

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0537

A Phase II/III Study Comparing Acupuncture-like Transcutaneous Electrical Nerve Stimulation (ALTENS) Versus Pilocarpine in Treating Early Radiation-Induced Xerostomia

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SCHEMA

For patients who have completed RT +/- chemotherapy for head and neck cancer; protocol treatment must begin at least 3 months after completion of RT +/- chemotherapy				
Phase II Component		Phase III Component		
R		S	Prior use of	R
E		T	pilocarpine	A
G	ALTENS (given with	R	1. No	N
I	Codetron [®])	A	2. Yes	D
S	2x weekly for 12 weeks	T		O
T		I	Time from cancer	M
E		F	treatment	I
R		Y	1. 3-6 mos.	Z
			2. > 6 mos. to 1 year	E
			3. > 1 year	

See Section 5.0 for pre-registration requirements. See Section 7.0 for further details of drug and ALTENS therapy.

Patient Population: (See Section 3.0 for Eligibility) **(8/26/09)**

Patients who have completed radiotherapy (standard or IMRT) +/- chemotherapy for head and neck cancers and who have grade 1-2 xerostomia according to the CTCAE v. 3.0 dry mouth/salivary gland xerostomia scale

Required Sample Size: **Phase II component, 45 patients**
 Phase III component, 144 patients

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ELIGIBILITY CHECKLIST (9/19/08) (8/26/09)

Case # _____

(page 1 of 3)

- _____(Y) 1. Was a complete history and physical examination (including an ENT exam with a nasopharyngeal scope) performed within 8 weeks of registration to rule out evidence of recurrence?
- _____(Y) 2. If the patient completed radiation treatment within the last 12 months, was a CT or MRI performed within 8 weeks of registration?
- _____(Y) 3. Has the patient completed radiotherapy (standard or IMRT) +/- chemotherapy for a head and neck cancer greater than or equal to 3 months and up to a maximum of 2 years prior to study entry and has a grade 1-2 xerostomia according to the CTCAE v 3.0 dry mouth/salivary gland xerostomia scale?
- _____(Y) 4. Does the patient have evidence of residual salivary function with unstimulated WSP equal to or greater than 0.1 ml/min (having refrained from eating or drinking oral fluid for 2 hours prior)?
- _____(Y) 5. If the patient has been on pilocarpine or cevimeline, was the pilocarpine or cevimeline discontinued 2 weeks prior to registration?
- _____(Y) 6. Is the Zubrod Performance Status 0-2?
- _____(Y) 7. Is the patient \geq 18 years of age?
- _____(Y) 8. Are patients who are sexually active willing/able to use medically acceptable forms of contraception?
- _____(Y/N) 9. Does the patient have history of prior invasive malignancy, except non-melanomatous skin cancer? (Note: Patients with chronic lymphocytic leukemia are not eligible.)
- _____(Y) If yes, has the patient been disease free for a period of three years?
- _____(N) 10. Has the patient been discontinued pilocarpine due to a serious adverse event?
- _____(N) 11. Does the patient have current contraindication to pilocarpine (e.g., uncontrolled asthma, miosis, hypersensitivity)?
- _____(N) 12. Is the patient on pilocarpine of ophthalmic or non-ophthalmic indications?
- _____(N) 13. Is the patient on regular medication which will induce xerostomia (e.g., tricyclic antidepressants, antihistamines with anticholinergic effects or narcotics)?
- _____(Y) 14. Was informed consent provided?
- _____(N) 15. Does the patient have unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?
- _____(N) 16. Has the patient had a transmural myocardial infarction within the last 6 months?

(Continued on the next page)

RTOG Institution # _____

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ELIGIBILITY CHECKLIST (9/19/08) (8/26/09)

Case # _____

(page 2 of 3)

- _____(N) 17. Has the patient had acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?
- _____(N) 18. Does the patient have chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy?
- _____(N) 19. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects? (Note: Laboratory tests for liver function and coagulation are not required for entry into this protocol.)
- _____(N) 20. If the patient is a female, is the patient pregnant?
- _____(N) 21. Does the patient have Sjögren's Syndrome?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the patient provided study-specific consent prior to study entry
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of Payment
- _____ 15. Will any component of the patient's care be given at a military or VA facility?

(Continued on the next page)

RTOG Institution # _____

RTOG 0537

ELIGIBILITY CHECKLIST (9/19/08)

Case # _____

(page 3 of 3)

- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date (This date will be populated automatically.)
- _____ (Y/N) 18. Has the patient used pilocarpine before?
- _____ 19. How long ago did the patient last receive treatment for their cancer?
_____ 3-6 months ago
_____ More than 6 months to 1 year ago
_____ More than 1 year ago
- _____ (Y/N) 20. Will the patient participate in the Quality of Life component (UWHNSS) of this study?
If no, please provide the reason from the following:
_____ 1) patient refused due to illness
_____ 2) patient refused for other reason: specify _____
_____ 3) not approved by institutional IRB
_____ 4) tool not available in patient's language
_____ 5) other reason: specify _____

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Xerostomia

Xerostomia is a very common complication in patients treated with radical radiation therapy for head and neck cancers. It represents a significant source of morbidity for this patient population. The condition is caused by radiation damage to the salivary glands leading to decreased salivary production. It has been shown that a reduction in salivary flow depends on the radiation dose delivered and the volume of salivary glands irradiated. Even low doses of radiation can cause a change in the quantity and quality of saliva and up to 100% of patients who undergo radiotherapy for head and neck cancers develop some degree of xerostomia.¹⁻² The symptom of radiation-induced xerostomia is often permanent and leads to difficulties in mastication, swallowing, and speaking. Other consequences include stomatitis, taste dysfunction, and increased susceptibility to dental caries.³ Treatment with saliva substitutes and stimulation of salivary flow by either mechanical or pharmacological methods provides some symptomatic relief but no long-lasting results when active treatment is stopped.³

1.2 Pilocarpine

Oral pilocarpine hydrochloride treatment has been extensively studied. In two randomized trials of patients who had received at least 40 Gy of external beam radiation for head and neck cancer and had clinically important xerostomia, oral pilocarpine was shown to produce a statistically significant improvement in patients' overall global assessment of symptomatic relief as compared with control subjects.⁴⁻⁵ Johnson, et al. reported that 207 patients were randomized to placebo; pilocarpine, 5 mg tid; or pilocarpine, 10 mg tid for a twelve-week period.⁴ In patients receiving 5 or 10 mg pilocarpine, overall improvement in xerostomia was noted in 54% of patients, compared to 25% in the placebo group ($p = 0.003$). Individual symptoms, such as oral dryness, mouth comfort, and speaking ability also were significantly improved. Saliva production was minimally improved but did not correlate with symptomatic relief. In a similar study, 162 patients were randomized to placebo or pilocarpine.⁵ Patients on the treatment arm received 2.5 mg tid of pilocarpine for four weeks, 5 mg tid for the following four weeks, and 10 mg tid for the last four weeks. Patients in consultation with their physicians were advised to titrate pilocarpine or placebo for improvement of symptoms or to reduce side effects at the end of each four-week period. In general, lack of efficacy was a cause for dose escalation while bothersome side effects were a cause for dose reduction. Pilocarpine produced a significant improvement in patients' assessment of their xerostomia symptoms compared with placebo (49% vs. 28.1%, $p = 0.02$). A slight increase in saliva production also was noted in the treatment group ($p < 0.05$).

However, Warde, et al. found no observed difference between the treatment and the placebo groups in the severity of xerostomia score with six month follow-up.⁶ In their trial, 130 head and neck cancer patients were randomized to receive either 5 mg pilocarpine or placebo three times daily during radiation treatment and continuing for one month after treatment. In addition, in RTOG 97-09, a randomized study of 249 patients with head and neck cancer, the concomitant use of pilocarpine during and for three months after radiation did not have a positive impact on quality of life or patient assessment of salivary function despite the maintenance of salivary flow.⁷

Pilocarpine is the only drug approved by the U.S. Food and Drug Administration for use as a sialogogue for radiation xerostomia. Despite its effectiveness in some cases, pilocarpine usage is limited by adverse cholinergic effects, such as sweating, nausea, rhinitis, and chills. In the three randomized trials reported above, 15 to 25% of patients in the treatment arms withdrew primarily because of intolerable side effects.⁴⁻⁶ In clinical practice, patients are often unable to tolerate sustained treatment with pilocarpine. In addition, xerostomia usually relapses when pilocarpine is stopped, and it does not increase regeneration of salivary gland tissue.⁸⁻⁹ At present, there still is no established standard of care in patients suffered from radiation-induced xerostomia. In a systematic review of available published evidence in managing symptomatic radiation-induced xerostomia, a trial of oral pilocarpine at a dose of 5 mg three times per day for two or more months for patients having pre-existing salivary function has been recommended.¹⁰ The ideal duration of treatment with pilocarpine is undefined. The decision to extend treatment beyond three months can be based only on clinical judgment and not on evidence.

1.3 Acupuncture

It has been proposed that acupuncture treatment may specifically stimulate the autonomic nervous system through selected afferent neurons causing increased activity of the

parasympathetic nervous system, which enhances the release of specific neuropeptides. The neuropeptides may have a number of trophic effects that include an increase in the local blood flow of the salivary glands causing an upward regulation in the metabolism of salivary gland cells that results in an increase in salivary production and possibly regeneration of tissue.¹¹⁻¹⁵

Recently, acupuncture treatment in patients with xerostomia has been demonstrated to be effective and associated with long-lasting results.^{8-9,16-18} In a small, randomized trial, 21 patients with radiation and non-radiation induced xerostomia (e.g., Sjogrens Syndrome) were randomized to 2 six-week periods of acupuncture separated by a two-week break (treatment arm) versus a similar schedule of placebo acupuncture in the control arm.⁹ Patients in the treatment arm were treated with stainless steel needles at 6-8 points chosen among local (near the salivary glands) and distal points selected according to the Traditional Chinese Medicine model.¹⁹ In the treatment arm, needles were inserted to depths 0.5 and 2.0 cm. In the control arm, superficial needling was performed, and needles only were inserted intradermally. Median salivary flow increased by 0.26 ml of saliva per minute in the treatment group versus 0 ml per minute in the control group ($p < 0.01$). This difference was maintained at nine months post treatment. Patients on the treatment arm reported feeling better more consistently and reported less frequent use of salivary stimulants. In a trial by Johnstone and colleagues, 38 patients with radiation-induced xerostomia were randomized to classical acupuncture or a placebo (i.e., superficial acupuncture).¹⁶ In this study, patients on the treatment arm demonstrated a significant improvement in salivary flow of 0.31 ml per minute versus a baseline flow of 0.13 mls per minute. ($p < 0.05$). Increased salivary flow was maintained for nine months post treatment. Patients on the treatment arm reported less dryness, hoarseness, and improved taste. Recent reports from Johnstone, et al. also suggested the efficacy of acupuncture in relieving symptoms refractory to oral pilocarpine therapy.¹⁷⁻¹⁸

These acupuncture studies have been criticized for the inclusion of patients without evidence of functioning salivary glands and for limited sample sizes. Despite these limitations, however, the studies by Blom and Johnstone provide evidence that suggests that acupuncture can have a positive effect on the treatment of radiation-induced xerostomia. The attractiveness of acupuncture is that it appears to provide a sustained benefit following initial treatment and is virtually free of side effects. In both trials, the only adverse events noted were infrequent small bruises at the acupuncture site or occasional tiredness following the initial treatment.

