic and non-analgesic medications, as well as the occurrence of adverse events, will be tabulated and presented as counts with percentages. The average weekly pain scores, MDASI-HN, and the PROMIS® measures will be reported with descriptive statistics (mean, standard deviation, median, and range). Patient level summaries of the pain score and PRO outcomes will be created by computing area under the curve (AUC) of weekly averages. Scatterplots will be used to explore their relationship which will be quantified by Spearman's correlation coefficient. Further correlational analysis will be done by linear regression and linear fixed models.

8.7 Rationale for not Having a Stopping Rule: This is a supportive care pilot study to determine

the efficacy of transdermal buprenorphine and oral tramadol drug combination in alleviating radiation-induced mucositis pain in head and neck cancer patients. These pain medications are FDA approved and have an established safety profile. In addition to the primary efficacy endpoint, we will be evaluating other secondary end points, such as real-time pain monitoring through the OM Pain App. This will continue, even if the study drug regimen is discontinued for lack of efficacy or some other unspecified reason. This would provide us invaluable pilot data for future studies in this setting. Moreover, we have made provisions for switching to standard-of-care pain medications, such as oral oxycodone in our study for patients who don't derive adequate pain relief from the study regimen. Hence, it is reasonable to exclude a formal stopping rule for this trial.

8.8 Missing Data

Missing data will be investigated, and multiple imputations will be used to account for missingness. Multiple imputations will be performed under the assumption that missing data are missing at random (MAR). If the validity of the MAR assumption is questioned, possible departures from MAR will be investigated by sensitivity analyses.

8.9 Research Environment

The study will be activated at the Medical College of Wisconsin (MCW) Cancer Center. The cancer center employs 57 full-time and two part-time staff. It is the only academic cancer center in Eastern Wisconsin, supporting more than 2.3 million people. The MCW Cancer Center Clinical Trials Office (CTO) will conduct the study and support all stages of the clinical trial process, including: protocol feasibility, regulatory support, compliance monitoring, consent development, IRB submission, budget development, contract negotiation, trial coordination and management, trial promotion and referrals, and patient screening, enrollment and consenting, data collection and management and results monitoring and reporting. The Division of Biostatistics at MCW will provide statistical support and perform analysis. As a recipient of a clinical and translational science award from NIH, with a recent five-year, $20 million renewal, the Medical College of Wisconsin is representing a consortium of Milwaukee institutions (Clinical and Translational Science Institute of Southeast Wisconsin [CTSI]) working in collaboration to advance biomedical research, clinical care, and education.

9 DATA AND SAFETY MONITORING PLAN (DSMP)

9.1 Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with safety and progress reports submitted to the DSMC.

9.2 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist, and the study biostatistician. While subjects are on study, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema.

The appropriateness of further subject enrollment and the specific intervention for the next subject enrollment is addressed. All meetings including attendance are documented.

9.3 Quality Assurance

The MCWCC Clinical Trials Office provides ongoing quality assurance audits. This protocol was classified as intermediate risk and will be reviewed internally by the MCW Cancer Center Clinical Trials Office Quality Assurance Staff according to the MCW Cancer Center Data and Safety Monitoring Plan and current version SOP, 6.5.2 Internal Quality Assurance Reviews.

9.4 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

9.5 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension, or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

10 REGULATORY COMPLIANCE, ETHICS, AND STUDY MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

10.1 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol.
- Federal regulations, as applicable, including 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.2 Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB. 10.3 Institutional Review Board

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Before obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB before implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individuals agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB approved and the subject (and legally authorized representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, the hospital staff was present for the consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with the study subject at the next appropriate opportunity. Patients who require reconsenting will be defined in the IRB-approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for the review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

10.4 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, [and the sponsor(s) and their agents] (include bracketed portion if applicable). This confidentiality includes clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The conditions for maintaining the confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked clinical research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the case report forms contain the study identifiers, subject initials, date of birth, and date of service.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor/s or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

10.5 Protection of Human Subjects

10.5.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study to ensure that the consent document accurately and communicates the nature of the research to be done and its associated risks and benefits.

10.5.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

10.5.3 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

10.6 Investigator Compliance

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

<u>Onsite Audits</u>

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11 DATA HANDLING AND RECORD KEEPING

11.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data are protected from physical damage as well as from tampering, loss, or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians, and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

11.2 Data Management Responsibilities

Principal Investigator
The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication, and investigational product(s), measurements, exams, evaluations, and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is a correlation between the case report forms and the source documents**.**

Research Coordinator
A research coordinator creates, collects, and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol-specified time points.

Research Nurse/Medical Staff
The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events, and compliance to study procedures.

Biostatistician
The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

11.3 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and

ALCOA Attribute	Definition
	during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

11.4 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document outcomes. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The clinical research coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

11.5 Study Record Retention

The principal investigator is required to maintain adequate records.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the

physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of the disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of the disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial (Transdermal Buprenorphine for the Treatment of Radiation-Induced Mucositis Pain in Head and Neck Cancer Patients: A Pilot Study) you participated in.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at
_____

Sincerely,

_____

APPENDIX 3: WHO MUCOSITIS GRADING SCALE

Grade	Description
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

APPENDIX 4. QUESTIONNAIRES

PROMIS®– COGNITIVE FUNCTION- SHORT FORM

Please respond to each question or statement by marking one box per row in the past seven days.

