NRG ONCOLOGY

NRG-HN006
(ClinicalTrials.gov NCT #04333537)

RANDOMIZED PHASE II/III TRIAL OF SENTINEL LYMPH NODE BIOPSY VERSUS ELECTIVE NECK DISSECTION FOR EARLY-STAGE ORAL CAVITY CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
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Protocol Agent

Imaging Agents	Supply	NSC #	IND #	IND Sponsor
99mTc-tilmanocept (Lymphoseek)	Commercial	N/A	Study Exempt from IND Requirements per 21 CFR 312.2(b)	N/A
99mTc-sulfur colloid	Commercial	N/A	Study Exempt from IND Requirements per 21 CFR 312.2(b)	N/A

Participating Sites

☒ U.S.
☒ Canada
☐ Approved International Member Sites

Document History

	Version Date
	Month, Day, Year
Initial	June 10, 2020

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<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
Regulatory Submission Portal:
(Sign in at www.ctsu.org,
and select Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u>
Contact the Study Data Managers of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
</table>

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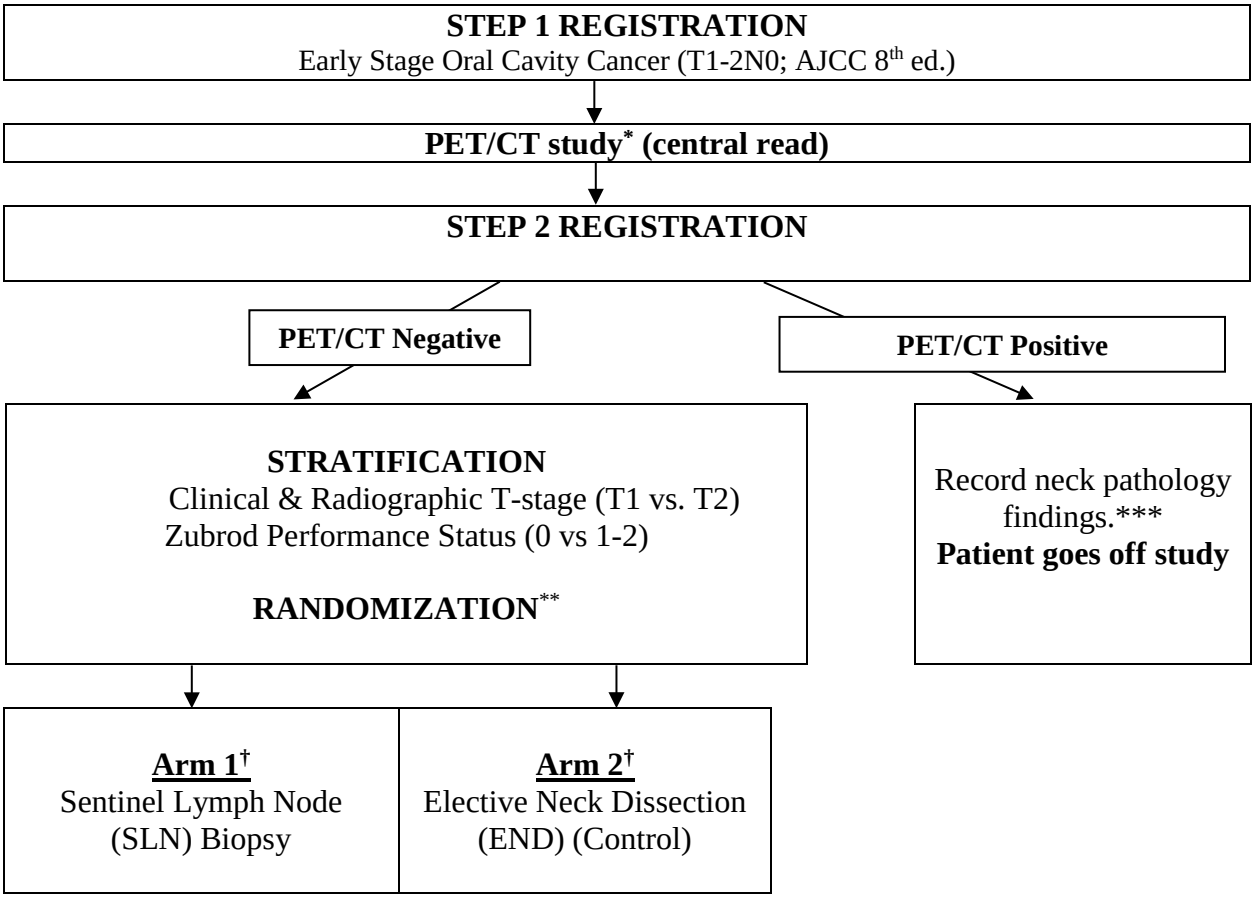
SCHEMA



* See Section 3.1 for details
** Randomization is 1:1
*** See Section 8.3 (and data submission table on the CTSU website) for details
† See Section 5 treatment details

Required Sample Size (Phase II: 228)
Required Sample Size (Phase III: 618 total, including enrolled patients from Phase II)

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Phase II: To determine if patient-reported neck and shoulder function and related quality of life (QOL) at 6 months after surgery using the Neck Dissection Impairment Index (NDII) is superior with Sentinel Lymph Node (SLN) biopsy compared to Elective Neck Dissection (END) for treatment of early-stage oral cavity squamous cell carcinoma (OCSCC) (cT1-2N0).

1.1.2 Phase III:

- To determine if disease-free survival (DFS) is non-inferior with SLN biopsy compared to END for treatment of early-stage OCSCC (cT1-2N0).
- To determine if patient-reported neck and shoulder function and related QOL at 6 months after surgery using NDII is superior with SLN biopsy compared to END for treatment of early-stage OCSCC (cT1-2N0).

1.2 Secondary Objectives

1.2.1 To compare patterns of failure (local-regional relapse and distant metastasis) between surgical arms.

1.2.2 To measure and compare overall survival (OS) between surgical arms.

1.2.3 To measure and compare the toxicity of the two surgical arms.

1.2.4 To measure longitudinal patient-reported neck and shoulder function and related QOL between surgical arms, using the following instruments:

- Neck Dissection Impairment Index (NDII)
- Abbreviated Disabilities of the Arm, Shoulder and Hand (QuickDASH)
- Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N)

1.2.5 To assess the length of hospitalization, post-operative drain placement, and operative morbidity between arms.

1.2.6 To estimate the negative predictive rate of FDG PET/CT for N0 neck in patients with T1 and T1-2 oral cavity squamous cell cancer (OCSCC) patients in the END arm.

1.2.7 To assess nodal metastases rates between arms.

1.2.8 To assess the pathologic false omission rate (FOR) in the SLN biopsy arm.

1.2.9 To determine if patient-reported neck and shoulder function and related QOL at 6 months after surgery using the NDII is superior with the SLN biopsy compared to the END in low-risk patients.

1.3 Exploratory Objectives

1.3.1 To compare changes in patient-reported outcomes (EQ-5D-5L) between surgical arms.

1.3.2 To collect biospecimens for future translational science studies.

1.3.3 To assess the DFS between arms in low-risk patients.

2. BACKGROUND

2.1 Oral Cavity Cancer

Head and neck cancer (HNC) is among the most common malignancies in the United States and globally, with more than 630,000 new cases and 350,500 deaths annually (Vigneswaran 2014). OCSCC represents a leading form of HNC worldwide. Definitive management of HNC at initial disease presentation offers patients the best opportunity for locoregional control and overall survival. However, despite advances in the treatment of HNC and understanding its causes [including human papillomavirus (HPV)], outcomes remain poor. Except for HPV-associated oropharyngeal cancer, 5-year DFS is generally less than 50% (Bernier 2004; Cooper 2004; Ang 2010).

2.2 Occult Nodal Metastasis

Patients with early-stage OCSCC (T1-T2), using the American Joint Commission on Cancer, AJCC 8th edition staging, who are clinically and radiographically node-negative (N0) may still harbor occult cervical metastases in 20%-30% of cases (Shah 1990; Byers 1997; Sparano 2004). Current management of these patients often includes END, even though 70%-80% of patients will be pathologically N0. An END involves comprehensive removal of lymph nodes in the neck, while preserving uninvolved normal tissue structures, including the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve (cranial nerve XI). Thus, many patients have comprehensive surgical management of the regional cervical nodal basin even though the majority of those necks will not contain disease.

Many patients will thus be exposed to potential morbidity related to neck dissection, due to mobilization/trauma to the spinal accessory nerve resulting in decreased shoulder mobility and strength. Such injuries have been correlated with patient-reported QOL tools, including the validated instrument, the NDII (van Wilgen 2004; Taylor 2002; Chepeha 2002; Gallagher 2015).

2.3 Sentinel Lymph Node Mapping and Biopsy

Sentinel lymph node (SLN) biopsy represents a less invasive surgical method for assessing cervical nodal metastasis, while potentially decreasing patient morbidity as compared to END. For SLN biopsy, the patient's primary tumor is injected with a radiotracer (e.g., 99mTc sulfur colloid or 99mTc-tilmanocept) that travels along the lymphatic channels to the cervical lymph nodes. The first echelon of nodes that are localized by the radiotracer represent the lymph nodes most likely to harbor metastatic disease. Following this mapping procedure, the SLN(s) can be biopsied as part of the surgical procedure when the primary tumor is excised. Typically, a smaller incision(s) is made in the neck and less surgical manipulation is required to remove a small number of lymph nodes rather than to dissect the entire lymph node basin (as performed during END). Pathological examination is then focused on a few nodes with the highest likelihood to harbor disease, rather than on a large number of nodes harvested from END. A recent study suggested that pathological assessment of all of the cervical lymph nodes from END may underestimate true clinical disease status; this multi-institutional retrospective assessment of clinically N+, but pathologically N0 (cN+/pN0) neck dissection specimens found a false-negative rate (FNR) of 15% (Amit 2014). Serial

sectioning of a limited number of SLN(s) and immunohistochemistry studies (e.g., cytokeratin AE 1/3) allow for comprehensive examination for metastatic disease deposits. Hence, a smaller, more focused surgical procedure (SLN biopsy) may produce more accurate pathologic findings than the larger surgical resection (END), in addition to potentially reducing side effects.

Effective mapping of the SLN(s) requires a radiotracer that can target the lymph nodes at highest risk for harboring metastatic disease. Traditional agents such as 99mTc-sulfur colloid and 99mTc-colloid albumen (Nanocoll) travel through the lymphatic channels by passive diffusion to the lymph nodes. 99mTc-tilmanocept (Lymphoseek) is specifically targeted to the CD206 (mannose receptor) expressed on reticuloendothelial cells, that reside within the lymph nodes. Although there are no direct comparisons of the performance of these radiotracers, the FNR for 99mTc-sulfur colloid was 9.8% in a phase II study performed in the US (ACOSOG Z0360) comparing SLN biopsy findings to those from the immediate completion neck dissection, and 14% for 99mTc-colloid albumen in the prospective SENT trial performed in the EU (Civantos 2010; Schilling 2015).

By contrast, 99mTc-tilmanocept demonstrated a 2.56% FNR in the phase III FDA registration trial (NEO3-06) (Agrawal 2015). Given the lack of direct comparison among the various radiotracer agents, this trial will permit the use of 99mTc-sulfur colloid and 99mTc-tilmanocept in this study. We will monitor SLN pathology findings for quality assurance, as previously done in ACOSOG Z0306 and NEO3-06.

2.4 Optimal Timing for a Clinical Trial Comparing SLN Biopsy and END

A number of factors have now converged to allow for a definitive study to compare SLN biopsy versus END for assessment of the clinically negative neck patients with early-stage OCSCC: 1) The recent trial comparing END versus therapeutic neck dissection (TND) demonstrated the need for active management of the neck in these patients (D'Cruz 2015); 2) SLN biopsy allows for potentially less invasive and less morbid assessment of neck disease status while focusing pathological analysis on those nodes most likely to harbor disease; and 3) The recent FDA approval of 99mTc-tilmanocept for oral cavity cancer represents a technological advance that may improve the FNR of SLN relative to END. Thus, a decisive phase III randomized prospective clinical trial comparing SLN biopsy versus END can focus the HNC clinical and research community and resources on establishing the standard of care for management of the neck in early-stage OCSCC. The clinical need and value of a SLN biopsy versus END trial has been stated in a number of recent publications (D'Cruz 2015; Cramer 2018; Koyfman 2019).