1.4 Acupuncture-Like Transcutaneous Electrical Nerve Stimulation (ALTENS)

Although the evidence for acupuncture's positive effect on xerostomia is quite promising, the reluctance of patients to have "needle therapy" and the requirement of expertise in performing the acupuncture treatment may make this treatment modality difficult to offer to patients in most conventional clinics. To overcome this drawback, non-invasive acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) has been studied as a needleless acupuncture alternative. ALTENS is carried out using a transcutaneous electrical nerve stimulation device that is used mainly for pain indications. By utilizing higher intensity and low frequency stimulation parameters, the device can activate A delta nerve fibers that are stimulated by acupuncture treatment with the typical "De qi" response.²³ Thus, stimulation with this device on appropriate acupuncture points for a particular indication can simulate real needle acupuncture treatment although essentially, this form of treatment is an ordinary TENS application. The use of electrode pads that are 3 to 4 cm in size also make the precise localization of acupuncture points (usually 0.5 to 2 cm in size) less important. Moreover, since there is no invasive needle insertion, the risk of injuring deep structures is eliminated and the use of sole surface anatomical information to locate acupuncture points is adequate without prior special training in acupuncture. Recently, a newer ALTENS device, the Codetron[®] unit, has been developed. This Codetron[®] unit has a unique stimulation randomization circuitry that reduces brain habituation to continuous electrical stimulation, making it more ideal for ALTENS applications.

ALTENS has been shown to give comparable results to acupuncture treatment for musculoskeletal pain disorders.²⁰⁻²² In conditions such as post-operative emesis and pain control, in which acupuncture has been shown to be effective, the use of ALTENS also demonstrated comparable effectiveness. To deliver higher intensity, low frequency, and less habituating stimulation to A delta nerve fibers that are stimulated by acupuncture treatment with the typical "De qi" response.²³ A randomized study comparing the effectiveness of ALTENS given with the

Codetron[®] unit to that of electroacupuncture (which, in contrast to ALTENS, involves insertion of needles into acupuncture points for electrical stimulation) for the treatment of chronic musculoskeletal pain, demonstrated that ALTENS given with Codetron[®] exerts comparable or better results than electroacupuncture.²⁴ There are minimal adverse events with the use of ALTENS given with Codetron[®]: mild ache and skin irritation at site of stimulation.²⁵

Recent evidence suggests that ALTENS also may be useful in treating radiation-induced xerostomia by a similar mechanism to acupuncture through stimulating a neuroreflex mechanism involving the autonomic nervous system.¹⁵ Laboratory studies have shown that electrical stimulation of the parasympathetic nerve to the parotid and submandibular glands in rats causes a mitogenic response as indicated by an increase in tritiated thymidine uptake of the glands.²⁶ In two clinical studies of patients with xerostomia resulting from various causes, there was significant improvement in salivary production and symptoms associated with xerostomia after electrical stimulation by using a device applied to the tongue and hard palate.²⁷⁻²⁸

A randomized phase I/II study recently completed at the Juravinski Cancer Centre examined the use of ALTENS treatment for established radiation-induced xerostomia in head and neck cancer patients previously treated with radical radiotherapy.²⁹ The study's primary objective was to evaluate if ALTENS (given with the Codetron[®] unit) improves radiation-induced xerostomia symptoms. Secondary objectives were to evaluate if ALTENS (given with the Codetron[®] unit) improves whole salivary production (WSP) and to identify the optimal combinations of acupuncture points for ALTENS stimulation. Patients enrolled in the study were randomized into three groups (A, B, and C) of different combinations of acupuncture treatment points selected according to the Traditional Chinese Medicine model utilized in previously mentioned acupuncture trials.^{9,16,19} The combinations of acupuncture points used in this study vary in the relative contribution of local and distal points, as well as potential sympathetic and parasympathetic stimulation.^{19,30} ALTENS treatment was given twice weekly for six weeks. Square electrical pulses of 250 ms duration were delivered in trains with a repetition rate of four hertz and randomly stimulated each acupuncture point. Each session of ALTENS treatment lasted for 20 minutes. This was followed by a two-week break then another six-week course of treatment. Standardized assessments of WSP over five minutes, both basal and citric acid-primed, were conducted at pre-treatment and at three, six, and twelve months after treatment completion. Patient-reported symptoms of xerostomia were assessed using a five-item questionnaire with a visual analogue scale (VAS) utilized in previous trials.⁴⁻⁵ The total VAS scores range from 0 to 500. Quality of life was evaluated using the Hamilton Head and Neck Radiotherapy Questionnaire (HNRQ),³¹ administered at the same time points as the WSP assessments.

Forty-six patients with previously treated head and neck cancers were recruited into the study. Both parotid glands in each patient were irradiated to a total dose of > 44 Gy with a mean dose of 50.5 Gy. Nine patients failed to complete the study for reasons unrelated to treatment (3 for personal reasons, 3 for unexpected heart events, 1 for prosthesis hemorrhage, 1 for tumor recurrence and 1 for severe back pain). The remaining 37 patients (Group A: 13, Group B: 10, Group C: 14) have all completed six-month follow up. There was no statistically significant difference between the groups in their baseline demographics, concurrent tobacco and alcohol usage, duration of xerostomia, pre-treatment WSP or xerostomia symptoms, pre-treatment VAS scores or quality of life assessments. For the 37 patients, the mean age was 59 years old (range: 30 – 85) with mean duration of 21.8 months (range: 4 – 87) of xerostomia symptoms prior to ALTENS treatment. Mean pre-treatment basal and citric-acid primed WSPs over 5 minutes were 0.26 ml (s.d.: 0.28, range: 0 – 1.29) and 1.07 ml (s.d.: 0.78, range: 0.09 – 3.49), respectively.

For all 37 patients, at three months follow up, the mean basal and citric-acid stimulated WSPs over 5 minutes increased by approximately 30% to 0.36 ml (s.d.: 0.39, range: 0 – 1.49) and 1.33 ml (s.d.: 0.81, range: 1.10 – 3.41), respectively. At six months post-ALTENS treatment, the mean basal and citric-acid primed WSPs over 5 minutes further increased to 0.37 ml (s.d.: 0.35, range: 0 – 1.44) and 1.61 ml (s.d.: 1.07, range: 0.30 – 5.07), respectively. The mean increases in both the basal and citric-acid primed WSPs at three- and six-month follow up were found to be statistically significant compared to pre-treatment levels ($p < 0.001$ and $p < 0.0001$ respectively). The mean increases remained statistically significant after covariate adjustments for concurrent

tobacco and alcohol usage and intervals between last fraction of radiation and start of ALTENS treatment. The increases in WSPs were sustained for six months after ALTENS treatment. The increase in citric-acid primed WSP was significantly better than the increase in basal WSP at six-month follow up ($p < 0.05$). This finding is compatible to the results of a recent long-term follow-up study of patients with xerostomia treated with acupuncture showing that significant increases in salivary flow rates at six-month follow up ($p < 0.01$) were found after twenty-four acupuncture treatments. Patients receiving additional acupuncture treatments had consistently higher salivary flow rates at three years follow up.⁷

In the Juravinski Cancer Centre study, there were significant associated improvements in all symptoms of xerostomia. The mean total VAS scores increased from 144 at baseline to 230 at 3 months and 220 at six-month follow up. T-tests for the differences (mean increase in total VAS score of +86 [s.d. 124] and +75 [s.d.104] at three-month and six-month follow up respectively) were significant: $p < 0.0005$ and $p < 0.0001$ at 3 and 6 months, respectively. Patients reported improvement in tongue dryness, speech, swallowing, and overall comfort of the mouth. Interestingly, there were reported improvements in taste ($p < 0.004$) and consistency (less thick) of both saliva ($p < 0.0001$) and oral mucous ($p < 0.04$). There were no statistically significant differences in the increases in WSPs or improvements in xerostomia symptoms between groups A, B, and C at 3 and 6 month follow up. However, there was a trend that patients in group A demonstrated the greatest improvements in their mean total VAS scores in all symptoms of xerostomia and reported greatest frequency of improvements in the consistency of both their saliva and oral mucous. There were no reported adverse events with the ALTENS treatment in this study. All patients reported the ease of treatment delivery and their willingness to undergo further treatment in the future.

These positive results support the hypothesis that ALTENS stimulation of relevant acupuncture points using traditional Chinese medicine principles may be effective in the treatment of radiation-induced xerostomia and should ideally be evaluated in a phase III placebo-controlled trial. However, since it is necessary in ALTENS treatment to induce a strong but subnoxious sensation during stimulation, the use of 'sham' ALTENS treatment, (similar to 'sham' acupuncture) as a placebo is not possible. The method of using low intensity stimulation or stimulating areas that are not acupuncture points may still induce an increase of endorphin secretion that may indirectly affect salivary function. Therefore, the use of these approaches as placebo also is not possible. A randomized study design directly comparing ALTENS treatment with an acceptable treatment, such as oral pilocarpine, in radiation-induced xerostomia therefore is appropriate to evaluate effectiveness and adverse event profiles of ALTENS treatment compared to treatment using pilocarpine.

Although there are reports that suggested a slight recovery of salivary function after radical radiation to the salivary glands,³² the majority of studies showed irreversible salivary dysfunction.³³⁻³⁵ Progressive salivary acinar necrosis and gland atrophy with associated decline in salivary function has been shown until 6 to 8 months after therapy.³⁶⁻³⁷ Effective intervention during this period of declining function may arrest the deteriorating process and thus, the best window to examine the potential salivary gland cells regeneration properties of ALTENS is likely to be prior to 6 months post radical radiation therapy.

We hypothesize that ALTENS stimulation of relevant acupuncture points (using traditional Chinese medicine principals) may be effective treatment of radiation-induced xerostomia. Therefore, we propose a phase II/III randomized prospective study of ALTENS treatment (given with the Codetron[®] unit) versus pilocarpine in treating radiation-induced xerostomia. Eligible study subjects will be randomized into two groups: ALTENS treatment, two (twenty-minute) treatments weekly for 12 weeks and oral pilocarpine, 5 mg three times daily for 12 weeks.

The proposed study is a successor trial to a single institutional phase II trial of ALTENS treatment conducted by Wong, et al. at McMaster University.²⁹ That study showed that patients did benefit with ALTENS treatment of their radiation-induced xerostomia.

Since there are no previous RTOG trials using ALTENS, the proposed trial will have two components. The first component will be a phase II trial to demonstrate that RTOG institutions can successfully accrue and treat patients with ALTENS. The protocol treatment schedule with

ALTENS calls for two twenty-minute sessions weekly for a total of 12 weeks. Treatment delivery for a patient will be considered successful if the patient completes at least 18 of the 24 protocol-prescribed sessions. In Wong's single institution phase II trial, over 90% of the patients completed all of their ALTENS prescribed sessions, which were given in somewhat different schedules, i.e., with a two-week break after 6 weeks of treatment. The two per week treatment will increase feasibility for recruited patients to plan for treatment in between daily routines. The shortened overall treatment time as compared to the aforementioned phase II trial will also increase the chance of patient completion of all of the prescribed ALTENS sessions.

1.5 Symptom Assessment and Quality of Life (QOL)

Symptom assessment and QOL are a critical component of any selected treatment, whether it is conventional care or a complementary and alternative medicine (CAM) therapy such as Acupuncture-Like Transcutaneous Electrical Nerve Stimulation (ALTENS). In the phase II component of the study, xerostomia burden will be assessed at baseline and at 6 months from randomization. In the phase III component of the study, xerostomia burden and QOL will be assessed at baseline and at 4, 6, 9, and 15 months from randomization. Two self-report instruments will be used. First, the change in xerostomia symptoms will be assessed using the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS). This instrument consists of 15 items on a 5-point Likert-type scale covering four major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues. It takes approximately 5 minutes to respond to the 15 items. Second, QOL will be assessed using the University of Washington Head and Neck Symptom Scale Quality of Life Questionnaire (UWHNSS). This questionnaire was designed specifically to address problems incurred by head and neck cancer patients. The scale consists of 10 symptom-specific categories, each of which describes important daily living function/limitations. Each category has 5 possible item choices, and takes 7-10 minutes to complete.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 Phase II component

Determine the feasibility of successfully delivering the ALTENS treatment (given with the Codetron® unit) in a cooperative group setting

2.1.2 Phase III component

Determine whether the ALTENS treatment reduces overall xerostomia burden, as measured by the University of Michigan 15-item Xerostomia-Related Quality of Life Scale (XeQOLS), compared to the pilocarpine treatment at 9 months from randomization

2.2 Secondary Objectives

2.2.1 Phase II component

Evaluate the effect of ALTENS treatment on overall xerostomia burden, as measured by the XeQOLS, at 6 months from registration;

2.2.2 Phase III component

Determine whether the ALTENS treatment reduces overall xerostomia burden, as measured by the XeQOLS, compared to the pilocarpine treatment at 4, 6, and 15 months from randomization;

2.2.3 Determine whether the ALTENS treatment reduces symptom burden in the four domains of the XeQOLS—physical functioning, social functioning, personal/psychological functioning, pain/discomfort—compared to the pilocarpine treatment at 4, 6, 9, and 15 months from randomization;

2.2.4 Determine whether the ALTENS treatment increases stimulated (citric acid primed) whole salivary production (WSP), as measured by sialometry, compared to the pilocarpine treatment at 4, 6, 9, and 15 months from randomization.