			Never		Rarely (Once)		Sometimes (Two or three times)		Often (once a day)		Very often (Several times)
PC2r	My thinking has been slow		□ 5		□ 4		□ 3		□ 2		□ 1
PC35r	It has seemed like my brain was not working as well as usual		□ 5		□ 4		□ 3		□ 2		□ 1
PC36r	I have had to work harder than usual to keep track of what I was doing		□ 5		□ 4		□ 3		□ 2		□ 1
PC42r			□		□		□		□		□

	I have had trouble shifting back and forth between different activities that require thinking		5		4		3		2	1

PROMIS® Gastrointestinal Disrupted Swallowing

Please respond to each question or statement by marking one box. In the past seven days…

		Never	Rarely	Sometimes	Often	Always
GISX31	How often did food get stuck in your chest when you were eating?	□ 1	□ 2	□ 3	□ 4	□ 5
GISX32	How often did food get stuck in your throat when you were eating?	□ 1	□ 2	□ 3	□ 4	□ 5
GISX33	How often did you feel pain in your chest when swallowing food?	□ 1	□ 2	□ 3	□ 4	□ 5
GISX34	How often did you have difficulty swallowing solid foods like meat, chicken or raw vegetables, even after lots of chewing?	□ 1	□ 2	□ 3	□ 4	□ 5
GISX35	How often did you have difficulty swallowing soft foods like ice cream, apple sauce, or mashed potatoes?	□ 1	□ 2	□ 3	□ 4	□ 5
GISX36	How often did you have difficulty swallowing liquids?	□ 1	□ 2	□ 3	□ 4	□ 5

GISX37	How often did you have difficulty swallowing pills?	□ 1	□ 2	□ 3	□ 4	□ 5

PROMIS® Gastrointestinal Constipation:

Please respond to each question or statement by marking one box.
In the past seven days…

GISX 1) How often did you pass very hard or lumpy stools?

1. Never → **If Never, go to #3**
2. One day
3. Two – Six days
4. Once a day
5. More than once a day

GISX 2) How much did hard or lumpy stools bother you?

1. Not at all
2. A little bit
3. Somewhat
4. Quite a bit
5. Very much

GISX3) How often did you strain while trying to have bowel movements?

1. Never → **If Never, go to #6**
2. Rarely
3. Sometimes
4. Often
5. Always

In the past 7 days…

GISX 4)	How much did you usually strain while trying to have a bowel movement?

1. Not at all
2. A little bit
3. Somewhat
4. Quite a bit
5. Very much

GISX5)	How much did straining during bowel movements bother you?

1. Not at all
2. A little bit
3. Somewhat
4. Quite a bit
5. Very much

GISX6)	How often did you feel pain in your rectum or anus while trying to have bowel movements?

1. Never → If **Never, go to #8**
2. Rarely
3. Sometimes
4. Often
5. Always

In the past seven days…

GISX7)	At its worst, how would you rate the pain in your rectum or anus during bowel movements?

1. Not bad at all
2. A little bad
3. Somewhat bad
4. Quite bad
5. Very bad

GISX 8)	How often after a bowel movement did you feel unfinished - that is, that you had not passed all your stool?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always

GISX 9)	How often did you use your finger or toilet paper to get out a stool?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always

PROMIS® GASTROINTESTINAL NAUSEA AND VOMITING

Please respond to each question or statement by marking one box.

In the past seven days…

GISX1)	How often did you have nausea—that is, a feeling like you could vomit?	

1. Never → **If Never, go to #3**
2. Rarely
3. Sometimes
4. Often
5. Always

GISX 2)	How often did you know that you would have nausea before it happened?	

1. Never
2. Rarely
3. Sometimes
4. Often

5. Always

GISX 3)	How often did you have a poor appetite?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always

In the past 7 days…

GISX4)	How often did you throw up or vomit?

1. Never
2. One day
3. 2-6 times per day
4. Once a day
5. More than once a day

PROMIS® questionnaires can be downloaded directly from

https://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures

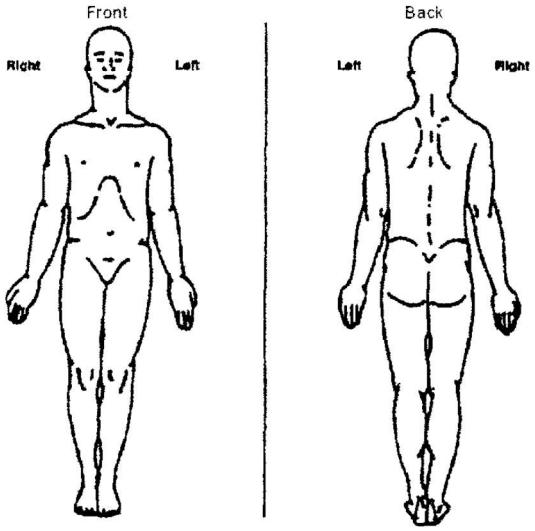
BRIEF PAIN INVENTORY (SHORT FORM)

Patient Initials:
Date of Birth (dd, mm, yyyy):
Visit Date (dd, mm, yyyy):

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 during the last week?

☐ 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 circling the one number that best describes your pain at its ***worst*** in the last 24hours.

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 circling the one number that best describes your pain at its ***least*** in the last week.

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 circling the one number that best describes your pain **on the *average weekly***.

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 circling the one 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

7.What treatments or medications are you receiving for your pain?

_____ _

8. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much ***relief*** *you* have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Relief — Complete Relief

9. Circle the one number that describes how much, during the past week, pain has interfered with your: A. General Activity

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

Scoring:

Pain Severity Score = Mean of items 3-6 (pain at its worst, pain at its least, average Pain
Interference Score = Mean of items 9A-9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life)

MDASI- HN questionnaires

Forms can be obtained from MDASI website

https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/md-anderson-symptom-inventory-head-and-neck-cancer-module.html

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