2.5 Rationale for FDG PET/CT Scans

The treatment strategy for head and neck squamous cell carcinoma (HNSCC) patients without evidence of lymph node involvement (N0 neck) has long been an issue of debate. Retrospective studies report a 20%–30% incidence of occult metastases across all primary locations (Woolgar 1999, Pillsburg and Clark 1997). FDG PET/CT is reliable in detecting lymph node metastases in HNSCC (Ryu 2016, Sun 2015). It has been reported that PET/CT imaging is cost-effective for staging N0 neck patients (Hollenbear 2001). When PET/CT achieves a high negative predictive value (NPV) for the N0 neck, it may

avoid unnecessary therapy for the neck, which will reduce expense, patient time lost from work, and treatment-related morbidities.

The primary analysis of the recently concluded ACRIN 6685 trial (Lowe 2019) (T2-T4 oral cavity, larynx and pharynx, included PET/CT scans and pathology for 268 clinical N0 neck sides from 210 participants. For visual assessment, the NPV of FDG PET/CT specific for N0 neck was 0.87 (95%CI, 0.8 to 0.93). For dichotomized SUVmax, the NPVs specific to the nodal basins were 0.94 (95% CI, 0.93 to 0.95) and 0.937 (95%CI, 0.928 to 0.952), at pre-specified cutoffs of 2.5 and 3.5, respectively. In addition, surgical treatment plans were changed in 21% of this group of patients based on PET/CT results. These findings suggest that FDG PET/CT leads to improved, tailored treatment for the clinical N0 neck. Neck dissection could potentially be avoided in cases with a negative PET/CT.

The primary analysis of ACRIN 6685 included 61.7% of T2 tumors with a NPV of 0.87 for visual analysis and 0.94 for semiquantitative SUVmax cutoff. For oral cavity tumors (64.1%), the NPV for visual analysis was 0.89 and 0.94 for SUVmax cutoff. As this trial population will include only T1 and T2 oral cavity tumors, it is anticipated that the NPV of FDG PET/CT for N0 neck in this cohort would be higher due to lesser prevalence of neck nodal metastases than observed in ACRIN 6685 cohort.

2.6 Rationale for Quality of Life (QOL) and Patient Reported Outcomes

Shoulder and neck pain and dysfunction can occur after a neck dissection for head and neck cancer, and is attributable to injury or sacrifice of the spinal accessory nerve (cranial nerve CNXI) during a neck dissection. Injury to the CN XI, may result in denervation of the trapezius muscle, which reduces the ability to raise the shoulder and is associated with shoulder and neck pain, functional loss, and worse QOL. In a review of 75 studies of head and neck cancer patients undergoing neck dissection, the prevalence of shoulder pain was 10%-100% after a radical neck dissection, 0-100% after a modified radical neck dissection, and 2%-25% after a selective neck dissection. Reduced range of motion after neck dissection ranged from 1%-13% (Gane 2017). Additionally, post-operative radiation may cause neck fibrosis resulting in reduced neck mobility, decreased neck muscle strength, risk for injury to the brachial plexus, and lymphedema; all of these normal tissue toxicities may impact function of the upper extremity, shoulder and neck, pain and health-related QOL. While preserving the spinal accessory nerve reduces the risk of developing musculoskeletal upper extremity complications, it does not eliminate the risk completely. The true extent of injury from a neck dissection and impact on shoulder and upper limb function and QOL is not fully understood. The QOL hypothesis of this study is that a less invasive surgical technique for SLN biopsy, compared to END, will reduce the risk of nerve and muscle injury during neck dissection, thereby resulting in less shoulder and neck related dysfunction and less impairment of shoulder-related QOL. The Neck Dissection Impairment Index (NDII) will be used to evaluate shoulder related QOL as a “go-no-go” decision to move forward into a phase III study, as described in the statistical section (Section 14).

2.7 Defining the Risk Groups

Risk groups for OCSCC patients escalate depending upon the need for adjuvant radiation therapy (RT) or adjuvant RT with concurrent chemotherapy. The low-risk OCSCC patients are defined as pathologic T1-2N0 (AJCC 8th edition staging) with no adverse features (i.e. close/positive margins (<5 mm), perineural invasion (PNI), lymphovascular space invasion (LVSI), and positive lymph nodes). Intermediate-risk OCSCC have PNI, LVSI, and/or close margin(s) of resection (cancer within 5 mm of a surgical margin) in the primary tumor or positive nodal status. High-risk OCSCC have a positive surgical margin or lymph node(s) extracapsular spread. Final risk classification will depend upon additional pathological data from the surgical excision of the primary tumor and the nodal status after END or SLN biopsy.

Review of the prospective SENT trial cohort reveals 60% (246/415) of patients were within the low-risk group with a 2-yr DFS of 96.9% (95% CI = 94.7-99.2%) (Schilling 2015 and personal communication with C. Schilling/M. McGurk). Retrospective review of a T1-2 lateral oral tongue patient cohort at MD Anderson Cancer Center (n=299) revealed a low-risk group comprising 70.6% (211/299) of patients with a 2-yr DFS of 89.8% (95% CI = 81.3-94.5%) (personal communication M. Zafereo). The retrospective cohort from Memorial Sloan Kettering Cancer Center and Princess Margaret Hospital informing AJCC TNM classification (8th edition) had 54.9% (531/967) of patients in the low-risk group with 2-yr DFS at 85% (81.9-88.1%) (Lydiatt 2017 and personal communication S. Patel). Finally, the retrospective Multi-institutional Oral Cavity Collaboration Conference (MOCCC) cohort was comprised of 75.5% (176/233) patients in the low-risk group with a 2-yr DFS of 75.6% (69.2%-82%) (personal communication N. Dunlap/S. Koyfman).

3 ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistics/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 REGISTRATION

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma of the oral cavity, including the oral (mobile) tongue, floor of mouth (FOM), mucosal lip, buccal mucosa, lower alveolar ridge, upper alveolar ridge, retromolar gingiva (retromolar trigone; RMT), or hard palate prior to registration;

3.1.2 Appropriate stage for study entry (T1-2N0M0; AJCC 8th ed.) based on the following diagnostic workup:

- History/physical examination within 42 days prior to registration;
- Imaging of head and neck within 42 days prior to registration;
  - PET/CT scan or contrast neck CT scan, or gadolinium-enhanced neck MRI or lateral and central neck ultrasound; CT portion of the PET/CT must be of diagnostic quality.
  - Chest imaging with either a chest x-ray, CT chest scan (with or without contrast) or PET/CT (with or without contrast) within 42 days prior to registration.

3.1.3 Surgical assessment within 42 days prior to registration. Patient must be a candidate for surgical intervention with sentinel lymph node (SLN) biopsy and potential completion neck dissection (CND) or elective neck dissection (END);

- Surgical resection of the primary tumor will occur through a transoral approach with anticipation of resection free margins;

3.1.4 Age ≥ 18;

3.1.5 Zubrod Performance Status 0-2 within 42 days prior to registration;

3.1.6 For women of child bearing potential, negative serum or urine pregnancy test within 42 days prior to registration.

3.1.7 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.1.8 Only English speaking patients (able to read and understand English) are eligible to participate as the mandatory patient reported NDII tool is only available in this language.

Prior to Step 2 RANDOMIZATION

3.1.9 FDG PET/CT required prior to step 2. Note: FDG PET/CT done prior to step 1 can be submitted for central review. However if the FDG PET/CT is not of diagnostic quality, per guidelines outlined in Section 11.1 then FDG PET/CT will have to be repeated prior to Step 2 registration.

PET/CT node negative patients, determined by central read described in Section 11.1, will proceed to randomization. PET/CT positive patients will go off study, but will be entered in a registry and data will be collected to record the pathological outcome of neck nodes for diagnostic imaging assessment and future clinical trial development.

NOTE: All FDG PET/CT scans must be performed on an American College of Radiology (ACR) accredited scanner (or similar accrediting organization).

3.2 Ineligibility Criteria

Prior to Step 1 REGISTRATION

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Definitive clinical or radiologic evidence of regional (cervical) and/or distant metastatic disease;

3.2.2 Prior non-head and neck invasive malignancy (except non-melanomatous skin cancer, including effectively treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or cervix) unless disease free for ≥ 2 years.

3.2.3 Diagnosis of head and neck SCC in the oropharynx, nasopharynx, hypopharynx, and larynx;

3.2.4 Unable or unwilling to complete NDII (baseline only);

3.2.5 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.2.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.7 Patient with severe, active co-morbidity that would preclude an elective or completion neck dissection;

3.2.8 Pregnancy and breast-feeding mothers.

3.2.9 Incomplete resection of oral cavity lesion with a positive margin; however, an excision biopsy is permitted.

3.2.10 Prior surgery involving the lateral neck, including neck dissection or gross injury to the neck that would preclude surgical dissection for this trial. Prior thyroid and central neck surgery is permissible; biopsy is permitted. Note: Borderline suspicious nodes that are ≥1 cm with radiographic finding suggestive of NOT malignant should be biopsied using U/S-guided FNA biopsy.

3.2.11 Underlying or documented history of hematologic malignancy (e.g., CLL) or other active disease capable of causing lymphadenopathy (sarcoidosis or untreated mycobacterial infection).

3.2.12 Actively receiving systemic cytotoxic chemotherapy, immunosuppressive, anti-monocyte or immunomodulatory therapy.

3.2.13 Currently participating in another investigational therapeutic trial.

4 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

PRE-TREATMENT ASSESSMENTS
(See section 3.1 for details)

Time point	*Procedure/Test*	*Notes*
Prior to Step 1 registration	☐ Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma of the oral cavity	

42 days prior to Step 1 registration	☐ History/physical examination ☐ Surgical Assessment* ☐ FDG PET/CT** or neck CT with intravenous iodinated contrast or gadolinium-enhanced neck MRI or lateral and central neck ultrasound ☐ Chest imaging ☐ Zubrod performance status ☐ Serum or urine pregnancy test***	**Patient must be a candidate for surgical intervention with SLN biopsy and potential CND or END.* *** PET/CT must be of diagnostic quality (see guidelines in Section 11.1).* ****Females of child bearing potential require a pregnancy test.*
Prior to Step 2 registration	☐ FDG PET/CT	*For central review (if FDG PET/CT done prior to step 1 registration is not of diagnostic quality, per guidelines outlined in Section 11.1, then FDG PET/CT will have to be repeated prior to Step 2 registration and images submitted for central review. See Section 3.1.10 for details).*
Prior to surgery	☐ Adverse Event Evaluation ☐ Surgical Assessment* ☐ Patient-Reported Outcomes: • NDII • QuickDASH • FACT-H&N • EQ-5D-5L ☐ Use of pain medications ☐ Specimen submissions for biobanking (optional)** ☐ SPECT/CT study (SLN mapping)*** ☐ Patient History form (patient reported)****	**Surgeon will assess patient fitness for surgical intervention with SLN biopsy and potential CND or END. This assessment must be done after step 2 registration and prior to surgery.* ***See Section 10.3.2 for details. Blood can be taken prior to or on the day of surgery.* ****Refer to section 5 and 11 for details.* ***** Patient history form is optional and can be completed any time prior to starting treatment.*

ASSESSMENTS DURING TREATMENT

Time point	*Procedure/Test*	*Notes*
Surgery	☐ Operative report for primary tumor resection and END or SLN biopsy* ☐ Surgical pathology report (primary tumor and END or SLN biopsy)* ☐ Adverse Events Evaluation ☐ Surgical pathology specimen (END or SLN biopsy) ☐ Specimens for biobanking (mandatory and optional)**	**Operative reports and surgical pathology reports are required – see data submission table on the CTSU website.* ***See Section 10.3.1 & 10.3.2 for details.*
At time of discharge from surgery	☐ Morbidity assessment (Clavien-Dindo Classification scale[CDC])* ☐ Adverse Events Evaluation	**Refer to section 5.1.2 for the scale*