2.2.5 Determine whether the ALTENS treatment increases unstimulated (basal primed) WSP, as measured by sialometry, compared to the pilocarpine treatment at 4, 6, 9, and 15 months from randomization;

2.2.6 Evaluate the potential benefit of ALTENS in change and overall quality of life, as measured by the University of Washington Head and Neck Questionnaire (UWHNSS);

2.2.7 Compare adverse events between treatments according to CTCAE v.3.0 criteria.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Conditions for Patient Eligibility (8/26/09)

- 3.1.1 Complete history and physical examination to demonstrate no clinical evidence of disease recurrence, including an ENT exam with a nasopharyngeal scope, if indicated, 8 weeks prior to registration;
- 3.1.2 CT or MRI scan within 8 weeks prior to registration except for patients who finished radiation treatment one or more years ago and clinically there is no evidence of recurrence;
- 3.1.3 Patients who have completed radiotherapy (standard or IMRT) +/- chemotherapy for head and neck cancers greater than or equal to 3 months and up to a maximum of 2 years prior to study entry and who have grade 1-2 xerostomia according to the CTCAE v.3.0 dry mouth/salivary gland xerostomia scale;
- 3.1.4 Patients must have evidence of residual salivary function with unstimulated (basal) WSP equal or greater than 0.1 ml/min³⁸ (having refrained from eating or drinking oral fluid for 2 hours prior);
- 3.1.5 Patients who have received pilocarpine or cevimeline previously are eligible; patients must discontinue prior pilocarpine or cevimeline use within 2 weeks prior to randomization;
- 3.1.6 Zubrod performance status of 0-2;
- 3.1.7 Age ≥ 18 years;
- 3.1.8 Serum pregnancy test for women of childbearing potential; women of childbearing potential and male participants must practice adequate contraception;
- 3.1.9 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (8/26/09)

- 3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (for example, carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible); patients with chronic lymphocytic leukemia are not eligible
- 3.2.2 Patients with normal saliva production (no salivary gland changes; no xerostomia);
- 3.2.3 Patients who have previously received and discontinued pilocarpine due to serious adverse events;
- 3.2.4 Patients with current contraindications to pilocarpine (e.g., uncontrolled asthma, miosis, hypersensitivity);
- 3.2.5 Patients who are on pilocarpine for ophthalmic or non-ophthalmic indications;
- 3.2.6 Patients who are on regular medications which will induce xerostomia (e.g., tricyclic antidepressants, antihistamines with anticholinergic effects or narcotics);
- 3.2.7 Severe, active co-morbidity defined as follows:
 - 3.2.7.1 Patients with unstable cardiac disease or those with a pacemaker in-situ are excluded.
 - 3.2.7.2 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
 - 3.2.7.3 Transmural myocardial infarction within the last 6 months;
 - 3.2.7.4 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - 3.2.7.5 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration
 - 3.2.7.6 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- 3.2.8 Pregnant females are excluded, as ALTENS stimulates acupuncture points that may be related to the Conception Meridian and, in theory, may affect uterine function.
- 3.2.9 Patients who have Sjögren's Syndrome

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations

- 4.1.1 Phase II component
Sites are required to administer the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS).

- 4.1.2 Phase III component
- 4.1.2.1 Whole Salivary Production (WSP)—basal and stimulated (see Section 11.4.3)
- 4.1.2.2 Sites are required to administer the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS).
- 4.1.2.3 If the patient consents to participate in the Quality of Life component of the study, sites are required to administer the Head and Neck Symptom Scale of the University of Washington Quality of Life Questionnaire (UWHNSS).
- 4.2 **Highly Recommended Evaluations/Management**
- 4.2.1 Complete history and physical examination to demonstrate no clinical evidence of disease recurrence prior to registration. The use of oral comfort agents and their frequency of usage should also be noted.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (8/26/09)

- 5.1.1 Institutions must agree to accrue at least 4 patients per year to the trial and will be required to register 2 eligible patients prior to receiving a Codetron[®] unit. Institutional accrual will be closely monitored by the Principal Investigator, Dr. Wong, and RTOG Headquarters. Institutional Principal Investigators or Research Associates must complete the Accrual Agreement form (Appendix VI) posted on the RTOG website, next to the protocol, and fax it to RTOG Headquarters (215-574-0300) prior to registration of the first patient. Upon receipt of the completed form, RTOG Headquarters will ship the Codetron[®] unit to the institution. The institution's Principal Investigator or Research Associate is responsible for contacting RTOG Headquarters (215-574-3191) if the unit does not arrive.

If an institution with a Codetron[®] unit does not accrue at least 2 patients during the first 6 months after opening the trial, the Codetron[®] unit will be offered to another RTOG institution. (After the first 3 months following the opening of the trial, Dr. Wong will notify institutions that the Codetron[®] unit will be offered to another RTOG institution within 3 months.) As long as an institution enrolls at least 4 patients per year, the institution can keep the machine. If an institution does not accrue at least 4 patients per year, they must return the Codetron[®] unit to RTOG Headquarters within 7-10 days following final notification from Dr. Wong.

At the completion of participant accrual, each participating RTOG institution with a Codetron[®] unit must return the unit to RTOG Headquarters within 7-10 days after the final patient completes ALTENS therapy. RTOG will provide pre-paid shipping labels to institutions when the Codetron[®] unit is shipped (for return shipments to RTOG Headquarters).

5.2 Regulatory Pre-Registration Requirements (8/26/09)

- 5.2.1 **U.S. sites and Canadian sites** must fax copies of the documentation below, along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution's first case:

- IRB/REB approval letter
- IRB/REB approved consent (English and native language Versions*)
***Note:** Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number.

5.2.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

- 5.2.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.2.3 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

- 5.2.3.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

- 5.2.3.2 **For institutions that have an approved LOI for this protocol:**

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.3 Registration

5.3.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://phrp.nihtraining.com/users/login.php>).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due. If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrrs.org

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Not applicable to this study.

7.0 PILOCARPINE HCL AND ACUPUNCTURE-LIKE TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (ALTENS) THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin at least 3 months after completion of radiation therapy +/- chemotherapy and within 2 weeks after registration (phase II component) or randomization (phase III component).

(8/26/09) The Phase II component of the trial includes Arm 2 (ALTENS therapy alone) only.

7.1 Arm 1: Oral Pilocarpine HCL Treatment

7.1.1 Drug Formulation and Dose Definition

Pilocarpine HCL (Salagen®, Pharmacia) is supplied as a white, round biconvex tablet. Each tablet contains 5 mg of pilocarpine HCL in combination with a non-drug substance of microcrystalline cellulose, stearic acid; coating: hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80 and titanium dioxide; ink: ethanol, ethylene glycol monoethyl ether, lecithin, methyl alcohol, N-butyl alcohol, propylene glycol, shellac and synthetic black iron oxide.

7.1.2 Mechanism of Action

Pilocarpine is a cholinomimetic agent with a broad spectrum of pharmacologic effects with predominant muscarinic action. It increases secretion of exocrine glands (e.g., sweat, salivary glands) and stimulates smooth muscles.

7.1.3 Administration and Duration of Treatment

Patients will receive 5 mg of pilocarpine orally three times a day for 12 weeks. No further treatment will be given after 12 weeks.

If the pilocarpine dose is missed, no make-up dose is necessary, but documentation of the missed dose is required. If treatment is held for more than 4 weeks, the patient is considered to be off protocol.

7.1.4 Storage

Pilocarpine should be stored at room temperature (15° to 30°C).

7.1.5 Supply

Commercially available

7.1.6 Adverse Events

Adverse events are dose-dependent and usually subside within 6 hours of discontinuation of therapy. For a dose of 5 mg three times a day, adverse events reported include sweating, nausea, rhinitis, chills, vasodilatation (flushing), urinary frequency, dizziness, asthenia, blurred vision, tremor, myalgia, cough, diarrhea, tachycardia, edema, skin rash, and headache.

7.1.7 Accountability

Patients will be asked to complete drug diaries and return all bottles of medication for counting to assess compliance with treatment.

7.1.8 Dose Modifications

Dose modification is permitted in case of intolerance to dose-dependent adverse events at the discretion of the study center investigator. Pilocarpine dose can only be reduced by a 5 mg daily dose each time.

7.2 **Arm 2: Acupuncture-Like Transcutaneous Electrical Nerve Stimulation (ALTENS)**

7.2.1 Codetron[®] Machines

The Codetron[®] machine is FDA approved for musculoskeletal pain management. Codetron[®] machines (Model 902-C) will be used for the study.

7.2.2 Mechanism of Action

The Transcutaneous Electrical Nerve Stimulation (TENS) device was developed for pain management. These devices utilize the electrical stimulation of sensory nerves to bring along pain signal suppression through the gate control mechanism and/or the endorphin release mechanism. The relative significance of these types of mechanisms utilized in a particular treatment depends on the stimulation parameters of the TENS device used. Using a stimulation frequency between 90 to 130 Hz and at a low intensity, the A beta nerve fibers will be excited resulting in the suppression of noxious stimulus through the C fibers of the spinal cord and thus blocking the signal to reach higher centers in the brain.

However, by utilizing higher intensity and low frequency, in the order between 2 to 5 Hz, the device can activate A delta nerve fibers that increase endorphin release into the blood stream resulting in a reduction in the activities of the noxious sensory pathway. The A delta nerve fibers are also found to be stimulated by needle acupuncture treatment with the typical “De qi” response.²³ Thus, stimulation with this device using these parameters on appropriate acupuncture points for a particular indication can simulate real needle acupuncture treatment although essentially, this form of treatment is an ordinary TENS application.

The Codetron[®] machine for this study has an onboard randomization circuitry that allows stimulation of each electrode to occur at random and reduces brain habituation to electrical stimulation.

7.2.3 Treatment Points

All patients will have the following acupuncture points stimulated using the Codetron[®] machines: bilateral SP6, ST36, LI4 and the indifferent electrode on CV24.³⁴ This combination of acupuncture points (Group A treatment) has been selected based on the findings in the aforementioned phase I/II trial. These acupuncture points were some of the points initially chosen, according to acupuncture principles, in positive xerostomia trials using acupuncture.^{8,9,16} All of the three acupuncture meridians—Stomach, Spleen, and Large Intestine— influenced by the acupoints ST36, SP6, and LI4, respectively, have their trajectories through the mouth and in particularly the parotid glands. ST36 has also been found to influence the balance of the autonomic nervous system, possibly through increased vagal and lower sympathetic response. CV24 is a traditional acupuncture point specifically indicated to stimulate salivary flow.

The locations of the acupuncture points are based on previous literature¹⁹ and are as follows:

LI4 • He Gu • Large Intestine 4

Location: *On the dorsum of the hand, approximately at the midpoint of the second metacarpal bone, in the belly of the first interosseus dorsalis muscle.*

SP6 • San Yin Jiao • Spleen 6

Location: *On the medial leg, 4 finger breadth superior to the tip of medial malleolus, on the posterior border of the tibia.*

ST36 • Zu San Li • Stomach 36

Location: *On the leg, one finger breadth lateral to the tibia's anterior crest, 4 finger breadth inferior to the depression to the lateral side of the patella.*

CV24 • Cheng Jiang • Conception Vessel 24

On the chin, in the depression in the center of the mentolabial groove, below the middle of the lower lip.

Treatment will be delivered using Codetron[®] machines with seven electrodes, i.e., six different (uncommon) electrodes and one indifferent (common) electrode. Self adherent Karaya electrode pads will be used for attaching each electrode on the patient's skin. Square pulses of 250ms duration will be delivered in trains with the repetition rate set at 4Hz (pulse code III on the machine).^{27,35} The level of stimulation (level 3 to 5 on the machine) will be adjusted to produce a deep strong, mild aching sensation at the attachment point of each electrode. Random switching among electrodes will be employed to prevent habituation.²¹ Each electrode will be switched on for 10s at a time. Each treatment session lasts 20 minutes.

7.2.4 Schedule for Administration of ALTENS Treatment (8/26/09)

Patients will be treated twice a week for 12 weeks. No further treatment will be given after 12 weeks. Patients can be off treatment for a maximum period of 2 weeks only. The resulting missed treatments can be delivered during the other weeks but only a maximum of three treatments per week is allowed. The total duration of the treatment must be 12 weeks and all assessments counted accordingly.

7.2.5 Adverse Events

TENS is non-invasive and has few reported side effects. Skin allergy reaction to materials of the electrodes has been reported to occur in 2% to 3% of patients.

7.2.6 Adjustments to ALTENS Treatment Related to Adverse Events

In the rare scenario that contact dermatitis develops at the site of electrode placement, the site and its corresponding acupuncture point will be treated medically at the discretion of the study center investigator. The electrodes can be reapplied to the site once the site has recovered for one week. However, in the event that the same bilateral sites of an acupuncture point are affected, or the CV24 point cannot be used due to dermatitis, ALTENS treatment will be discontinued.

If a grade 3 skin reaction occurs at CV24, ALTENS should be held until the skin reaction becomes less than grade 1. For other sites, if there are grade 3 skin reactions at one acupuncture point site, that point should not be treated until the skin reactions become grade 1. Other points can continuously be treated. If more than one acupuncture point site shows a

grade 3 skin reaction, ALTENS should be held until the skin reaction becomes less than grade 1.

7.2.7 Codetron® Supply (8/26/09)

Each RTOG institution participating in the study will receive one Codetron® unit with 2 sets (1 set per patient) of electrodes. Institutions can contact RTOG Headquarters if additional electrodes are needed. Member institutions are free to open the trial if the site has or plans to buy a Codetron® unit. The Codetron® unit is FDA approved for musculoskeletal pain management. The Study Chairs will contact the RTOG institutions that previously have successfully accrued to RTOG Head and Neck trials to gauge interest at these sites in opening this trial and in receiving a Codetron® unit.

Institutions must agree to accrue at least 4 patients per year to the trial and will be required to register 2 eligible patients prior to receiving a Codetron® unit. Institutional accrual will be closely monitored by the Principal Investigator, Dr. Wong, and RTOG Headquarters. Institutional Principal Investigators or Research Associates must complete the Accrual Agreement form (Appendix VI) posted on the RTOG website, next to the protocol, and fax it to RTOG Headquarters (215-574-0300) prior to registration of the first patient. Upon receipt of the completed form, RTOG Headquarters will ship the Codetron® unit to the institution. The institution's Principal Investigator or Research Associate is responsible for contacting RTOG Headquarters (215-574-3191) if the unit does not arrive.

If an institution with a Codetron® unit does not accrue at least 2 patients during the first 6 months after opening the trial, the Codetron® unit will be offered to another RTOG institution. (After the first 3 months following the opening of the trial, Dr. Wong will notify institutions that the Codetron® unit will be offered to another RTOG institution within 3 months if accrual does not increase.) As long as an institution enrolls at least 4 patients per year, the institution can keep the machine. If an institution does not accrue at least 4 patients per year, they must return the Codetron® unit to RTOG Headquarters within 7-10 days following final notification from Dr. Wong that the Codetron® unit will be offered to another institution.

At the completion of participant accrual, each participating RTOG institution with a Codetron® unit must return the unit to RTOG Headquarters within 7-10 days after the final patient completes ALTENS therapy. RTOG will provide pre-paid shipping labels to institutions when the Codetron® unit is shipped (for return shipments to RTOG Headquarters).

7.2.8 Compliance to Treatment

All treatments will be delivered at the involved study centers. Each study center will be provided with a manufacturer's user manual showing the proper administration of ALTENS given with the Codetron® device. Additionally, PowerPoint slides describing the administration procedure will be posted on the RTOG Website (<http://www.rtog.org>) next to the protocol. All persons administering ALTENS at the site will be required to review the user manual and PowerPoint slides to ensure consistency of treatment. Sites will e-mail digital photos of electrode attachments of each subject at the first treatment to Dr. Wong (raimond.wong@jcc.hhsc.ca) for documenting proper electrode placement (see Section 12.1). **"RTOG 0537: Electrode placement photos" should be included in the subject line of the e-mail.**

7.3 Complementary Therapy Reviews

The Principal Investigator, Raimond Wong, M.D., will perform a Supportive Care Review of all patients who receive or are to receive pilocarpine or ALTENS therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of pilocarpine or ALTENS therapy treatment data as specified in Section 12.1. The scoring mechanism is:

- Per protocol: All treatments were given correctly
- Variation, acceptable: Deviation other than that deemed unacceptable
- Deviation, unacceptable: Ineligible patients were treated; Arm 1: Pilocarpine not given; other salivary stimulating drugs were used Arm 2: CV24 not used or more than one acupuncture point defined in the protocol was not treated
- Not evaluable for therapy review: Specify reasons

- Incomplete therapy: Arm 1: Patient received less than 200 doses of pilocarpine over 12 weeks of treatment (<79% prescribed); Arm 2: Patient received less than 19 of the 24 scheduled ALTENS treatments (<79% prescribed)

A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Principal Investigator, Raimond Wong, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Wong will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.4 Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, (MedDRA version 9.0) for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.4.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [*CTEP, NCI Guidelines: Adverse Event Reporting Requirements*. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.5 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.4.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs.**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG case number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.4.3

Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.5 AdEERS Expedited Reporting Requirements

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

7.5.1 Phase 2 and 3 Trials Utilizing a Commercially Available Agent: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days¹ of the Last Dose of the Investigational Agent (Pilocarpine) in this Study (Arm 1)

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days
¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a Commercially Available agent require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> Grade 4 and Grade 5 unexpected events AdEERS 10 calendar day report: <ul style="list-style-type: none"> Grade 3 unexpected events with hospitalization or prolongation of hospitalization Grade 5 expected events 									
² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.									
Please see exceptions below under section entitled "Additional Instructions or Exceptions."									
March 2005									

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
 - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercially Available Agent:

Sites will follow the adverse event reporting instructions described above in Sections 7.4 and 7.5 for adverse events attributed to the Codetron[®] machine. AdEERS accepts adverse events attributed to devices, and AdEERS automatically generates and issues a MedWatch report to the FDA.

In AdEERS, sites will be cued to provide the following information for the Codetron[®]:

- Brand name: Codetron®;
- Common name: TENS
- Device type: Transcutaneous nerve stimulator
- Manufacturer name: EHM Rehabilitation Technologies/Recept Pharmacy
- Manufacturer city: Fort Worth
- Manufacturer state/province: Texas
- Expiration date: None

Sites also will be required to provide the model, lot, catalog, and serial numbers of the machine utilized (these will be visible on each Codetron®).

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.1 All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.2 Oral comfort agents including supplemental water and artificial saliva

9.1.2.1 If oral comfort agents are used, the type of agent and frequency of use per day must be reported. Patients can report 1-10 times, 10-20 times, 20-30 times, or 30 plus times per day.

9.2 Non-permitted Supportive Therapy

9.2.1 Oral stimulating agents or salivary gland medical stimulants

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

(8/26/09) In the **phase II** component of the study, patients will be assessed for xerostomia burden only (XeQOLS) pre-treatment and at 6 months after registration. In the **phase III** component of the study, patients will be assessed for basal and stimulated whole salivary production (WSP), xerostomia burden, and QOL pre-treatment and at 4, 6, 9, and 15 months after randomization. In the **phase III** component of the study, patients must be offered the opportunity to participate in the quality of life assessment (See Section 11.4.2). Sites are not permitted to delete the quality of life assessment from the protocol or from the protocol sample consent.

11.1 Study Parameters: See Appendix II for a summary of assessments and time frames.

11.2 Evaluation During Phase III Component Treatment

11.2.1 Arm 1: Adverse events will be evaluated once every two weeks. In the event of intolerable adverse events, patients will be evaluated at the discretion of the study center investigator.

11.2.2 Arm 2: Patients will be evaluated for adverse events, but not endpoints assessment, twice per week at each treatment visit, for 12 weeks.

11.2.3 Information regarding patient usage of salivary comfort agents and (for Arm 1 only) pilocarpine diaries will be collected.

11.3 Evaluation During Phase III Component Follow Up

11.3.1 Patient-reported change in xerostomia symptoms on the XeQOLS (see Appendix IV), patient-reported QOL on the UWHNSS (see Appendix V), and whole salivary production (WSP) over five minutes (both basal and citric acid-primed) will be assessed.

11.3.2 Information regarding patient usage of salivary comfort agents will be collected.

11.4 Symptom Assessments and Quality of Life (QOL)

11.4.1 The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS)

The subjective impact of salivary gland dysfunction and xerostomia will be assessed using the Xerostomia-Related Quality of Life Scale (XeQOLS) developed at the University of Michigan.⁴³ This scale consists of 15 items covering four major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues. The reliabilities of the four domains and the total XeQOLS score were determined with a sample of 283 head and neck cancer patients being treated for parotid-sparing and standard

bilateral-neck radiation therapy.⁴⁴⁻⁵⁰ All Cronbach coefficients were statistically significant for the four domains: physical (r=0.85), personal/psychological (r= 0.87), social (r=0.86), and pain/discomfort (r=0.89). Internal validity was determined in conjunction with responses to a previously validated four-item subjective xerostomia tool,⁵¹ and coefficients for the four domains and the total score were significant at p<0.05. External validity was determined by correlating the four domains with objectively determined unstimulated and stimulated parotid flow rates from treated and spared parotid glands from the same population. Correlations were all significant (p<0.05), except for the social domain (p<.0.069). It takes approximately 5 minutes to respond to the 15 items in the scale.

11.4.2 The Head and Neck Symptom Scale of the University of Washington Quality of Life Questionnaire (UWHNSS)

Hassan and Weymuller of the University of Washington, Seattle, developed the University of Washington Quality of Life Questionnaire.⁴² This questionnaire was designed specifically to address problems incurred by head and neck cancer patients. The questionnaire was tested on 75 head and neck cancer patients and was compared to two established tools, the Karnofsky Performance Scale (KPS) and the Sickness Impact Profile (SIP), for validity, acceptability, reliability, and responsiveness. The overall results demonstrated that the University of Washington Head and Neck Symptom Scale (UWHNSS) [see Appendix V] was equivalent to the Karnofsky and SIP for reliability and responsiveness; it was the preferred test format for 97% of the tested patients. The scores on the UWHNSS correlated well with the KPS and SIP, indicating validity. The test-retest reliability coefficient was 0.95. The scale consists of ten symptom-specific categories, each of which describes important daily living function/limitations of head and neck cancer patients. Each category has five possible item choices, and takes 7-10 minutes to complete. The highest level or "normal" is scored 10 points while the lowest (or greatest dysfunction) is scored 50 points. The options between are in multiples of 10. The patient is asked to circle the statements which best describe their current status. The scores are totaled and then adjusted to obtain the final range from 0 to 100. The lower the score, the greater the QOL; conversely, the higher the score, the lower the QOL.