FOLLOW-UP ASSESSMENTS

Time point	*Procedure/Test/Treatment*	*Notes*
3 months post-surgery (or post radiation completion date if RT is received), then as clinically indicated	☐ FDG PET/CT or neck CT with intravenous iodinated contrast or gadolinium-enhanced neck MRI or lateral and central neck ultrasound – follow up imaging should be same assessment patient had pre-treatment	*If FDG PET/CT is ordered at follow up then it should be done 12-14 weeks post-surgery.*
3 weeks after neck surgery then at 3, 6, 9 and 12 months; during year 2 – at 4, 8 and 12 months; during year 3 – at 6 and 12 months, then annually	☐ Physical Exam* ☐ Adverse Events Evaluation ☐ Morbidity assessment (Clavien-Dindo Classification scale [CDC])** ☐ Chest x-ray or chest CT or PET/CT*** ☐ Use of pain medications****	**General history and physical by one of the following: Radiation Oncologist, Medical Oncologist, Oto-laryngologist (ENT), or Head and Neck Surgeon. The entire oral cavity should be clearly visualized. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended at these time points but not required.* ***Required at 3 weeks post-surgery only. Refer to section*

		5.1.2 for the scale ****As clinically indicated.* *****Required at 3 weeks post-surgery, and 3, 6 and 12 months post-surgery only.* Biopsy of any lesion(s) suspicious for tumor recurrence is urged.
3 weeks after neck surgery then at 3, 6, and 12 months	☐ Patient-Reported Outcomes: • NDII • QuickDASH • FACT-H&N • EQ-5D-5L	
3 weeks and 6 months after surgery. If RT is received, within 1 week of post radiation completion date.	☐ Specimens for biobanking (optional)	*See Section 10.3.2 for details.*

Outcomes Criteria
No evidence of disease (NED): All patients must have not measurable tumor following surgery.

Local-Regional Relapse: Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; both imaging and biopsy confirmation are strongly recommended. The type of LRR will be further categorized as follows:

Local Relapse – Recurrent cancer in the primary tumor bed without disease in the neck.

Regional Relapse – Cancer present in the cervical lymph node(s) without disease present in the primary tumor bed.

Local-Regional Relapse – Cancer present both in the primary tumor bed and cervical lymph node(s)

Distant Relapse: Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary lung mass/nodule should be considered a second primary upper aerodigestive neoplasm unless proven otherwise. If there is any question whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Principal Investigator, Dr. Lai.

Second Primary Neoplasm: All second primary neoplasms will be biopsy proven with documentation of specific histology. Modified rigorous criteria for a second primary (below) have been adapted from the definition by Warren and Gates (1932). Localized non-melanoma

skin cancers are not considered new primary tumors.

- A distinct lesion separated from the primary tumor site by > 2 cm of normal epithelium;
- A new cancer with different histology;
- Any cancer, regardless of head and neck mucosal subsite, occurring 5 or more years after
- initial treatment;
- In the lung, new primary tumors, if squamous cell cancer, must have histologic findings of dysplasia or CIS.

Second Primary Upper Aerodigestive Neoplasm: The emergence of a new, invasive malignancy in the upper aerodigestive tract as a second primary should be documented. These neoplasms include lung cancer, esophageal cancer (including GE junction cancer), or 2nd primary head and neck cancer that is clearly remote from the index cancer (e.g., pyriform sinus cancer developing in a patient whose original diagnosis was tongue cancer). If there is any question whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Principal Investigator, Dr. Lai.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Surgery

Note: Surgeons must be credentialed to perform neck dissection and sentinel lymph node biopsy prior to enrolling patients on the trial (see Section 5.1.3 and 8.1.3 and Appendix IV for details).

5.1.1 Evaluation and Timing

- Surgeon will assess patient fitness for surgical intervention with SLN biopsy and potential CND or END.
- Protocol surgery must begin within 30 days after central review of N0 neck status by PET/CT study.
- Prior surgery for confirmation of tumor pathology is permitted, but incomplete resection with a positive margin is not.
- Resection of the primary tumor and surgical management of the neck (sentinel lymph node dissection or elective neck dissection) should occur within the same surgical encounter. The SLN biopsy should not be performed as a staged procedure after wide local excision of the oral cavity cancer.
- Sentinel node biopsy should occur between 1 to 30 hours after injection of radiotracer. For FOM tumors, radiotracer injection should occur the day prior to surgery (>12 hours) in order to minimize “shine through” effect.

5.1.2 Surgical Technique

<u>Resection of the primary tumor</u>

Resection of the primary tumor should aim to achieve ≥5 mm negative margins on final pathological analysis. The final margin may be assessed on the initial tumor resection or on separate margin specimens as specified by the surgeon (e.g., posterior margin). This should be specified in the operative report and/or pathology report.

Margin assessment may be performed during the initial resection by frozen section pathology.

Consider margin assessment from the resection specimen by the pathologist rather than surgeon directed margin determination from the tumor specimen or resection bed. DOI assessment, if obtained in the frozen section analysis, should not alter management of the neck.

Surgeon preference will dictate the order of the surgery. In many situations, the surgeon may initially resect the primary tumor to permit time for margin assessment by frozen section pathology during the SLN biopsy.

Surgical resection of the primary tumor should not require transcervical delivery or approach. Surgical repair of the primary tumor site should not require vascular access in the neck for a free flap reconstruction.

Re-resection of the close/positive surgery margin is permitted. The surgeon may elect to return to the operating room for re-resection of the primary tumor to achieve a negative pathological margin. This may also coincide with a CND if the patient has a positive SLN.

Neck Dissection

Elective Neck Dissection (END) will include at least levels I, II and III (i.e. supraomohyoid neck dissection). Level IIB should be included in the dissection of level II, but is not required. The surgeon will specify if level IIB and/or level IV was included in the neck dissection. For oral cavity lesions ≤ 1 cm from the midline of the oral cavity, bilateral END is indicated.

In the event of a positive SLN, the completion neck dissection (CND) should be completed within 6 weeks of the initial surgical procedure and ideally within 4 weeks. This may be facilitated by pre-scheduling the CND procedure and canceling that event with a negative SLN pathology report. The time interval between the positive SLN biospy and CND will be recorded. CND will include at least levels I, II and III (i.e. supraomohyoid neck dissection). Level IIB should be included in the dissection of level II and is required if the positive SLN(s) was identified in level IIA and/or IIB. The surgeon will specify if level IIB and/or level IV was included in the neck dissection. The surgeon should include the neck levels and sublevels (e.g., IIB) where a positive SLN was identified. For oral cavity lesions ≤ 1 cm from the midline of the oral cavity, CND is indicated on the side of the neck where a positive SLN is identified. In the scenario of a well-lateralized oral cavity cancer, if the ipsilateral SLN(s) are negative, but the contralateral SLN(s) are positive, then only the contralateral CND is required. The surgeon may elect to perform bilateral CND, but the rationale should be clearly documented.

The neck dissection should be oriented and ideally separately partitioned in order to identify levels of lymph nodes encompassed in the dissection. Pathology reporting should reflect the neck levels.

Sentinel Lymph Node Biopsy

It is highly recommended that sentinel lymph node mapping and biopsy utilize a single radiotracer injection. The injected activity will be different depending on whether the SLN biopsy occurs on the same day or on the day following the SLN imaging. In some situations (e.g., surgical schedule - surgery on Monday may preclude Sunday radiotracer injection), two separate radiotracer injections may be required, although single day injection is preferred.

Specific details on radiotracer injection activities and volumes are provided in Section 11.2.

The patient will then undergo both planar (2D) and SPECT/CT (3D) imaging to establish the lymphatic drainage patterns of the radiotracer. SPECT/CT provides accurate anatomical localization and depth evaluation of SLNs. **SPECT/CT imaging is mandatory for patients in Arm 1 only.** Specific details on planar and SPECT/CT imaging are provided in Sections 11.2.1 and 11.2.2. The surgeon and nuclear medicine physician should discuss signal(s) most likely to represent first-echelon SLN(s) most likely to harbor metastatic disease.

An optical tracer may be used during the surgery at the discretion of the surgeon.

Incision placement should favor retrieval of the SLN(s) over facilitating a potential future neck dissection if there are potential conflicts between these concerns. A new incision for a CND can be made without risk to healing and typically the SLN biopsy incisions are not associated with a cosmetic defect.

Given the concern of "shine through" effect in the FOM subsite, the surgeon may consider exploration of the level I neck as needed (Stoecki 2016). Careful technique and experience may reduce the risk of missing SLN(s) in this scenario.

Sentinel lymph node identification begins with pre-operative identification of positive signal with a gamma probe prior to incision. Sentinel lymph nodes will have a gamma count rate at least 10 times higher than background and be at least 10% of the hottest sentinel lymph nodes excised. An instantaneous gamma count measurement may be taken *in vivo* and *ex vivo*, but may be further confirmed with an *ex vivo* average reading taken over 10 seconds. In a typical SLN biopsy case, up to 3 SLNs are usually excised from the involved side of the neck; when both sides of the neck are involved, up to 6 SLNs may be excised in total. There are clinical situations where more SLNs may be identified. A preoperative discussion between the surgeon and the nuclear medicine physician should provide guidance regarding the localization of the first-echelon SLNs.

Exploration of the neck for SLN(s) requires identification and careful manipulation around critical structures (e.g., spinal accessory nerve, internal jugular vein, etc.).

Nodes that do not meet the criteria for SLN should be submitted as "non-sentinel lymph node" and submitted for routine pathological examination rather than serial sectioning.

In the rare situation that SLN(s) are identified by SPECT/CT, but cannot be localized intraoperatively, the surgeon may remove specific neck level(s) most likely associated with the SLN(s). The resected tissue may then be assessed *ex vivo* for the SLN(s), but all portions of the removed tissue should be submitted for pathological assessment. The surgeon may also elect to perform an END and document the decision-making process for this decision.

If lymphatic mapping is not visualized by SPECT/CT, then the surgeon may elect repeat the radiotracer injection prior to surgery or perform an END with primary tumor resection.

If a SLN appears grossly suspicious for metastatic disease, the surgeon may elect to perform an immediate CND. This is a very rare occurrence.

Reconstruction/Closure of the Primary Tumor Site

The primary tumor site surgical defect may be closed at the discretion of the attending surgeon. Primary closure is recommended when appropriate, but may also be performed with split-thickness skin or other grafts and local/regional flaps. Healing by secondary intention may also be appropriate.

Recording surgical and perioperative morbidity

The Clavien-Dindo Classification (CDC) will be used to record issues with the surgical procedure (see Section 4 for time points).

The CDC scale is a tool to assess postoperative morbidity after surgery (Dindo and Clavien 2004).

Grades	**Definition**
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis)
- IVb	Multiorgan dysfunction

Grade V	Death of a patient

**brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.*

Source: https://www.assessurgery.com/clavien-dindo-classification/

- **Pre-specified Surgical Complications (including surgical device)**
  These adverse events will be used to assess morbidity per the assessment tables in Section 4:
  1. Bleeding/hematoma
  2. Seroma
  3. Abnormal scarring
  4. Lip weakness
  5. Chyle leak
  6. Tongue weakness and/or numbness
  7. Phrenic nerve injury
  8. Oral cavity fistula
  9. Shoulder weakness/decreased range of motion
  10. Pulmonary embolus
  11. Heart attack
  12. Stroke

5.1.3 Surgical Quality Assurance Program

A surgical quality assurance program has been established as part of this trial, for the purpose of surgeon credentialing, surgical quality assurance reviews and continuing assessment of SLN biopsy and neck dissection quality.

Credentialing for NRG-HN006

Each surgeon will provide operative reports and pathology reports for 10 surgical cases, including SLN biopsy. These operative cases may be for an oral cavity cancer or skin cancer (or breast cancer). Those patients receiving SLN biopsy will need to have at least six months follow-up without locoregional recurrence or an immediate neck dissection for comparison (oral cavity patients) for credentialing. See Section 8.1.3 for details on pre-registration Protocol Specific Requirements.