11.4.3 Whole Salivary Production (Basal and Stimulated)

Whole salivary production (WSP) will be measured by expectoration weight. One gram of saliva produced will be considered as one ml of saliva.

11.4.3.1 Basal whole salivary production: Patients will be informed to refrain from eating, drinking, and smoking at least two hours prior to each measurement. For each measurement, patients will be asked to expectorate continuously into a pre-weighted dry plastic container over a 5-minute period without swallowing. The collected saliva with the plastic container will be weighed (total weight) immediately after each collection. The total weight minus the weight of the container will be the weight or volume of whole saliva collected. The WSP will be expressed in ml/min calculated by dividing the measured weight or volume of WSP by five.

11.4.3.2 Stimulated whole salivary production (citric-acid primed test): Stimulation will be elicited by asking patients to rinse 5 ml of 2% citric acid solution in the mouth for 15 seconds and then completely expectorate the citric acid. This is followed by the whole saliva collection procedure as described in Section 11.4.3.1. The WSP will be expressed in ml/min calculated by dividing the measured weight or volume of WSP by five.

12.0 DATA COLLECTION

Data should be submitted to:

*RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (8/26/09)

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) WSP (L4), XeQOLS (QF), and UWHNSS (HP) – Phase III only	Within 2 weeks of study entry
Digital photos of electrode attachments	Within 2 weeks after treatment begins E-mailed as JPEG files to the Principal Investigator, Raimond Wong (raimond.wong@jcc.hhsc.ca)
Treatment Form (TF)	Monthly during treatment (1, 2, and 3 months)
Follow-up Form (F1) WSP (L4), XeQOLS (QF), and UWHNSS (HP) – Phase III only	4, 6, 9, and 15 months from randomization

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

13.1.1.1 Phase II component

Successful delivery of ALTENS treatment (given with the Codetron[®] unit)

13.1.1.2 Phase III component

Overall xerostomia burden, 9 months from randomization, as measured by the University of Michigan 15-item Xerostomia Related Quality of Life Scale (XeQOLS)

13.1.2 Secondary Endpoints

13.1.2.1 Phase II component

(Beneficial) treatment response, defined as a 20% improvement in overall xerostomia burden (XeQOLS score) from baseline to 6 months from registration

13.1.2.2 Overall xerostomia burden at 4, 6, and 15 months from randomization, as measured by the XeQOLS

13.1.2.3 Symptom burden 4, 6, 9, and 15 months from randomization, as measured by the four domains of the XeQOLS: physical functioning, social functioning, personal/psychological functioning, pain/discomfort

13.1.2.4 Stimulated (citric acid primed) whole salivary production (WSP) 4, 6, 9, and 15 months from randomization, as measured by sialometry

13.1.2.5 Unstimulated (basal primed) WSP 4, 6, 9, and 15 months from randomization, as measured by sialometry

13.1.2.6 Quality of Life (QOL) as measured by the University of Washington Head and Neck Questionnaire (UWHNSS)

13.1.2.7 Adverse events based on CTCAE v.3.0

13.2 Sample Size

13.2.1 Stratification and Randomization

Patients will be stratified before randomization with respect to prior use of pilocarpine (no vs. yes) and length of time from completion of chemotherapy and/or radiation therapy (3-6 months vs. 6-12 months vs. > 12 months) in the phase III component. The treatment allocation scheme described by Zelen⁵² will be used because it balances patient factors other than institution. Within each stratum, patients will be randomized in a 1:1 ratio to either ALTENS or pilocarpine treatment.

13.2.2 Sample Size Derivations

13.2.2.1 Phase II component

The sample size calculations for the phase II component address the primary hypothesis that RTOG institutions can successfully accrue and treat patients with ALTENS. In Wong's single institution phase II trial, protocol treatment called for two 20-minute sessions weekly for a total of 12 weeks (including a 2-week interim break). Over 80% (37/46) of the patients completed all 24 sessions.⁵³

The RTOG protocol treatment schedule calls for two 20-minute sessions weekly for a total of 12 weeks (with no interim break). Treatment delivery for a patient will be considered successful if the patient completes at least 19 of the 24 protocol prescribed sessions.

The following tables provides the boundaries for the number of patients successfully completing treatment based on Fleming's⁵⁴ two-stage design with a targeted 85% successful treatment delivery rate, statistical power set at 0.87 and type I error set at 0.13. The first stage of the phase II component will utilize one-third of the required sample size, thus permitting an earlier formal evaluation of treatment delivery.

Phase II Component			
Step	Total Number Evaluable	Lower Limit of Patients With Successful Treatment ^a	Upper Limit of Patients With Successful Treatment ^b
1	13	8	13
2	39	30	31

a. If the number is equal to or below the lower limit, the phase III component will not be pursued.

b. If the number is equal to or above the upper limit, the phase III component will be pursued.

Adjusting by approximately 15% to allow for patients that are found retrospectively ineligible, or for whom no treatment data are submitted or who experience disease progression or death, **the total sample size required for the phase II component is 45 patients.** Three additional patients will be entered for each stage.

13.2.2.2 Phase III component (8/26/09)

The sample size calculations for the phase III component will address the specific primary hypothesis that the use of the ALTENS treatment (Arm 2) will result in a statistically significant change in overall xerostomia burden as compared to the use of the pilocarpine treatment (Arm 1) based on the 15-item XeQOLS.

The mean change in overall xerostomia burden from baseline (pre-treatment) to 9 months from randomization will be of interest. We expect that patients receiving pilocarpine (Arm 1) will have a minimal change in overall xerostomia burden, if any. We hypothesize that patients receiving ALTENS (Arm 2) will experience a statistically significant change in overall xerostomia burden from baseline to 9 months from randomization:

$$H_0: \Delta\mu_1 = \Delta\mu_2 \text{ vs. } H_A: \Delta\mu_1 \neq \Delta\mu_2$$

where $\Delta\mu_i$ is the mean change in xerostomia from baseline to 9 months for patients in arm i.

The individual patient change scores are assumed to be normally distributed. There are no data currently available to hypothesize a difference in the mean change of XeQOLS scores between treatment arms. Therefore, an effect size of 0.50 was chosen for sample size calculation on what was thought by the study team to represent such a change that a positive study would be more persuasive to implement the use of ALTENS treatment (given with the Codetron[®] unit). The effect size here is simply the difference between the means divided by the standard deviation. The phase II component will provide an estimate of this standard deviation under the assumption that the standard deviation is the same for both arms. The magnitude of the difference tested for between arms will also be estimated. Based on a two-sided t-test with alpha=0.05, 130 patients would be required to have 80% statistical power to detect an effect size of 0.5 in the XeQOLS change scores between the two treatment arms. The EAST software v4.0⁵⁵ was used for calculating the sample size

with one planned interim analysis. The nominal significance level for the interim and the final test were set at 0.003 and 0.049, respectively, to preserve an overall significance of 0.05. Adjusting by approximately 15% to allow for patients that are found retrospectively ineligible or die prior to the 9-month (from randomization) assessment, **the total sample size required for the phase III component of the study is 144 patients.**

13.3 Patient Accrual (8/26/09)

Based on patient accrual to RTOG 9709, a head and neck symptom management trial, there will be negligible accrual (6 patients) during the initial 6 months while institutions are obtaining IRB approval and learning to use the Codetron[®] unit. After this initial period, it is projected that this study will accrue approximately 3 patients per month and that it will take 19 months to accrue the sample size of 45 patients for the phase II component. McMaster University will be limited to accruing 5 of these patients. If the average monthly accrual for the last 6 months of the phase II component is less than 3, the phase III component will not be undertaken.

For the phase III component, the patient accrual is projected to increase to at least 4 patients per month. It will take approximately 3 years to accrue the projected sample size of 144 patients. The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually during the phase III component. If the average monthly accrual rate for the trial in the fifth and sixth quarters after study activation (i.e., in months 13-18) is less than 20% of the rate projected in the paragraph above (i.e., less than 1 patient per month), the study will close to further accrual. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., between 1-2 patients per month), the trial will be placed on probation for 6 months. If the average monthly accrual rate at the end of the probationary period is less than 50% of projected (2 patients per month), the study will close to future accrual.

13.4 Analysis Plan

13.4.1 Phase II Analysis of Treatment Delivery, Toxicity Burden, and Patient Benefit

A two-stage analysis of the phase II component will be prepared after evaluable patient accrual has reached 13 and 39, respectively. Ineligible patients and patients without treatment data will not be evaluated. Successful completion of treatment is defined for this study as a patient receiving 19 of the 24 scheduled ALTENS treatments. Toxicity burden will be evaluated to identify patients not completing treatment due to excessive toxicity.

In addition to establishing feasibility, the phase II component also must show that 25% of patients have a treatment response (see Section 13.1.2.1) before the phase III component is pursued.

Patient accrual will not be suspended when the 13 patients needed for stage 1 analysis are entered because of the limited number of machines and the lack of major toxicities anticipated with ALTENS. Patient accrual will be suspended when the 39 patients needed for stage 2 analysis are entered on study.

For the first stage of the analysis, if 8 or fewer of all 13 evaluable patients successfully complete treatment, the phase II component will be stopped, and the phase III component will not be pursued. If all 13 patients successfully complete treatment, then feasibility of the treatment in a cooperative group setting will be established. Feasibility and treatment response results will be provided to NCI for approval to proceed with the phase III component.

If only 9 to 12 of 13 patients successfully complete treatment in the first stage, the second stage analysis will take place when 39 patients have accrued. If ≥ 31 of 39 patients are reported to have successfully completed treatment, then feasibility of the treatment in a cooperative group setting will be established. Feasibility and treatment response results will be provided to NCI for approval to proceed with the phase III component.

13.4.2 Interim Efficacy Analysis

The interim efficacy analysis for the phase III component will be reported to the RTOG Data Monitoring Committee (DMC) when 50% of eligible patients (65 patients) have been potentially followed for at least 9 months.

The analysis guidelines are detailed below. The significance level for the interim analysis is 0.003. The significance level for the final analysis is 0.049, preserving an overall significance level of 0.05.

13.4.3 Primary Endpoint

The primary endpoint of the phase III component is change in overall xerostomia burden, from baseline (pre-treatment) to 9 months from randomization, as measured by the University of Michigan 15-item Xerostomia Related Quality of Life Scale (XeQOLS).

All randomized patients that are eligible for the study will be included in the comparison of treatment arms, regardless of treatment compliance (intent-to-treat analysis).

Patients who die prior to the 9-month (from randomization) assessment will be analyzed separately. If these patients are not equally distributed between the two treatment arms, a sensitivity analysis will be conducted to determine the impact of the exclusion.

Imputation methods will be used to determine values for all live patients missing the 9-month (from randomization) assessment. Multiple imputation procedure provides a valid strategy for dealing with missing data sets, properly reflecting the uncertainty due to missing values. In the propensity score method, logistic regression model will be used to generate a propensity score for each live patient indicating the probability of that observation being missing given patient baseline XeQOLS score and treatment group. The observations are then grouped based on these propensity scores, and an approximate Bayesian bootstrap imputation is applied to each group.⁵⁶

The XeQOLS consists of four domains—physical functioning (4 items), pain/discomfort (4 items), personal/psychological functioning (4 items), social functioning (3 items). Each item is scored from 0 to 4 with higher scores indicating increased xerostomia burden. Each domain score is the average response within each domain. The overall score is the average response and ranges from 0 to 4. The change scores from baseline to 9 months from randomization are of interest.

We hypothesize that patients receiving ALTENS treatment (Arm 2) will experience a statistically significant different change in overall xerostomia burden than patients receiving pilocarpine treatment (Arm 1):

$$H_0: \Delta\mu_1 = \Delta\mu_2 \text{ vs. } H_A: \Delta\mu_1 \neq \Delta\mu_2$$

where $\Delta\mu_i$ is the mean change in xerostomia from baseline to 9 months for patients in arm i .

Treatment will be tested at the 0.05 significance level using analysis of covariance along with the stratification variables and the baseline XeQOLS score. If data normality assumptions are not met, nonparametric methods will be used to test the hypothesis.⁵⁷

13.4.4 Secondary Endpoints

13.4.4.1 Xerostomia Burden (XeQOLS)

Change in overall xerostomia burden, from baseline to 4, 6, 9, and 15 months from randomization as measured by the XeQOLS will be assessed in addition to the primary endpoint of 9 months from randomization.

In addition to comparing the change scores at specific time points, trends in overall xerostomia burden will be modeled using the general linear mixed-effect model.⁵⁸ The model allows for adjustments using stratification variable and other covariates of interest.

Additionally, change and overall trends in each of the four XeQOLS domains will be assessed.

13.4.4.2 Whole Salivary Production

Unstimulated (basal primed) and stimulated (citric acid primed) WSP will be measured by sialometry.

We hypothesize that patients receiving ALTENS treatment (Arm 2) will experience a statistically significant different change in WSP than patients receiving pilocarpine treatment (Arm 1):

$$H_0: \Delta\mu_1 = \Delta\mu_2 \text{ vs. } H_A: \Delta\mu_1 \neq \Delta\mu_2$$

where $\Delta\mu_i$ is the mean change in WSP from baseline to 9 months for patients in arm i .

The two-sided t-test will be used to test the hypothesis at the 0.05 significance level. If data normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis. In addition to comparing the change scores at 4, 6, 9, and 15 months, overall trends in WSP will be modeled using the general linear mixed-effect model. Missing data will be addressed similar to the primary endpoint.

13.4.4.3 Quality of Life (University of Washington Head and Neck Questionnaire)

The UWHNSS includes ten categories—pain, disfigurement, activity, recreation/entertainment, employment, eating, saliva, taste, speech, mucus/phlegm. Patient scores on the UWHNSS range from 0 to 100 with higher scores indicating declining quality of life. The change scores from pretreatment to 9 months will be compared between the treatment arms.

We hypothesize that patients receiving ALTENS treatment (Arm 2) will experience a statistically significant different change in QOL than patients receiving pilocarpine treatment (Arm 1):

$$H_0: \Delta\mu_1 = \Delta\mu_2 \text{ vs. } H_A: \Delta\mu_1 \neq \Delta\mu_2$$

where $\Delta\mu_i$ is the mean change in QOL from baseline to 9 months for patients in arm i.

The two-sided t-test will be used to test the hypothesis at the 0.05 significance level. If data normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis. In addition to comparing the change scores at 4, 6, 9, and 15 months from randomization, overall trends in WSP will be modeled using the general linear mixed-effect model. The model allows for adjustments using stratification variable and other covariates of interest. Missing data will be addressed similar to the primary endpoint.

13.4.4.4 Incidence of Adverse Events

Adverse events are reported according to CTCAE v3.0. Differences in incidence rates at 6 months from the completion of treatment between the two treatment arms will be tested using the two-sided chi-square test at the 0.05 significance level. Univariate logistic regression will be used to model the distribution of acute adverse events. Multivariate logistic regression will be used to model the distribution of acute adverse events, adjusting for covariates, including, but not limited to treatment arm, prior use of pilocarpine, time since completion of chemotherapy and/or radiation, and age. Both unadjusted and adjusted odds ratios and their respective 95% confidence interval will be computed.⁵⁹

13.5 Interim Reports to Monitor Study Progress

Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints.

The RTOG Data Safety and Monitoring Board (DSMB) will monitor the phase II component of the study for safety and feasibility. The RTOG Data Monitoring Committee (DMC) will monitor the phase III component of the study for safety and efficacy.

This study will also be monitored by the Clinical Data Update System (CDUS) version 3.0. Quarterly CDUS reports are submitted electronically.

13.6 Reporting the Initial Treatment Results

The primary hypothesis of this study is whether the use of ALTENS treatment will significantly change the overall xerostomia burden at 9 months from randomization compared to pilocarpine treatment. This final analysis will occur after each patient has been potentially followed for at least 9 months from randomization. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. The primary hypothesis of ALTENS treatment benefit will be compared using the paired t-test after imputing for missing values as specified in the analysis plan. Also, where feasible, treatment

comparisons with respect to all endpoints will be compared within each racial and ethnic category.

13.7 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 9709, a head and neck symptom management trial, the projected accrual by gender, race, and ethnicity is shown below:

Planned Gender and Minority Inclusion

	Gender		
	Females	Males	Total
Ethnic Category			
Hispanic or Latino	0	3	3
Not Hispanic or Latino	46	140	186
Ethnic Category: Total of all subjects	46	143	189
Racial Category			
Native American or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	11	14	25
Native Hawaiian or other Pacific Islander	0	1	1
White	35	127	162
Racial Category: Total of all subjects	46	143	189

REFERENCES

1. Dreizen S, Brown L, Handler S, Levy B. Radiation-induced xerostomia in cancer patients. *Cancer*. 38: 73-278, 1976.
2. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck: A consecutive study of salivary flow and patient discomfort. *Eur J Cancer*. 28: 457-462, 1992.
3. Greenspan D. Xerostomia: Diagnosis and management. *Oncology*. 10(3): 7-11, 1996.
4. Johnson J, Ferretti G, Nethery W, Valdez I, Fox P, Ng D. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *NEJM*. 329(6): 390-395, 1993.
5. LeVeque F, Montgomery M, Potter D, Zimmer M, Rieke J, Steiger B. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *J Clin Onc*.11(6): 1124-1131, 1993.
6. Warde P, O'Sullivan B, Aslandis J, Kroll B, Lockwood G, Math M. A phase III placebo controlled trial of oral pilocarpine in patients undergoing radiotherapy for head and neck cancer. *Int J Rad Oncol Biol Phys*. 54(1): 9-13, 2002.
7. Fisher J, Scott C, Scarantino C, et al. Phase III quality-of-life study results: Impact on patients' quality of life to reducing xerostomia after radiotherapy for head-and-neck cancer—RTOG 97-09. *Int J Rad Oncol Biol Phys*. 56:3, 832–836, 2003.
8. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Disease*. 6(1): 15-24, 2000.
9. Blom M, Dawidson I, Angmar-Mansson B. The effect of acupuncture on salivary flow rates in patients with xerostomia. *Oral Surg, Oral Med, Oral Path*. 73: 293-298, 1992.
10. Hodson DI, Haines T, Berry M. Symptomatic treatment of radiation-induced xerostomia in head and neck cancer patients. Head and Neck Cancer Disease Site Group. Practice guideline report; no. 5-5. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar [online update].
11. Blom M, Lundeberg T, Dawidson I, Angmar-Mansson. Effects on local blood flux of acupuncture stimulation used to treat xerostomia in patients suffering from Sjorgren's syndrome. *J Oral Rehab*. 20: 541-548, 1993.
12. Dawidson I, Angmar-Mansson B, Blom M, Theodorsson E, Lundeberg T. Sensory stimulation (acupuncture) increases the release of vasoactive intestinal polypeptide in the saliva of xerostomia sufferers. *Neuropeptides*.32: 543-548, 1998.
13. Andersson S. The functional background in acupuncture effects. *Scand J Rehab Med*. 29: 31-60, 1993.
14. Nishijo K, Mori H, Yosikawa K, Yazawa K. Decreased heart rate by acupuncture stimulation in humans via facilitation of cardiac vagal activity and suppression of cardiac sympathetic nerve. *Neuroscience Letter*. 227:165-168, 1997.
15. Haker E, Egekvist H, Bjerring P. Effect of sensory stimulation (acupuncture) on sympathetic and parasympathetic activities in healthy subjects. *J Autonomic Nervous System*. 79: 52-59, 2000.
16. Blom M, Dawidson I, Fernberg J, Johnson G, Angmar-Mansson B. Acupuncture treatment of patients with radiation-induced xerostomia. *Oral Oncol Eur J Cancer*. 32B: 182-190, 1996.
17. Johnstone P, Niemtzow R, Riffenburgh R. Acupuncture for xerostomia: Clinical update. *Cancer*. 94(4): 1151-1156, 2002.

REFERENCES (continued)

18. Johnstone P, Peng Y, May B, Inouye W, Niemtow R. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Rad Oncol Biol Phys.* 50(2): 353-357, 2001.
19. Cheng X. *Chinese Acupuncture and Moxibustion*. Beijing: Foreign Languages Press, 1987.
20. Fox E, Melzack R. Transcutaneous electrical stimulation and acupuncture: Comparison of treatment for low-back pain. *Pain.* 2:141-148, 1976.
21. Laitinen J. Acupuncture and transcutaneous electric stimulation in the treatment of chronic sacrolumbalgia and ischialgia. *Amer J Chinese Med.* 4:169-175, 1976.
22. Gadsby J, Flowerdew MW. Transcutaneous electrical nerve stimulation and acupuncture-like transcutaneous electrical nerve stimulation for chronic low back pain. *Cochrane Database Systematic Review.* 2(CD000210), 2000.
23. Pomeranz B, Niznik G. Codetron, a new electrotherapy device overcomes the habituation problems of conventional TENS devices. *Amer J Electromedicine.* First quarter: 22-26. 1987.
24. Cheng R, Pomeranz B. Electrotherapy of chronic musculoskeletal pain: Comparison of electroacupuncture and acupuncture-like transcutaneous electrical nerve stimulation. *Clin J Pain.* 2:143-149, 1987.
25. *Codetron Operational Manual*. EHM Rehabilitation Technology Inc., 1990.
26. Schneyer C, Humphreys-Beher M, Hall H, Jirakulsomchok D. Mitogenic activity of rat salivary glands after electrical stimulation of parasympathetic nerves. *Amer J Phys.* 264:935-938, 1993.
27. Weiss WJ, Brenman H, Katz P, Bennett J. Use of an electronic stimulator for the treatment of dry mouth. *J Oral Maxillofacial Surg.* 44:845-850, 1986.
28. Talal N, Quinn J, Daniels T. The clinical effects of electrostimulation on salivary function of Sjogren's syndrome patients: A placebo controlled study. *Rheumatology Int.* 12:43-45, 1992.
29. Wong R, Sagar S, Whelan T, Fargas-Babjak A. The use of acupuncture-like transcutaneous nerve stimulation (CODETRON) in the treatment of radiation-induced xerostomia in head and neck cancer patients treated with radical radiotherapy. *Int J Rad Oncol Biol Phys.* 57(2): 472-480, 2003.
30. Wong J. *A Manual of Neuro-Anatomical Acupuncture, Volume I: Musculo-Skeletal Disorders*. Toronto: The Toronto Pain and Stress Clinic Inc; 1999.
31. Browman G, Levine M, Hodson, Sathya J, Russell R, Skingley P, et al. The Head and Neck Radiotherapy Questionnaire: A morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. *J Clin Oncol.* 11: 863-872, 1993.
32. Eneroth CM, Henrikson CO, Jacobsson PA. Effect of fractionated radiotherapy on salivary gland function. *Cancer.* 30: 1147-1153, 1972.
33. Wescott WB, Mira JG, Starcke EN, Shannon IL, Thornby JI. Alterations in whole saliva flow rate induced by fractionated radiotherapy. *AJR Am J Roentgenol.* 130: 145-149, 1978.
34. Mossman K, Shatzman A, Chencharick J. Long-term effects of radiotherapy on taste and salivary function in man. *Int J Rad Oncol Biol Phys.* 8: 991-997, 1982.
35. Mira JG, Wescott WB, Starcke EN, Shannon IL. Some factors influencing salivary function when treating with radiotherapy. *Int J Rad Oncol Biol Phys.* 7: 535-541, 1981.