Surgical Quality Assurance Reviews

All surgeons will be subject to continuous auditing regarding node acquisition via SLN biopsy and neck dissection, to be performed by an ad-hoc Surgical Quality Assurance Working Group (SQAWG), developed by NRG Oncology. The SQAWG will review operative reports and pathology reports for every patient. See Section 12 for more information about the Modality Reviews. Surgeons without experience with SLN biopsy for oral cavity cancers will participate in an education course overseen by the SQAWG.

5.2 Chemotherapy and Other Systemic Anti-Cancer Therapies

The chemotherapy recommendations are based on standard of care therapy and do not compromise any portion of the experimental question of this protocol. They are reflective of consensus-based NCCN Head and Neck Cancer-Clinical Practice Guidelines in Oncology

(accessed October 4, 2019). The majority of study participants will not require chemotherapy. Use of chemotherapy may be allowed, depending on specific phase of treatment and high risk features as defined below.

5.2.1 Pre-Treatment Phase and Treatment Phase:

The use of chemotherapy, immune therapy or other anti-cancer agent is **not** allowed regardless of route of administration either during the pre-treatment phase or treatment phase (prior to surgery).

5.2.2 Follow-Up Phase:

In the follow-up phase, systemic therapy may be given in the following circumstances:

Directly after surgery, with radiation: Chemotherapy use should be in accordance with the following recommendations, consistent with NCCN guidelines:

- If the surgical pathology final report indicates that EITHER positive margins AND/OR lymph node extra-capsular extension/extra-nodal extension were detected then chemotherapy should be added concurrently to adjuvant radiation.

- If the surgical pathology final report indicates that NEITHER positive margins NOR lymph node extra-capsular extension/extra-nodal extension were detected then **NO chemotherapy, immune therapy or other anticancer agent use is permitted.** In select cases, chemotherapy use may be permitted if the treating physician feels patient safety will be compromised without the use of chemotherapy AND after concurrence of the study chair. Those situations will require a clearly documented rationale in the case report form.

- Chemotherapy should only be given with concurrent radiation. In patients who require chemotherapy, cisplatin is given concurrently with adjuvant radiation on the following schedules:
  1. Bolus cisplatin every 3 weeks; or
  2. Weekly cisplatin

- Chemotherapy EXCLUSION or SUBSTITUTION may be permitted if the treating physician feels patient safety will be compromised with the use of cisplatin AND after concurrence of the study chair. Those situations will require a clearly documented rationale in the case report form.

  NOTE: The choice of regimen, dosing adjustments, criteria for pausing or discontinuing therapy once it has started, usage of supportive or adjunctive medicines will all be based on standard institutional practice and physician discretion. Recommended guidelines are included in Appendix I.

  After radiation: Systemic therapy is permitted in cases of documented cancer after completion of treatment phase. Institutional standards regarding treatment of persistent, recurrent or second primary cancers should be followed.

5.3 Radiation Therapy

5.3.1 Indications for Adjuvant Radiation Therapy or Chemoradiation

Patients will be dispositioned for observation, adjuvant radiation therapy, or adjuvant chemoradiation based on final pathology, regardless of surgical treatment arm. If patients require adjuvant radiation for any indication (primary site or nodal disease), both the primary site and at-risk neck should be treated. Patients should not receive radiation therapy to either the primary site or neck ALONE. Patients that are dispositioned to adjuvant radiation therapy or adjuvant chemoradiation will have their digital RT data submitted using TRIAD (see Section 8.2.1). Summary for the dosimetric digital data submission is located in the table located in Section 13.2.

Indications for adjuvant treatment:

Indications for adjuvant radiation therapy alone:

1. Primary site features:
    a. Perineural invasion
    b. Lymphovascular invasion
    c. pT3/T4
    d. Close margins (<5 mm)
2. Nodal features:
    a. pN1 or above

    *Based on institution standards, investigators may choose to omit adjuvant radiation in patients with pN1 disease and no other risk factors.

Indications for adjuvant chemoradiation:

1. Primary site features:
    a. Positive margins (defined as tumor on ink)
2. Nodal features:
    a. Extranodal extension

Note: Refer to Appendix II for the Radiation Schema tables for Intermediate/High Risk patients for lateralized or midline tumors.

Indications for observation:

Patients who do not meet criteria for adjuvant radiation or chemoradiation should be observed.

Note: Intensity Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) are mandatory for this study. Proton therapy is not permitted.

Note: All participating institutions must be credentialed for head and neck IMRT and IGRT prior to registering patients to the study (see Section 8.2 for details).

Adjuvant treatment must begin within 42 days after completion of surgical therapy (primary tumor resection and elective or completion neck dissection (see Table 5.3.5C).

5.3.2 Recommended guidelines for Adjuvant Radiation Therapy or Chemoradiation

Treatment Technology

Megavoltage energy photon beam irradiation with energy ≥ 4 MV (6MV energy is preferred) with the exception of the MRIdian Co-60 delivery system. Proton therapy is not allowed. IMRT techniques, including static field IMRT, helical IMRT (Tomotherapy) and VMAT are allowed. Matched conventional anterior neck field is not allowed. All institutions must be credentialed for head and neck IMRT and IGRT. For IGRT, the treatment machine must be equipped to provide daily MRI, kV, or MV image guidance. The minimum requirements for image guidance are given in Section 5.3.9.

Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

Patients will be treated supine and must have an immobilization device for the head and neck (e.g. aquaplast mask) made prior to the treatment planning CT scan. Intraoral immobilization devices may be utilized for tongue position control or immobilization. It is strongly encouraged that the participating centers also include the shoulders in the immobilization to further ensure accurate patient set-up on a daily basis.

Simulation

The treatment planning CT scan should be performed with IV contrast (unless contraindicated). The treatment planning CT scan must be performed with the immobilization device and in the treatment position. All tissues to be irradiated must be included in the primary planning images. Slice thickness should be ≤ 3 mm. The scanning limits should at least encompass the orbits superiorly and extend at least 1 cm below the suprasternal notch inferiorly. Metal artifact reduction technique in CT scanner can be used for cases with dental filling or other high-density objects.

Imaging for Structure Definition and Image Registration/Fusion

A diagnostic pre-operative CT, MRI or FDG-PET/CT may be fused to the planning CT scan to facilitate target and normal structure delineation and is recommended. All diagnostic image sets used for RT planning structure delineation must be submitted with the RT digital data (see data submission table in Section 13.2).

Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be

applied exactly as indicated.

Table 5.3.2A: Definition of Target Volumes and Margins

Standard Name	Description	Validation Required/Required when applicable/Optional
CTV_6000	CTV to receive 60 Gy	**Required**
PTV_6000	PTV to receive 60 Gy	**Required**
PTV_Eval_6000	PTV_6000 minus high risk OARs (subtract 5 mm from the skin if needed)	**Required when applicable**
CTV_5600	CTV to receive 56 Gy	**Required**
PTV_5600	PTV to receive 56 Gy	**Required**
PTV_Eval_5600	PTV_5600 minus high risk OARs (subtract 5 mm from the skin if needed)	**Required when applicable**
CTV_6600	CTV to receive 66 Gy	**Required when applicable**
PTV_6600	PTV to receive 66 Gy	**Required when applicable**
PTV_Eval_6600	PTV_6600 minus high risk OARs (subtract 5 mm from the skin if needed)	**Required when applicable**

Detailed Specifications

CTV_6000: This volume will receive 2 Gy per day. CTV_6000 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, and pathologic findings) plus regions of pathologically positive lymphadenopathy that have been surgically resected; all of these should have a margin of 5-10 mm to create final CTV_6000.

CTV_5600: This volume will receive 1.87 Gy per day. CTV_5600 will include all other areas felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV_6000, including any regions that have been dissected (and not found to have pathologically positive disease) or are at-risk for disease spread. For example, this would apply to the entire operative bed, ipsilateral low neck, contralateral hemineck (when applicable), and perineural tracts (when applicable).

Elective nodal volumes based on primary site:

1. **Oral Tongue (lateralized ≥1 cm from midline):** CTV_5600 should include the ipsilateral neck not meeting criteria for CTV_6000. Generally, this should include level I, II, III, IV, and V (level V may be excluded for node negative patients). The contralateral neck may be omitted based on the discretion of the treating physician for these well-lateralized tumors.
2. **Oral Tongue (<1 cm from midline):** CTV_5600 should include the bilateral neck not meeting criteria for CTV_6000. Generally, this should include level I, II, III, IV, and V (level V may be excluded for node negative patients). All patients with oral tongue primary tumors <1 cm from midline are required to have the contralateral neck treated electively. Typically, this will include levels I, II, III, and IV.
3. **Floor of Mouth:** CTV_5600 should include the bilateral neck not meeting criteria for CTV_6000. Generally, this should include level I, II, III, IV, and V (may be excluded for node negative patients). All patients with floor of mouth tumors are required to have the contralateral neck treated electively. Typically, this will include levels I, II, III, and IV.
4. **Retromolar Trigone**: CTV_5600 should include the ipsilateral neck not meeting criteria for CTV_6000. Generally, this should include level IB, II, III, IV, and V (level V may be excluded for node negative patients). The contralateral neck should be omitted for well-lateralized lesions; however, the contralateral neck may be treated based on the discretion of the treating physician. Reasons to consider contralateral treatment include: extensive oral tongue, tonsil, floor of mouth or alveolar ridge involvement. In this case, the contralateral coverage will typically include levels I, II, III, and IV.
5. **Buccal Mucosa**: CTV_5600 should include the ipsilateral neck not meeting criteria for CTV_6000. Generally, this should include level IB, II, III, IV, and V (level V may be excluded for node negative patients). The contralateral neck may be omitted for well-lateralized lesions; however, the contralateral neck can be treated based on the discretion of the treating physician. Reasons to consider contralateral treatment include: extensive oral tongue, tonsil, floor of mouth or alveolar ridge involvement. In this case, the contralateral coverage will typically include levels I, II, III, and IV.
6. **Hard palate**: CTV_5600 should include the bilateral neck not meeting criteria for CTV_6000. Generally, this should include level IB, II, III, IV, and V (level V may be excluded for node negative patients). All patients with hard palate cancers are required to have the contralateral neck treated electively. Typically, this will include levels IB, II, III, and IV.

CTV_6600 (optional): This volume may be defined at the discretion of the treating radiation oncologist. This would include regions felt to be at particularly high risk for recurrence (e.g. area of the extracapsular extension or positive margin of resection). Note: This area will be receiving a daily fraction dose of 2.2 Gy and thus, the volume of CTV_6600 should be kept as small as possible.

Planning Target Volumes (PTV_6000, PTV_5600, PTV_6600): The PTV is created from the CTV with additional margins to compensate for the variability of treatment

setup and internal organ motion. The PTV margin should be based on institutional standard of care, for patients treated for head and neck cancer with the type of immobilization used for this trial; it should range from 3-5 mm based on institutional experience. A minimum margin of 3 mm around the CTV is required in all directions to define each respective PTV, except the situations in which:

- the CTV is adjacent to spinal cord and/or brainstem. In such situations, the margin can be reduced at the discretion of the treating physician.
- the CTV results in a PTV that extends beyond the patient's body surface. The PTV should be constrained to at least 3 mm from within the external contour, while still including the CTV. The use of tissue equivalent bolus material is indicated in situations where the disease is at or just under the skin surface. The PTV should align with the skin surface when bolus is used.

Evaluation Planning Target Volumes (PTV_Eval_6000, PTV_Eval_5600, PTV_Eval_6600): PTV_Eval volumes are created for coverage evaluation from PTV volumes minus impinging high priority OARs (SpinalCord, and/or BrainStem, and/or BrachialPlexus_R/L) minus 5 mm from the skin if needed to limit the dose to the critical structures. Other volumes, such as tuning or optimization structures, can be employed to drive the IMRT treatment planning process. Such volumes should be considered to be treatment-planning tools that are not reported or sent for review.