REFERENCES (continued)

36. Busuttill A. Irradiation-induced changes in human salivary glands. *Clin Otolaryngol.* 2:199–206, 1977.
37. Frank RM, Herdly J, Philippe E. Acquired dental defects and salivary gland lesions after irradiation for carcinoma. *J Am Dent Assoc.* 70: 868–883, 1965.
38. Scrimger R, Kanji A, Parliament M, Warkentin H, Field C, Jha N, Hanson J. Correlation between saliva production and quality of life measurements in head and neck cancer patients treated with intensity-modulated radiotherapy. *Am J Clin Oncol* 30 (3), 2007
39. Scarantino C, LeVeque F, Swann RS, White R, Schulsinger A, Hodson DI, Meredith R, Foote R, Brachman D, Lee N. Effect of pilocarpine during radiation therapy: results of RTOG 97-09, a phase III randomized study in head and neck cancer patients. *J Support Oncol* 4 (5): 252-258, 2006
40. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. *Biometrics.* 38: 143-151, 1982.
41. EaST. A software package for the design and interim monitoring of group sequential clinical trials. CYTEL Software Corporation. Cambridge, MA. 199
42. Hassan SJ, Weymuller EA, Jr. Assessment of quality of life in head and neck cancer patients. *Head & Neck.* 15(6): 485-496, 1993.
43. Henson BS, Inglehart MR, Eisbruch A, Ship, JA. Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncology.* 37: 84-93, 2001.
44. Ship JA, Eisbruch A, D'Hondt E, Jones RE. Parotid sparing study in head and neck cancer patients receiving bilateral radiation therapy: 1 year results. *J Dent Res.* 76: 807-13, 1997.
45. Jones RE, Takeuchi T, Eisbruch A, Hazuka M, Ship JA. Ipsilateral parotid sparing study in head and neck cancer patients receiving radiation therapy: One year results. *Oral Surg Oral Med Oral Path Oral Radiol Endo.* 81: 642-8, 1996.
46. Eisbruch A, Ship JA, Martel MK, Ten Haken RK, Marsh LH, Wolf GT, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: Techniques and early results. *Int J Rad Oncol Biol Phys.* 36(2): 469-80, 1996.
47. Eisbruch A, Marsh LH, Martel MK, Ship JA, Ten Haken R, Pu AT, et al. Comprehensive irradiation of head and neck cancer using conformal multisegmental fields: Assessment of target coverage and noninvolved tissue sparing. *Int J Rad Oncol Biol Phys.* 41(3): 559-68, 1998.
48. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity modulated irradiation of head and neck cancer. *Int J Rad Oncol Biol Phys.* 45(3): 577-87, 1999.
49. Henson BS, Eisbruch A, D'Hondt E, Ship JA. Two-year longitudinal study of parotid salivary flow rates in head and neck cancer patients receiving unilateral neck parotid-sparing radiotherapy treatment. *Oral Oncol.* 35(3): 234-41, 1999.
50. D'Hondt E, Eisbruch A, Ship JA. The influence of pre-radiation salivary flow rates and radiation dose on parotid salivary gland dysfunction in patients receiving radiotherapy for head and neck cancers. *Spec Care Dent.* 18(3): 102-8, 1998.
51. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. *J Amer Dent Assoc.* 115(4): 581-4, 1987.
52. Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis.* 27:365-375, 1974.

REFERENCES (continued)

53. Wong R, Jones G, Sagar S, Fargas-Babjak A, Whelan T. A phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation in the treatment of radiation-induced xerostomia in head and neck cancer patients treated with radical radiotherapy. *Int J Rad Oncol Biol Phys.* 57(2): 472-480, 2003.
54. Fleming T. One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 1982; 38:143-151.
55. EaST. A software package for the design and interim monitoring of group sequential clinical trials. CYTEL Software Corporation. Cambridge, MA. 2005.
56. Yuan, Yang C. Multiple Imputation for Missing Data: Concepts and New Developments, SAS Institute Inc, Rockville, MD, 2002.
57. Randles RH, Wolfe DA. Introduction to the Theory of Nonparametric Statistics. New York: John Wiley & Sons, 1979.
58. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. New York: Springer Verlag, Inc; 2000.
59. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley & Sons, 2000.

APPENDIX I

RTOG 0537

Informed Consent Template for Chemoprevention Trials (English Language)

A Phase II/III Study Comparing Acupuncture-like Transcutaneous Electrical Nerve Stimulation (ALTENS) Versus Pilocarpine in Treating Early Radiation-Induced Xerostomia

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have completed radiation therapy with or without chemotherapy for head and neck cancer and you have dry mouth due to a lack of saliva (xerostomia) as a result of radiation therapy.

Why is this study being done?

Dry mouth (xerostomia) is a common side effect of radiation therapy for head and neck cancer. There are two parts to this study. **The part of the study you participate in depends on when you join the study. You will participate in Part A or Part B, but not both.**

Part A: The purpose of this part of the study is to find out what effects, good and/or bad, ALTENS therapy (**A**cupuncture-**L**ike **T**ranscutaneous **E**lectrical **N**erve **S**timulation) has on patients treated for head and neck cancer and dry mouth (xerostomia). ALTENS therapy is like acupuncture treatment, but the acupuncture points are stimulated with mild electrical stimulation without the use of needles. Currently, ALTENS therapy is not a standard treatment for radiation-induced dry mouth and is considered investigational. The ALTENS therapy will be given with a machine called a Codetron[®]. Although this machine has not been approved by the FDA for the treatment of dry mouth (xerostomia), it has been approved by the FDA for managing certain types of pain.

If Part A patients complete their ALTENS therapy (have at least 19 of the scheduled 24 treatments) without severe side effects, the second part of the study, or Part B, will begin.

Part B: The purpose of this part of the study is to compare the effects, good and/or bad, of ALTENS therapy to the use of the drug pilocarpine on patients treated for head and neck cancer and dry mouth to find out which is better. Pilocarpine is the only drug approved by the FDA for radiation-induced dry mouth. In Part B, participants will get either the ALTENS treatment or the drug pilocarpine.

How many people will take part in the study?

About **45** people will take part in the first part of this study. About **144** people will take part in the second part of this study.

What will happen if I take part in this research study?

Before you begin the study...(8/26/09)

You will need to have the following exams, tests or procedures to find out if you can be in the study. These procedures are part of regular cancer care. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Complete history and physical examination
- ENT (head and neck) physical examination including a nasopharyngeal scope if indicated
- CT scan or MRI scan if indicated
- Salivary production assessment to determine if the amount of salivary production meets the requirement for joining the study. You will be asked to provide saliva in a small dry plastic container for measurement of the amount of saliva you are able to produce within a 5-minute time span without swallowing.
- Serum pregnancy test for women of childbearing potential

Part A treatment:

You will receive ALTENS therapy two times a week for 12 weeks. In ALTENS therapy, an electronic device that is designed to stimulate particular points or nerves in the body through electrodes placed on the skin will be used. There will be no needle used. The procedure of each treatment will consist of placing seven electrodes on a set of points/nerves of the body selected in advance. Each electrode will be turned on randomly, one at a time, for stimulation by the machine. Each stimulation lasts 10 seconds. Each treatment will take about 20 minutes. You will be evaluated for side effects two times a week at each treatment visit.

Also, you will be asked to complete 1 questionnaire: *The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS)* before your first treatment and at 6 months after study entry. It takes about 5 minutes to fill out the XeQOLS questionnaire.

Part B treatment:

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in group 1, you will take one pilocarpine pill by mouth (5 mg) three times a day for 12 weeks. You will be evaluated for side effects once every 2 weeks during treatment.

If you are in group 2, you will receive ALTENS therapy two times a week for 12 weeks. In ALTENS therapy, an electronic device that is designed to stimulate particular points or nerves in the body through electrodes placed on the skin will be used. There will be no needle used. The procedure of each treatment will consist of placing seven electrodes on a set of points/nerves of the body selected in advance. Each electrode will be turned on randomly, one at a time, for stimulation by the machine. Each stimulation lasts 10 seconds. Each treatment will take about 20 minutes. You will be evaluated for side effects two times a week at each treatment visit.

In Part B treatment, participants in both groups will be asked to do the following:

Prior to first treatment:

- Complete 1 questionnaire: *The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS)*. It takes about 5 minutes to fill out the XeQOLS questionnaire.
- Provide saliva in a small dry plastic container for measuring the amount of saliva you are able to produce within a 5-minute time span without swallowing

During treatment:

Provide information on the use of salivary comfort agents and (for group 1 participants only) information on pilocarpine usage in a daily “pill diary”. In the pill diary, group 1 participants will be asked to write down how many pills they have taken each day.

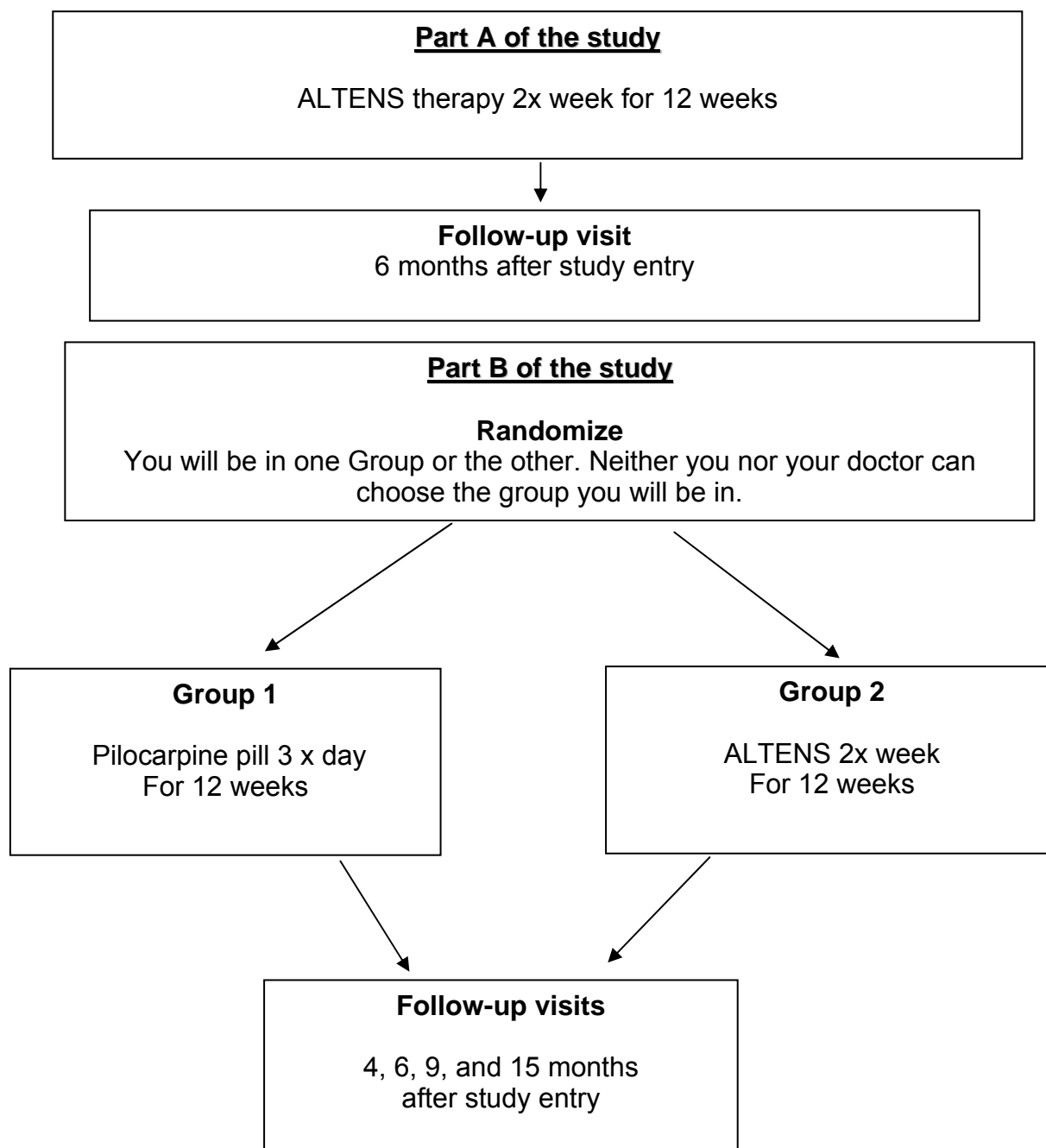
When you are finished with ALTENS therapy or taking pilocarpine:

You will be seen in follow-up visits at 4, 6, 9, and 15 months after study entry and will be asked to:

- Provide saliva in a small dry plastic container for measuring the amount of saliva you are able to produce within a 5-minute time span without swallowing
- Complete 1 questionnaire: *The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS)*
- Provide information on the use of salivary comfort agents.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

The part of the study you participate in depends on when you join the study. You will participate in Part A or Part B, but not both.

(8/26/09) Patients taking part in Part A: You will receive treatment (ALTENS) for 12 weeks. You will be seen in a follow-up visit with your study doctor 6 months after study entry.

Patients taking part in Part B: You will receive treatment (either ALTENS or pilocarpine) for 12 weeks. You will be seen in follow-up visits with your study doctor 4, 6, 9, and 15 months after study entry.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop ALTENS treatment or taking the pilocarpine. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the pilocarpine include those which are:

Likely

- sweating
- headache

Less Likely

- nausea
- rhinitis (inflammation of the mucous membrane of the nose)
- chills
- vasodilatation ("flushing", or redness of the face and neck)
- urinary frequency
- dizziness
- asthenia (lack/loss of strength)
- cough
- diarrhea
- palpitation
- tremor
- skin rash
- muscle ache
- blurred vision

Rare but serious

- hypersensitive reactions affecting blood pressure, skin, or airway

Risks and side effects related to ALTENS include those which are:

Likely

- dull ache at the points of stimulation during treatment
- bruising at the points of stimulation

Less Likely

- skin allergy reaction

Reproductive risks: Pregnant females are not eligible to participate in this study because ALTENS treatment may affect the uterus. You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope ALTENS will be more useful in treating dry mouth (xerostomia) than pilocarpine with less side effects and with longer lasting effects, there is no proof of this yet. We do know that the information from this study will help doctors learn more about ALTENS as a treatment for this side effect of cancer therapy. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your dry mouth without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.

What are the costs of taking part in this study?

The Codetron[®] machines will be provided free of charge to institutions/centers taking part in this study through funding from the Office of Complementary and Alternative Medicine, (OCCAM) of the National Cancer Institute.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [*investigator's name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from your institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number).

Please note: This section of the informed consent form is about additional research, a quality of life questionnaire, that patients taking part in Part B of the main study are being asked to fill out. You may take part by filling out the questionnaire if you want to. You can still be a part of Part B of the main study even if you say “no” to filling out the quality of life questionnaire. Please mark your choice below.

For patients taking part in Part B of the study: Quality of Life Questionnaire

We want to know your view of how your life has been affected by cancer and its treatment, including the experience of dry mouth. If you take part in Part B of the main study, you will be asked to complete 1 questionnaire: *The Head and Neck Symptom Scale of the University of Washington Quality of Life Questionnaire (UWHNSS)* prior to the start of treatment and at 4, 6, 9, and 15 months from study entry. It takes about 7-10 minutes to fill out the UWHNSS questionnaire.

This quality of life questionnaire looks at how you are feeling physically and emotionally after you have completed study treatment. This information will help doctors better understand what effects the pilocarpine and ALTENS treatment have on people who have been treated for head and neck cancer. In the future, this information may help patients and doctors as they decide which treatments to use to help people with head and neck cancer.

Please circle your answer.

I agree to fill out the Quality of Life Questionnaire.

YES

NO

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [*insert total of number of pages*] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II (8/26/09)

STUDY PARAMETER TABLE: See Sections 3.0, 11.2, and 11.3 for details

	Pre-Treatment (may be required for eligibility)	During Treatment For Arm 1: once every 2 weeks for 12 weeks For Arm 2: twice per week for 12 weeks	Follow-Up (4, 6, 9, 15 months from study entry)
History/physical	X		
ENT exam	X		
CT or MRI scan	X		
Performance status	X		
Whole Salivary Production (WSP) [L4]	X		Phase III only
XeQOLS (QF)	X		At 6 months only during Phase II
UWHNSS (HP)	Phase III only		Phase III only
Serum pregnancy test	X		
Usage of salivary comfort agents		X	X
Pilocarpine diaries		Arm 1 only	
Informed consent	X		
Adverse event evaluation*	X	X	X

*And as needed based on reporting requirements

APPENDIX III (8/26/09)

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction**
- 1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
- 4 Completely disabled. Cannot carry on self-care. Totally confined to bed**
- 5 Death**

APPENDIX IV

*University of Michigan Xerostomia- Related Quality of Life Scale (XeQOLS) [15 Item]

These questions are concerned with your oral health and how it affects your life. Please answer the questions by checking the box that describes best how true each statement has been for you during the **past 7 days**:

1. My mouth/throat dryness limits the kinds or amounts of food I eat.

Not at all A little Somewhat Quite a bit Very Much

2. My mouth/throat dryness causes discomfort.

Not at all A little Somewhat Quite a bit Very Much

3. My mouth/throat dryness causes a lot of worry or concern.

Not at all A little Somewhat Quite a bit Very Much

4. My mouth/throat dryness keeps me from socializing (going out).

Not at all A little Somewhat Quite a bit Very Much

5. My mouth/throat dryness makes me uncomfortable eating in front of other people.

Not at all A little Somewhat Quite a bit Very Much

6. My mouth/throat dryness makes me uncomfortable speaking in front of other people.

Not at all A little Somewhat Quite a bit Very Much

7. My mouth/throat dryness makes me nervous.

Not at all A little Somewhat Quite a bit Very Much

8. My mouth/throat dryness makes me concerned about the looks of my teeth and mouth.

Not at all A little Somewhat Quite a bit Very Much

9. My mouth/throat dryness keeps me from enjoying life.

Not at all A little Somewhat Quite a bit Very Much

10. My mouth/throat dryness interferes with my daily activities.

Not at all A little Somewhat Quite a bit Very Much

APPENDIX IV (Continued)

11. My mouth/throat dryness interferes with my intimate relationships.

- Not at all A little Somewhat Quite a bit Very Much

12. My mouth/throat dryness has a bad effect on tasting food.

- Not at all A little Somewhat Quite a bit Very Much

13. My mouth/throat dryness reduces my general happiness with life.

- Not at all A little Somewhat Quite a bit Very Much

14. My mouth/throat dryness affects all aspects of life.

- Not at all A little Somewhat Quite a bit Very Much

15. If you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?

- Delighted Mostly Satisfied Mixed: equally satisfied/dissatisfied Mostly dissatisfied Terrible

*Henson BS, Inglehart MR, Eisbruch A, Ship JA. (2001).

APPENDIX V

The Head and Neck Symptom Scale of the University of Washington Quality of Life Questionnaire (UWHNSS)

Each of the following items lists different numbered statements. Think about what each statement says, then place a circle around the one statement that most closely describes how you have been feeling during the past week, including today. Please circle only one statement for each item.

Example: In the past week and today, if you have not experienced any pain from your cancer or treatment, you would circle sentence 10 for Item I (I have no pain).

I PAIN (General)

A General

- 10 I have no pain.
- 20 There is mild pain not needing medication.
- 30 I have moderate pain - requires regular medication (codeine or non-narcotic).
- 40 I have severe pain controlled only by narcotics.
- 50 I have severe pain not controlled by narcotics.

B Mouth

- 10 I have no pain in my mouth.
- 20 I have mild pain but it is not affecting my eating.
- 30 I have moderate pain that is affecting my eating.
- 40 I have severe pain and need medication in order to eat.
- 50 I have severe pain and cannot eat even with the medication.

C Throat

- 10 I have no pain in my throat.
- 20 I have mild pain but it is not affecting my eating.
- 30 I have moderate pain that is affecting my eating.
- 40 I have severe pain and need medication in order to eat.
- 50 I have severe pain and cannot eat even with the medication.

II DISFIGUREMENT

- 10 There is no change in my appearance.
- 20 The change in my appearance is minor.
- 30 My appearance bothers me but I remain active.
- 40 I feel significantly disfigured and limit my activities due to my appearance.
- 50 I cannot be with people due to my appearance.

III ACTIVITY

- 10 I am as active as I have ever been.
- 20 There are times when I can't keep up with my old pace, but not often.
- 30 I am often tired and I have slowed down my activities although I still get out.
- 40 I don't go out because I don't have the strength.
- 50 I am usually in a bed or chair and don't leave home.

IV RECREATION / ENTERTAINMENT

- 10 There are no limitations to recreation at home and away from home.
- 20 There are a few things I can't do but I still get out and enjoy life.
- 30 There are many times when I wish I could get out more but I'm not up to it.
- 40 There are severe limitations to what I can do, mostly I stay home and watch TV.
- 50 I can't do anything enjoyable.

APPENDIX V (Continued)

- V EMPLOYMENT
- 10 I work full time.
 - 20 I have a part time but permanent job.
 - 30 I only have occasional employment.
 - 40 I am unemployed.
 - 50 I am retired (circle one below):
 - 51 not related to cancer treatment
 - 52 due to cancer treatment
- VI EATING
- A Chewing
- 10 I can chew as well as ever.
 - 20 I have slight difficulty chewing solid foods.
 - 30 I have moderate difficulty chewing solid foods.
 - 40 I can only chew soft foods.
 - 50 I cannot chew soft foods.
- B Swallowing
- 10 I swallow normally.
 - 20 I cannot swallow certain solid foods.
 - 30 I can only swallow soft foods.
 - 40 I can only swallow liquid foods.
 - 50 I cannot swallow.
- VII SALIVA
- A Amount
- 10 I have a normal amount of saliva.
 - 20 I have a mild loss of saliva.
 - 30 I have a moderate loss of saliva.
 - 40 I have a severe loss of saliva.
 - 50 I have no saliva.
- B Consistency
- 10 My saliva has normal consistency.
 - 20 My saliva is slightly thicker.
 - 30 My saliva is moderately thicker.
 - 40 My saliva is extremely thicker.
 - 50 I have saliva that dries in my mouth and/or on my lips.
- VIII TASTE
- 10 I can taste food normally.
 - 20 I can taste most foods normally.
 - 30 I can taste some foods normally.
 - 40 I can taste few foods normally.
 - 50 I cannot taste any foods normally.
- IX SPEECH
- 10 My speech is the same as always.
 - 20 I have difficulty with saying some words, but can be understood over the phone.
 - 30 I have moderate difficulty saying some words, and cannot use the phone.
 - 40 Only my family and/or friends can understand me.
 - 50 I cannot be understood.

APPENDIX V (Continued)

- X MUCUS OR PHLEGM
- A Amount
- 10 I have a normal amount of mucus.
 - 20 I have a mild amount of mucus.
 - 30 I have a moderate amount of mucus.
 - 40 I have a severe amount of mucus.
 - 50 I have no mucus.
- B Consistency
- 10 My mucus has normal consistency
 - 20 My mucus is slightly thicker.
 - 30 My mucus is moderately thicker.
 - 40 My mucus is extremely thicker.
 - 50 I have no mucus.

Comments: _____

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Patient's Signature: _____ Date: ____/____/____