5.3.3 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Table 5.3.3A: Definition of Critical Structures and Margins

Standard Name	Description	Validation Required/Required when applicable/Optional
SpinalCord	Spinal cord	**Required**
SpinalCord_PRV05	Spinal cord with 5 mm expansion for Planning Risk Volume (PRV)	**Required**
BrainStem	Brainstem	**Required**
BrainStem_PRV03	Brainstem with 3 mm expansion for Planning Risk Volume (PRV)	**Required**
Lips	Lips	**Required**

Cavity_Oral	Uninvolved oral cavity	**Required**
Parotid_L	Left parotid gland	**Required**
Parotid_R	Right parotid gland	**Required**
Pharynx	Uninvolved pharynx	**Required**
Esophagus_S	Upper (cervical) Esophagus	**Required**
Larynx_SG	Glottic and supraglottic larynx	**Required**
Bone_Mandible	Mandible	**Required**
Glnd_Submand_R	Right submandibular salivary gland	**Required when applicable (if present)**
Glnd_Submand_L	Left submandibular salivary gland	**Required when applicable (if present)**
BrachialPlexus_R	Right brachial plexus	**Required**
BrachialPlexus_L	Left brachial plexus	**Required**
Cochlea_L	Left cochlea	**Required**
Cochlea_R	Right cochlea	**Required**
External	External patient contour encompassing all patient anatomy	**Required**
E-PTV	All tissue excluding all PTVs	**Required**

Detailed Specifications

SpinalCord: The cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is the brainstem and inferior to this is the cord. The inferior border of the spinal cord is at approximately T3-4 (i.e. just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan.

SpinalCord_PRV05: Planning Risk Volume (PRV) spinal cord defined as SpinalCord + 5 mm in all directions.

BrainStem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The BrainStem shall be defined based on the treatment planning CT scans.

BrainStem_PRV03: Planning Risk Volume (PRV) brainstem defined as BrainStem + 3 mm in all directions.

Lips: The lip contour extends from the inferior margin of the nose to the superior edge of the mandibular body. The lateral border is at the lateral commissure. The lip contour should include the inner surface of the lips. Lips will be defined in their entirety (upper and lower) based on the treatment planning CT scan.

Cavity_Oral: The oral cavity will be defined as a composite structure posterior to lips consisting of the anterior 1/2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and superiorly the palate, and inferiorly to the plane containing the tip of the mandible (external to PTVs).

Parotid_R/L: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scans. The parotid gland is an irregular shaped gland wedged between the ramus of the mandible and the mastoid process. The superior border is the zygomatic arch, inferiorly, the gland extends to the angle of the mandible. The anterior border is the masseter muscle; in 20% of cases the parotid gland extends anteriorly over the surface of the masseter muscle, and posteriorly, to the anterior border of the sternocleidomastoid. Laterally, it extends to the platysma and medially, to the posterior belly of the digastric muscle, styloid process and parapharyngeal space. The retromandibular vein is included in the parotid gland contour.

Pharynx: This will be defined as the pharyngeal mucosa and wall plus adjacent constrictor muscles deemed not to require treatment (external to PTVs). This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs. The posterior border is the pre-vertebral muscle. See Figure 5.3.3A or https://www.sciencedirect.com/science/article/pii/S0167814009005659#bib14 for more details.

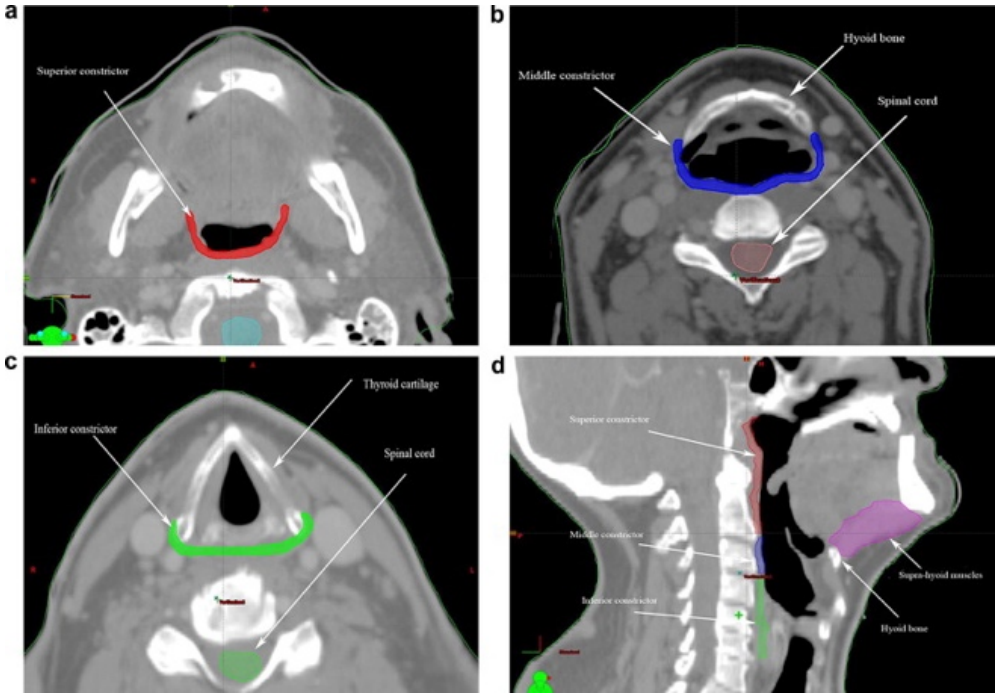


Figure 5.3.3A From Bhide et al (2009): Each of the pharyngeal constrictors was outlined as an arch-shaped structure with concavity facing anteriorly, in line with the mucosa (a-c). Posterior border of each of the muscles was the pre-vertebral muscle. Pharyngeal mucosa lining the muscles was included in outlines as it is quite thin and difficult to exclude with great accuracy with currently available CT images. Superior constrictor was outlined from the base of the skull up to the superior end of hyoid. Middle constrictor was outlined from the superior end to the inferior end of the hyoid bone. Inferior constrictor was outlined from the inferior aspect of hyoid to inferior end of cricoid cartilage. A sagittal view of all of the outlined pharynx is shown (d).

Esophagus_S: This will be defined as a tubular structure that starts at the bottom of the pharynx and extends to the thoracic inlet.

Larynx_SG: This will be defined as the glottic and supraglottic larynx, including theinfrahyoid epiglottis, the aryepiglottic folds, arytenoids, false cords, and true cords, up to but not including the medial border of the thyroid cartilage, and including the cricoid cartilage to the inferior edge of the arytenoid cartilage, but not the hypopharynx. Posteriorly, the contour extends to the anterior edge of the pharyngeal wall.

Bone_Mandible: This includes the entire bony structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

Glnd_Submand_R/L: Submandibular glands will be defined in their entirety based on treatment planning CT scan; they should be contoured if present. The submandibular glands are paired salivary glands composed of a large superficial lobe and a smaller deep process that are continuous with each other around the posterior border of the mylohyoid

muscle. The superior border is the mylohyoid muscle and medial pterygoid muscle. Inferiorly, the gland abuts fatty tissue. Anteriorly, the gland is adjacent to the lateral surface of the mylohyoid muscle and posteriorly it abuts the parapharyngeal space and sternocleidomastoid. The lateral border is platysma and the mandibular surface. The medial border is the lateral surface of the mylohyoid muscle and the anterior belly of the digastric.

BrachialPlexus_R/L: To contour the brachial plexus OAR use a 5-mm diameter paint tool. Start at the neural foramina from C5 to T1; this should extend from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles. For CT slices, where no neural foramen is present, contour only the space between the anterior and middle scalene muscles. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head. The first and second ribs serve as the medial limit of the OAR contour. See Figure 5.3.3B and https://www.redjournal.org/article/S0360-3016(08)00416-1/fulltext for more details.

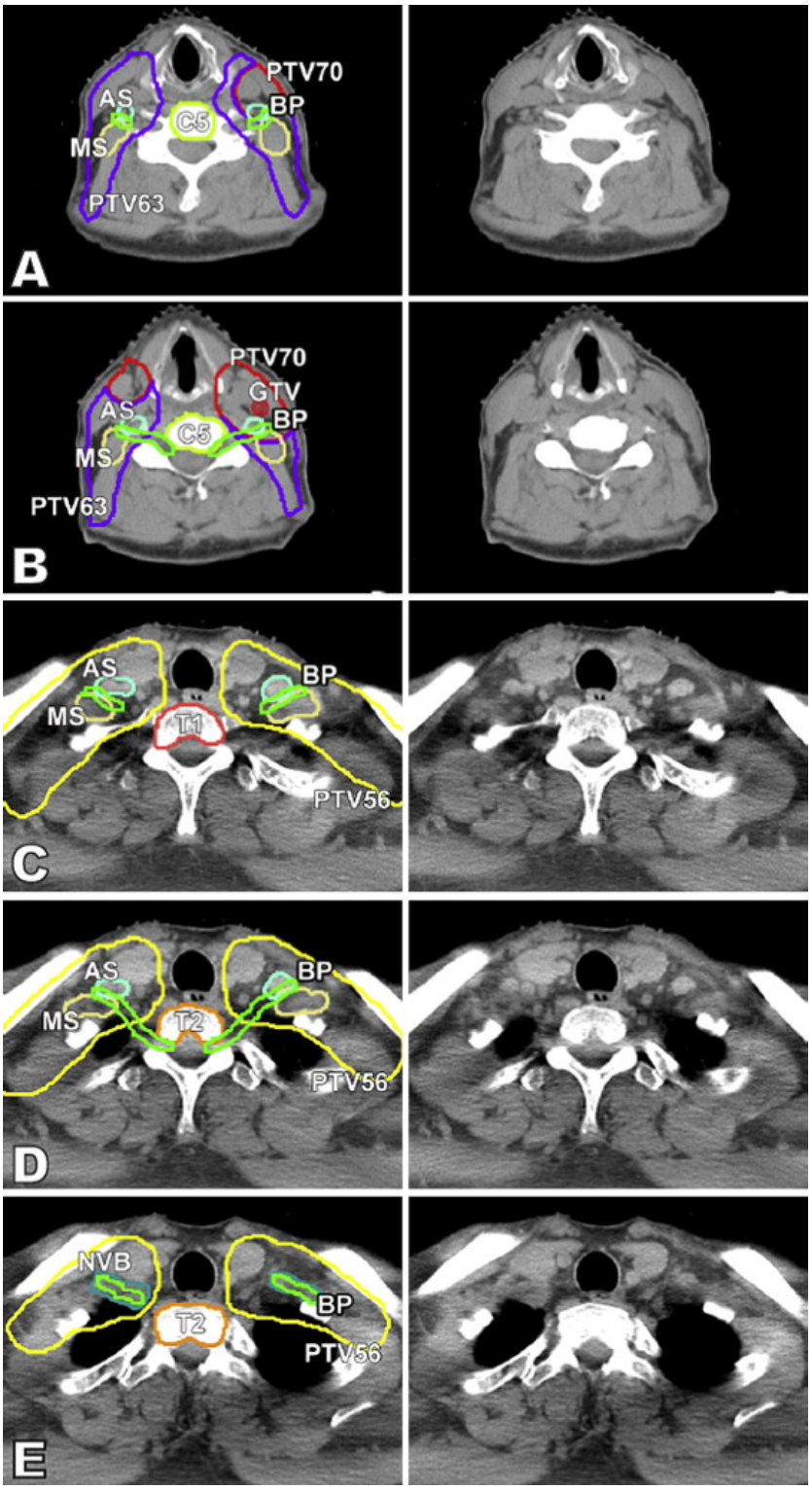


Figure 5.3.3B From Hall et al (2008): Major anatomic landmarks (Anterior and Middle Scalene muscles, and the neurovascular bundle) for identifying the brachial plexus on the axial images of a treatment planning computed tomography scan.

Cochlea_R/L: The cochlea lies near the most lateral extent of the internal auditory canal, anterior to the internal auditory canal. The spiral canals of the cochlea appear as a small round lucency within the temporal bone. The cochlea should be defined in its entirety limited by vestibular apparatus posteriorly and middle ear laterally. See Figure 5.3.3C and https://pdfs.semanticscholar.org/2e9b/73b254b27d7f8724348057291b5a776c7b37.pdf for more details.

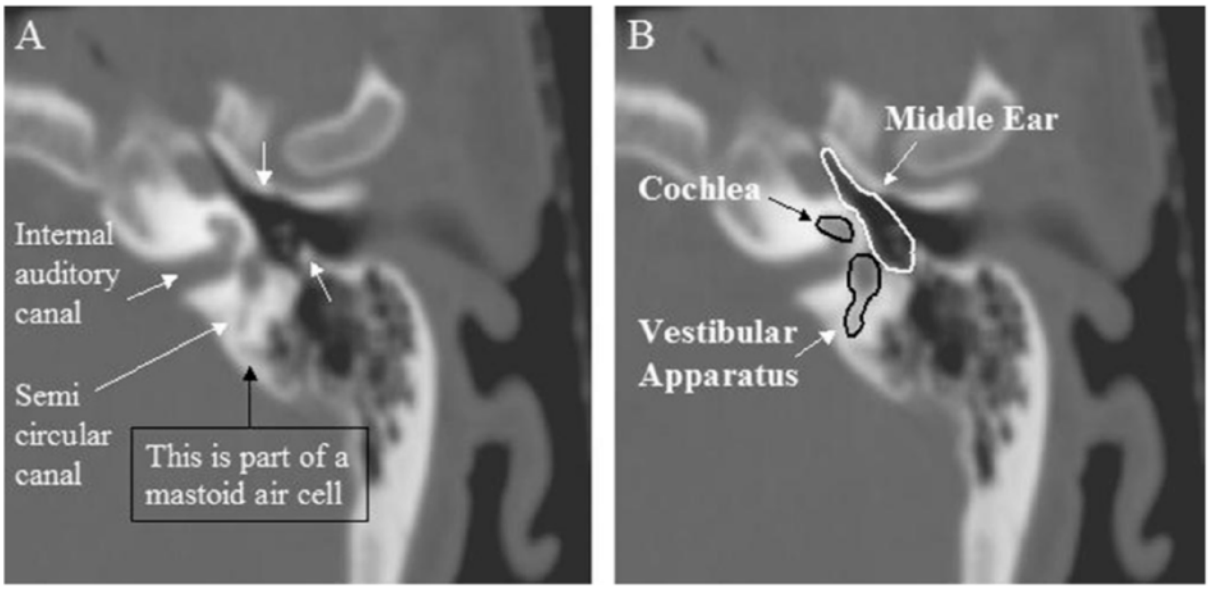


Figure 5.3.3.C From Pacholke et al (2005): Major anatomic landmarks for identifying the cochlea on the axial images of a treatment planning computed tomography scan. The best way to locate the cochlea is to first identify the internal auditory canal. The image on the left (A) shows the anatomy of the temporal bone at the level of the inner ear without outlines of auditory structures. Important landmarks on this image are the internal auditory canal, the semicircular canals of the vestibular apparatus, and the bony prominences that mark the attachment of the tympanic membrane (un-marked arrows). The spiral canals of the cochlea appear as small curved or round lucencies within the temporal bone (B). Note that portions of a mastoid air cell may look similar to a semicircular canal.

E-PTV: This will be defined as tissue located within external contour of the patient outside of all PTVs.

5.3.4 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Table 5.3.4A: Dose Prescription and Plan Normalization

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_6000 or PTV_Eval_6000	60	2.0	30	Covering ≥ 95% of PTV_6000
PTV_5600 or PTV_Eval_5600	56	1.87	30	Covering ≥ 95% of PTV_5600
PTV_6600 or PTV_Eval_6600	66	2.2	30	Covering ≥ 95% of PTV_6600

Plan should be normalized such that 95% of the volume of PTV_6000 (PTV_Eval_6000) or if present PTV_6600 (PTV_Eval_6600) receives the prescribed dose with a minimum dose (defined as dose to 99% of PTVs) greater than 95% of the prescription dose and a maximum dose (defined as dose encompassing 0.03 cc of the PTV) less than 110-115% of the prescription dose.

It is recognized that portions of PTV close to the skin or critical PRVs (spinal cord, brainstem, and brachial plexus) may receive significantly less than the prescription doses. PTV_Eval_6000, PTV_Eval_5600, or PTV_Eval_6600 should be created in this situation to evaluate target coverage. When under-dosing PTV_6000, PTV_5600, or PTV_6600 care should be taken to ensure that the cold spots within these PTVs do not exist within the GTV. In cases of high-dose PTVs close to skin, tissue equivalent bolus must be utilized to ensure adequate dose coverage.

It is also recognized that PTVs abutting or enclosing higher dose PTVs will have regions of maximum dose that may exceed their prescribed dose in order to achieve acceptable minimal doses to the higher dose PTVs which are considered a higher priority target.

5.3.5 Compliance Criteria

Section 5.3.1 outlines basic pathologic indications for treating patients postoperatively. We recognize there are some discrepancies in indications treating postoperatively at some institutions. In general, our study team recommends following the prescriptive treatment algorithm outlined in the protocol document. We recognize that some institutions may choose to omit adjuvant radiation in certain patients (i.e. pN1 disease as the only risk factor). Institutions should apply the same principles for deciding on adjuvant therapy regardless of treatment arm. Additionally, section 5.3.2 outlines specific elective nodal volumes based on the primary tumor site. We recognize that variations may exist between institutions in terms of treatment volumes based on the primary site, which is why we allow for some variation in volumes. We strongly suggest that institutions adhere to a standardized approach for all patients regardless of treatment arm (i.e.,

bilateral or unilateral elective neck volumes for lateralized oral tongue cancers).

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

VxGy [cc], VxGy [%], Vx%[cc], Vx%[%]: Volume [cc or %] receiving Dose [Gy, or %]
CVxGy[cc],CVxGy[%],CVx%[cc],CVx%[%]:Complement Volume [cc or %] receiving Dose [Gy, or %]
Dxcc[Gy], Dxcc[%], Dx%[Gy], Dx%[%]: Dose [Gy or %] to Volume [cc or % of total volume]
DCxcc[Gy], DCxcc[%], DCx%[Gy], DCx%[%]: Dose [Gy or %] to Complement Volume [cc or % of total volume]
Minimum dose is defined to D99%[Gy] or D99%[%]
Maximum dose is defined as D0.03cc[Gy] or D0.03cc[%]
Mean[Gy] or Mean[%]: Mean dose in Gy or %

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Table 5.3.5A: Target Volume and OAR Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Notes
PTV_6000 or PTV_Eval_6000	D95%[Gy]	>= 60	>= 58.8 and <=61.2	
	D99%[Gy]	>= 57	>= 54	
	D0.03cc[Gy]	<= 66	<= 69	Only applicable in absence of PTV_6600
PTV_5600 or PTV_Eval_5600	D95%[Gy]	>= 56	>= 53.2	
PTV_6600 or PTV_Eval_6600	D95%[Gy]	66	>= 64.7 and <=67.3	
	D99%[Gy]	>= 62.7	>= 59.4	
	D0.03cc[Gy]	<= 72.6	<= 75.9	

SpinalCord_PRV05	D0.03cc[Gy]	<= 48	<= 50	
SpinalCord	D0.03cc[Gy]	<= 45	<= 48	
BrainStem_PRV03	D0.03cc[Gy]	<= 50	<= 52	

Per Protocol range is excluded from Variation Acceptable range.

Table 5.3.5B: Recommended Dose Acceptance Criteria for Other Normal Tissue, but Not To Be Used for Plan Score

Structure	**Recommended Dose Acceptance Criteria***
Lips	D0.03cc[Gy] <= 45
Cavity_Oral (uninvolved)	Mean[Gy] <= 35; Avoid hot spots > 60 Gy
Parotid_R/L(individual)	Mean[Gy] <= 26 (for contralateral); V30Gy[%] <= 50 (for ipsilateral)
Pharynx (uninvolved)	V50Gy[%] <= 33; Mean[Gy] <= 45; V60Gy[%] <= 15
Esophagus_S	V45Gy[%] <= 33; Mean[Gy] <= 35; V54Gy[%] <= 15
Larynx_SG	Mean[Gy] <= 35
Bone_Mandible	D0.03cc[Gy] <= 66 in absence of PTV_6600; D0.03cc[Gy] <= 72.6 in presence of PTV_6600; Avoid hot spots
Glnd_Submand_R/L (contralateral)	Mean[Gy] <= 39
BrachialPlexus_R/L	D0.03cc[Gy] <= 66
Cochlea_R/L	Mean[Gy] <= 35
E-PTV	D1cc[Gy] <= 63 in absence of PTV_6600; D1cc[Gy] <= 69.3 in presence of PTV_6600

*Please keep OAR doses as low as reasonably achievable without compromising coverage to PTVs.

Table 5.3.5C: Delivery Compliance Criteria

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Start date (after surgery)	Within 42 days	43-56 days	> 56 days
Overall Treatment time	< 45 days	45-50 days	> 50 days without a medically

			appropriate indication for delay
Non-Medically Indicated Treatment Interruptions	0-2	3-4	>=5

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed three treatment days at a time and five treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding four treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

It is allowed that patients receive BID treatments with minimum 6-hour inter-fraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time confined to 6 weeks or 45 consecutive days.

5.3.6 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities must be listed in order of decreasing importance.

Prioritization for IMRT Planning:

1. SpinalCord and SpinalCord_PRV05
2. BrainStem and BrainStem_PRV03
3. PTV_6000 or PTV_Eval_6000
4. PTV_5600 or PTV_Eval_5600
5. PTV_6600 or PTV_Eval_6600 (if applicable)
6. BrachialPlexus_R/L
7. Contralateral Parotid_R/L
8. Larynx_SG and Pharynx
9. Lips and Cavity_Oral
10. Esophagus_S
11. Contralateral Glnd_Submand_R/L
12. Ipsilateral Parotid_R/L
13. Cochlea_R/L
14. Bone_Mandible
15. E-PTV

Required algorithms:

Acceptable choices of algorithm are listed at: http://rpc.mdanderson.org/RPC/home.htm

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These

principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial (e.g., conical collimators in stereotactic radiosurgery).

Primary dataset for dose calculation
If treatment planning CT is acquired with IV contrast, whether the density of the contrast should be overridden to a representative background electron density should be tested to demonstrate such density overridden is negligible to dose calculation. In addition, image artifacts such as streaks near metal, dental implants, fillings, clips or other high-density objects should be overridden with appropriate HUs.

Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

Adaptive planning (Re-planning)
In cases of weight loss > 10% or substantial swelling in the neck or face, the immobilization mask may be adjusted or re-made in order to preserve adequate immobilization, and a repeated simulation CT may be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same, except to respect clear anatomic barriers such as skin or fascial or muscle planes. Re-planning DICOM data and final plan sum dose statistics should be submitted at the end of treatment.

5.3.7 Patient-Specific Quality Assurance

Any patient-specific QA that needs to be acquired should follow institutional guidelines and AAPM task group report recommendations.

For IMRT/VMAT plans, patient specific QA is highly recommended. The recommended patient specific QA criteria is for 90% of the comparison points to pass a ± 3%/2 mm Gamma Index analysis.

5.3.8 Daily Treatment Localization/IGRT

IGRT is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section, we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

Daily IGRT is mandatory for this study and for this, sites must be head and neck IGRT credentialed (see Section 8.2). This information will be archived by the submitting institution, so it can be made available for possible future review.

5.3.9 Management of Radiation Dose to the Patient from IGRT

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;

- Linear-accelerator mounted kV and MV conebeam CT (CBCT) images;
- Linear-accelerator mounted MV helical CT images (e.g., Tomotherapy);
- In room CT or CBCT
- MRI scouts or MRI 2D/3D images
- Other mechanism, after discussion with the Study Chair and Medical Physics Co-chair.

The institution's procedure to register treatment day imaging dataset with the reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level;
- If the fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g., optic nerves and/or optic chiasm).

Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5-5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments.

NRG Oncology is concerned about the estimated doses given from IGRT and is committed to limiting the imaging dose when IGRT is used in any of its protocols. Radiation doses from IGRT are small enough dose contributions that if there is only one imaging study done per treatment session, the dose does not need to be incorporated into treatment planning and is not expected to have any clinical relevance to the patient. However, the imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Permitted Supportive/Ancillary Care and Concomitant Medications

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.

5.4.2 Participation in Other Trials

Patients are not to participate in other therapeutic trials. However, trials that do not add experimental therapeutic agents are allowed. (e.g. imaging trials, quality of life, etc) with

concurrence of the study chair.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Not applicable.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Imaging Agents

Commercial Agents

The commercial agents in NRG-HN006 are 99mTc-tilmanocept (Lymphoseek) and 99mTc-sulfur colloid.

7.1.1 Adverse Events Associated With 99mTc-tilmanocept (Lymphoseek) and 99mTc-sulfur colloid:

- Allergic-type reaction

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

7.3 Adverse Events for Commercial Study Agents
Refer to the package insert for detailed pharmacologic and safety information

7.4 Expedited Reporting of Adverse Events
All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods
- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS-24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page; contact NRG Oncology at 1-215-574-3191 for source documentation assistance.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements for Adverse Events
Arms 1 and 2: Any Phase Study Involving Surgical Intervention and/or a Commercial Imaging Agent[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

7.4.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.4.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.5 Routine Reporting Requirements for Adverse Events

All Adverse Events **must** be reported in routine study data submissions from start of protocol treatment and for 30 days after end of protocol treatment, i.e surgery, regardless of relationship to protocol treatment. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

In follow up, defined as starting > 30 days from end protocol treatment (surgery), only report AEs reasonably related (possibly, probably, definitely) to protocol treatment.

7.6 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient from the time of consent to 90 days after the end of treatment must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based

Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), or consenting/treating/drug shipment investigator in OPEN, must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI CTSU.

8.1.1 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or by calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

8.1.2 Additional Requirements for Protocol NRG-HN006 Site Registration

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).
- Surgeon Credentialing (see Section 8.1.3 for details) – at least one surgeon must be credentialed prior to patient enrollment.
- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider (see further information below).

- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process

- IRB/REB approved consent (Canadian sites only: English and native language versions)
  Note: Canadian Institutions must submit English version of consent form to NRG Regulatory (CanadianRegulatory@NRGOncology.org) for review prior to submission to CTSU. Certification/verification of IRB/REB consent translation must be provided with submission to CTSU as well (described below).

  Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

RTI Provider

To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) credentialed provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in protocol section 8.2 to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will notify your institution when all credentialing requirements have been met and the institution is credentialed to enter patients onto this study. The credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated. Upon site registration approval in RSS, the enrolling site may access the Oncology Patient Enrollment Network (OPEN) to complete enrollments (section 8.3). The enrolling site will select their credentialed provider treating the subject in OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Additional Requirements for sites in Canada

Prior to clinical trial commencement, sites in Canada must also complete and submit to NRG Regulatory (CanadianRegulatory@NRGOncology.org):

- Clinical Trial Site Information Form
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Delegation of Tasks (DTL) Log
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions).

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

8.1.3 Surgeon Credentialing

Participating surgeons must complete and sign a credentialing form prior to their institutions entering any patients onto this study. This form can be accessed on the protocol-specific page of the CTSU website. The study Research Associate will email the completed form to the Principal Investigator Dr. Stephen Lai (sylai@mdanderson.org) and the Surgical Oncology Co-Chair Dr. Steven Chang (schang1@hfhs.org) for review and approval. Dr. Lai and Dr. Chang will email approval to NRG Data Management and the Site Research Associate, then the Research Associate submits the form to the Regulatory Submission Portal on the CTSU website. Institutions should allow adequate processing time (7-10 days) before registering the first patient.

8.1.4 Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or

- Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-HN006*.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

8.1.5 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the → Regulatory section and select → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

8.1.6 Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.2 RT-Specific Pre-Registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. The credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

RT Credentialing Requirements	**Web Link for Procedures and Instructions: http://irochouston.mdanderson.org**	
	Treatment Modality	**Key Information**

	Photons	
Facility Questionnaire	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Phantom Irradiation	X	An IMRT H&N phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that an institution, depending on its treatment delivery modalities, may be required to irradiate a phantom on different delivery machines such as TomoTherapy and CyberKnife**.**
IGRT Verification Study	X	Institutions must be credentialed for boney anatomy IGRT in order to enroll patients. Instructions for IGRT credentialing are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that if an institution has been approved for boney anatomy IGRT credentialing the site will not have to re-credential for this study.
Credentialing Issued to:		
Institution	X	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.2.1 Digital Radiation Therapy Data Submission to NRG Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.

- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.3 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB

approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.3.2 Summary of Registration Procedures

This is a 2-step registration study.

- All eligibility criteria must be met prior to Step 1 registration.
- FDG PET/CT submission for central review required on all patients prior to Step 2 registration.
    - The central review will take approximately 3-5 business days from receipt of imaging, provided that the images are query free. A query will be issued in Medidata Rave if additional information is required on the images. See Section 11 for further details.
    - NRG Oncology will notify the sites via an e-mail once the central read is complete. Sites can complete Step 2 registration at this time. PET/CT negative patients will be randomized to an arm. PET/CT positive patients will go off study but will be entered in a registry and data will be collected to establish the pathological outcome of neck nodes for future clinical trials (Refer to Data submission table on the CTSU website).

8.4 Medidata Patient Cloud ePRO Registration

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application to register a patient and information about the training is in the ePRO Appendix. The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial. There are multiple versions of the app available. The **Patient Cloud** App will be used on this study. Ensure

that the patient downloads the correct version of the ePRO app. Note only 1 version of the app is active per protocol.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.5 CRA Patient Registration Instructions for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study participants. Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs. https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html

9.0 DRUG INFORMATION

Not applicable.

10. PATHOLOGY/BIOSPECIMEN

Pathology Review Guidelines

This study requires standardized local pathology review of SLN biopsies at all participating sites (see Section 10.1 for Guidelines), and mandatory central pathology review. The central pathology review includes: 1) prospective review within 2-3 weeks post-surgery on negative SLN biopsies; and 2) retrospective central pathology review for Quality Assurance, data analysis, etc. For this review, submission of biospecimens to NRG Oncology Biospecimen Bank at the University of California - San Francisco (NRGBB-SF) is recommended for all patients. See Section 10.2 for specimen collection and shipping details. In addition, remaining tissue of consenting patients will be stored at the NRGBB-SF for tissue banking and translational research (strongly encouraged but not mandatory).

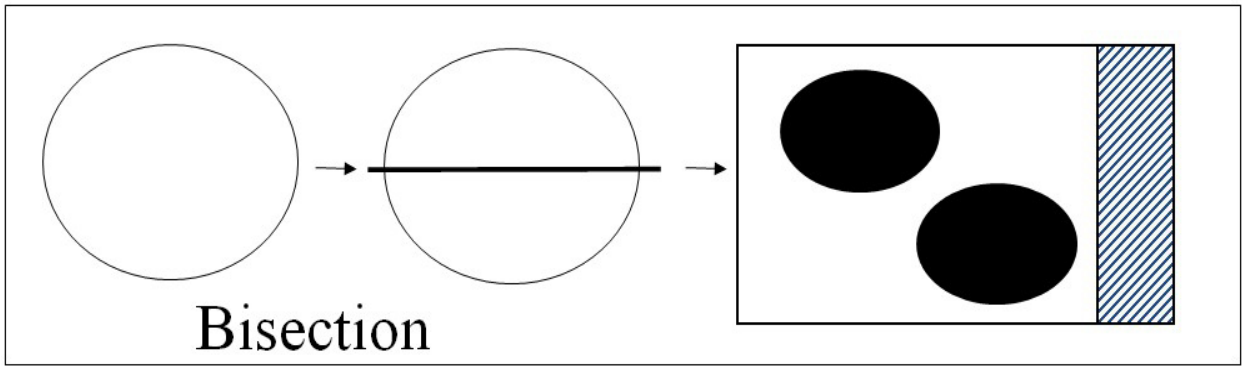
10.1 Local Pathology Review Guideline (Enrolling Institutions)

10.1.1 Primary Tumor Grossing, Sectioning, Staining, and Reporting

The primary tumor should be processed with routine pathology and reported following the AJCC 8th edition staging guideline.

10.1.2 SLN Biopsy Grossing, Sectioning, and Staining, including IHC Staining

- Frozen section analysis of sentinel lymph nodes is not advised.
- The sentinel nodes will be submitted by surgeons in designated containers to distinguish from the non-sentinel nodes from the same patient. (For SND, the best way is to submit individual levels in different containers. All the nodes will be fixed in 10% Formalin.
- The laterality, neck level, numbers and sizes of sentinel lymph nodes should be recorded in gross description. (In most of cases, the numbers of SLN would be within five). The nodes will be cut through the hilum to peripheral, bisected, for lymph nodes measuring 0.3-0.6 cm; both slices are put face-down in the cassettes, as a better chance to identify the metastatic tumors, as most of them are centered towards the hilum area reportedly. For lymph nodes measuring more than 0.6 cm, the technique of "breadloafing" perpendicular to the long axis of the nodes in 2-3 mm thickness for each slice will be applied to microscopically maximize the examined surface of the lymph nodes. Lymph nodes measuring less than 0.3 cm are submitted as whole (Figure 10-1). Three H&E levels of sections with 130 micrometers intervals will be cut and routinely stained with H&E. Three unstained slides will be saved in adjacent sections for each H&E slide. If H&E slides are negative, IHC for Pan-Cytokeratin (AE1/AE3) will be performed on one unstained slide, either on the first unstained slide or on the one adjacent to the H&E slide that shows any suspicious features. (Using this method, about 0.5 mm tissue will be cut from each slice and examined microscopically. Enough tissue should be retained in the tissue block for archiving.) The trimmed and the 130 micrometers interval paraffin rolls will be collected in 1ml Eppendorf tubes and save at -80C for future research (Figure 10-2).
- Other than routine pan-cytokeratin antibodies, p40 (nuclear stain in squamous cells) is recommended in cases with suspicious keratin debris or degraded non-viable cells.



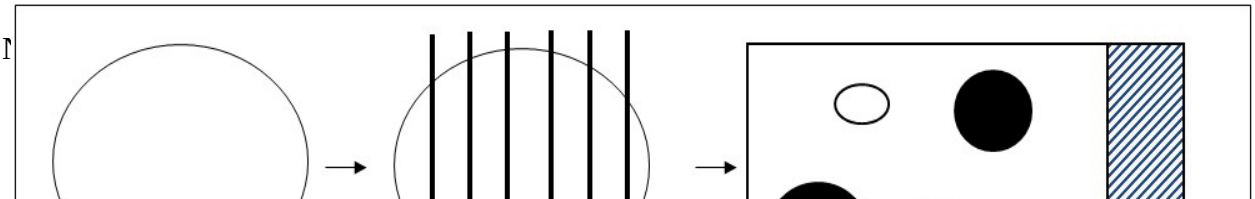


Figure 10-1: SLN grossing. For lymph nodes measuring 0.3-0.6 cm, the nodes will be bisected throughout the hilum to peripheral, and both slices are put face-down. For lymph nodes measuring more than 0.6 cm, the technique of "breadloafing" perpendicular to the long axis of the nodes in 2-3 mm thickness for each slice will be applied to microscopically maximize the examined surface of the lymph nodes. Lymph nodes measuring less than 0.3 cm are submitted as whole.

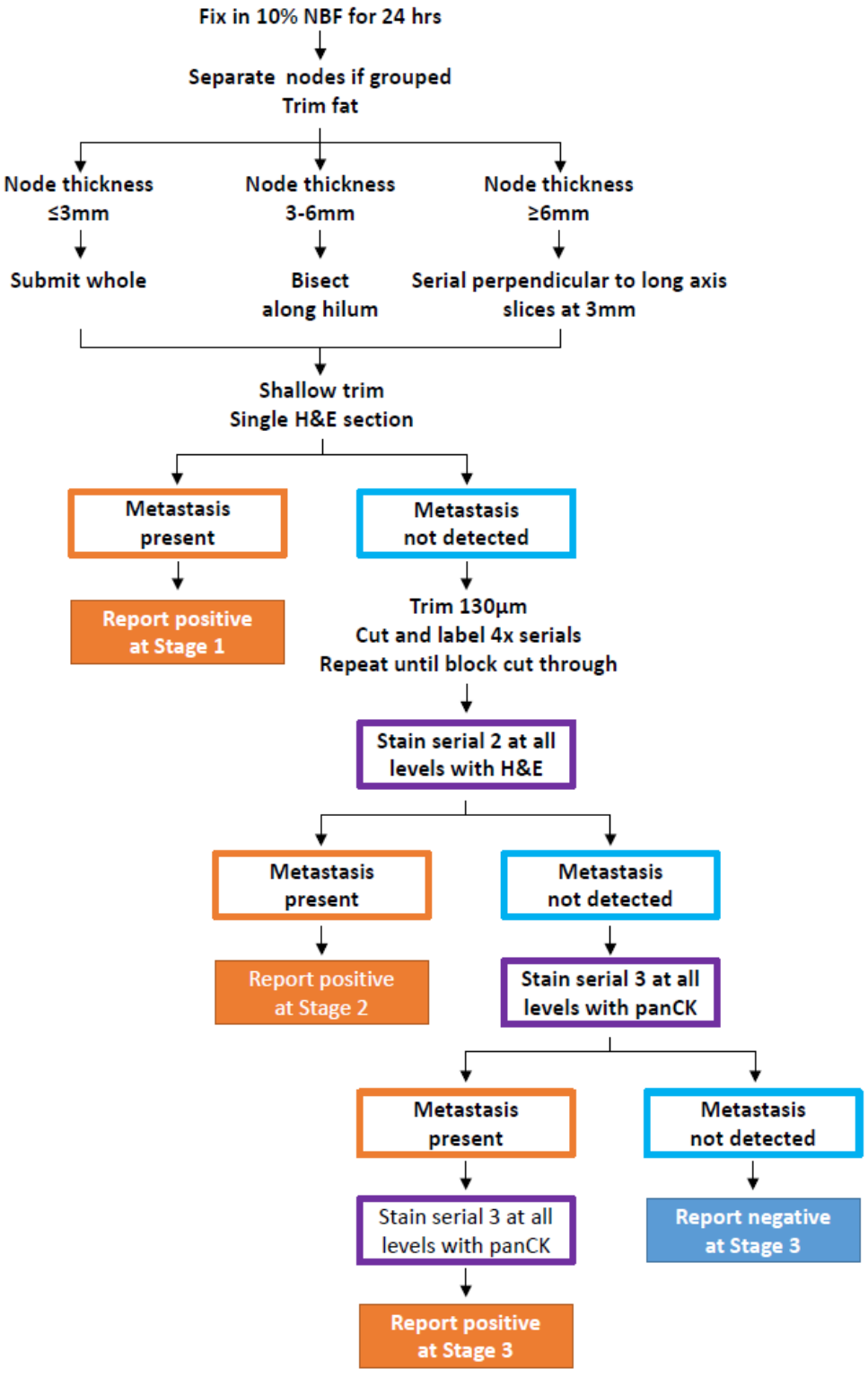


Figure 10-2: Laboratory and microscopy algorithm for SLN biopsy

10.1.3 Non-SLN (neck dissections) Grossing, Sectioning, Staining, and Reporting

The Non-SLN neck dissection specimens should be processed with routine pathology and reported following the AJCC 8th edition staging guideline.

Handling of the "non-sentinel" LNs in a neck dissection specimen to ensure that results will be reported by neck levels (IA, IB, IIA, IIB, etc.). We recommend that surgeons should divide the neck dissections into individual levels and separate them into individual labeled containers.

10.2 Central Pathology Review Guidelines

10.2.1 Mandatory Prospective Review to confirm the SLN biopsy diagnosis

Prospective central review to confirm the SLN biopsy diagnosis will be performed by the University of Texas MD Anderson Cancer Center, Department of Pathology, and NYU Langone Health, Department of Pathology, utilizing standard pathologic criteria. The primary central reviewer of each case will be one of the Pathology Co-Chairs, Dr. Diana Bell or Dr. Cheng Liu. Slides must be sent to the NRGBB for Aperio scanning for digital pathology review.

Mandatory Prospective Central Pathology Review

- Central pathology review on all negative SLN biopsies in Phase II and III. If the central review is proven to be a logistical burden for reviewers given the data from the phase II, central pathology review based on a subsample will be proposed for the phase III portion.
- Central pathology review will be conducted rapidly, and sites can expect central pathology results within 2-3 weeks following SLN biopsy if all submission materials have been received.
- Discrepancies between central review diagnosis and original pathology diagnosis will be communicated to the local pathologist. If the diagnosis between central review and original review is different, the Pathology Co-Chair will contact the site pathologist. Determination of a positive SLN biopsy by central review will be reported to NRG Oncology, and NRG Oncology will notify the site and will require that the patient have a CND. (For details of CND procedure, see Section 5.1.2 (Neck Dissection).
- Aperio digitalized images including all three H&E level slides and one cytokeratin immunohistochemistry slide on the SLN biopsy slides should be uploaded to the participating site's uploading system, and sites should provide the central reviewers with the link to the pathology site, and login information. Email to: diana.bell@mdanderson.org and cheng.liu@nyulangone.org.

- If the participating pathology cannot digitalize the slide images, they should send the slides directly to the NRGBB-SF. Images will be digitalized and the NRGBB-SF will provide access to the central review pathologists within the same timeline. See Section 10.2 for shipping and specimen details. Central reviewers will contact the site if further material is needed to successfully perform the review.
- NRGBB-SF digital pathology facility will provide scanning, storage, and sharing service for the central pathology review.

10.2.2 Retrospective Review of selected SLN cases

- Retrospective central review of all SLN negative cases submitted will be done to assess SLN biopsy technique regarding grossing, sectioning, and staining, including IHC staining. This review will be performed at MD Anderson by the central review group. The primary reviewer will be the Pathology Co-Chairs, Dr. Bell and Dr. Liu. It conducts in clusters, such as semi-annually or annually. The review includes, but is not limited to, review of the original pathology reports and data analysis.
- On cases of SLN biopsies that are found positive for small volume disease, including micrometastasis or isolated tumor cells only, as well as those with only positive immunohistochemistry findings, the local labs should send the digital pathology scanning of the representative histology and IHC slides to central pathology review (same uploading site as prospective review). The cases in question may be 10-20% of the total enrolling cases.
- If indicated, tissue blocks or unstained slides of specific cases should be made available for retrospective pathology review upon request. Additional review on cases that are identified in analyzing of the original pathology reports with uncommon findings, potential discrepancy, and consultation initiated by local pathologists.

10.3 Biospecimen Submission Tables

10.3.1 Mandatory Specimen Submissions

See detailed specimen collection/processing/shipping instructions on the protocol-specific page of the CTSU website.

<u>Mandatory Specimen Collection #1:</u> Central pathology review of SLN biopsy and neck pathology for all SLN Negative Patients.

- Aperio images or slides can be submitted for the central review. If submitting images, sites are responsible for providing links and login information to the central reviewers at MDACC and NYU. If submitting slides, send to the NRGBB-SF at the address below.
- Forms: Study-Specific ST form; Pathology Report with procedure date and accession number visible, all other PHI must be redacted. Forms must be submitted to the biospecimen bank for all patients, electronically to both the bank and the central reviewer for cases with Aperio images.
- When central review has been completed, slides will be returned to sites upon request.

Ship all slides and material for central review to:
NRG Oncology Biospecimen Bank- San Francisco
2340 Sutter Street, Room S341

San Francisco, CA 94115 415-476-7864/ nrgbb@ucsf.edu			
Mandatory Specimen Type	**Collection Time Points**	**Collection Information and Requirements**	**Shipping**
Three levels of H&E slides and one IHC stained slide for PanCK from all the negative SLN biopsy in Phase 2 and Phase 3 (digitalized images)*	Surgery	Digitalized Aperio images uploaded and stored for the duration of the trial. See 10.2.1 for instructions. Sites unable to provide digitized images can provide H&E and Pan CK stained slides.	Images to be provided to MDA. For cases without available digitalized images, stained slides should be shipped priority overnight ambient temperature to NRGBB-SF

***** If reviewers determine that a case needs further work-up by the central reviewers, tissue blocks or unstained slides must be sent to the NRGBB.

10.3.2 Optional Specimen Submissions

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

See detailed specimen collection/processing/shipping instructions on the protocol-specific website.

This study includes optional collection of biospecimens for future analyses, for example to assess biomarkers in association with treatment complications. An application for any correlative science studies to be performed on these biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

See detailed specimen collection/processing/shipping instructions at on the protocol-specific page of the CTSU website.

Optional Specimen Collection for Tissue Biobanking for Potential Future Research
Forms: Study-Specific ST Form, pathology report with accession number and date of procedure visible. All other PHI information should be redacted.
FFPE Punch Kits: can be requested at the same time as blood kits from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.
Frozen Specimen Kits: Request from NRGBB-SF by email nrgbb@ucsf.edu. Each kit comes with one pre-paid label per patient for batch shipment of frozen specimens on dry ice. Sites should only ship frozen specimens Monday-Wednesdays, Monday-Tuesday (Canada), but not during holiday weeks.
Shipping: Sites pay for FFPE shipments. Sites can ship FFPE samples Monday-Friday.

Ship specimens to:
NRG Oncology Biospecimen Bank – San Francisco
UCSF – Dept of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:
Email: NRGBB@ucsf.edu
415-476-7864/Fax 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements/ Instructions for Site	Shipping
ON ALL CONSENTING PATIENTS: H&E slide(s) of primary tumor	Surgery	H&E slide can be duplicate cut slides, does not have to be diagnostic slides. H&E must match the block being submitted.	Ship ambient temperature to NRGBB-SF by overnight courier

ON ALL CONSENTING PATIENTS: FFPE Block of primary tumor (same as H&E)	Surgery	Site should make every effort to submit the Block for this study. If site is unable to submit a Block then the following alternative is acceptable: A) Two 2mm (or 3mm) punches (tumor size dependent) embedded in paraffin* with a corresponding H&E. (punch kits available from NRG BB-San Francisco) Note: Unstained slides are not an acceptable alternative for tissue/punch blocks for banking studies.	Ship ambient temperature by overnight carrier to NRGBB-SF (use cold packs during warm weather)
ON ALL CONSENTING SLN CASES: FFPE Block, or the trimmed 130 micrometers interval paraffin rolls collected in 1ml Eppendorf tubes (see 10.1.2 for details)	Surgery	Corresponding FFPE Block. If site is unable to submit a Block then the following alternative is acceptable: A 2mm punch or the trimmed 130 micrometers interval paraffin rolls will be collected in 1ml Eppendorf tubes and save at -80C for future research Note: Unstained slides are not an acceptable alternative for tissue/punch blocks for banking studies.	Ship overnight by carrier to the NRGBB-SF.

ON ALL CONSENTING PATIENTS: Serum- Red top tube	Pre-treatment: (Before or on the day of surgery) Post treatment: 3 weeks and 6 months. If RT is received, within 1 week of post radiation completion date.	Process serum and aliquot minimum of 0.5 ml per vial into 5 cryovials. Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice. Forms: Study-Specific ST form	Ship on Dry Ice by Overnight Courier to NRGBB-SF
ON ALL CONSENTING PATIENTS: Plasma- 1 Purple Top EDTA tubes (10 mls, centrifuged and processed for plasma collection)	Pre-treatment: (Before or on the day of surgery) Post treatment: 3 weeks and 6 months. If RT is received, within 1 week of post radiation completion date.	Process plasma and aliquot a minimum of 0.5 ml plasma into each of five 1.0 ml cryovials. Place into biohazard bag and immediately freeze tubes upright at -70 to -90º C. Store frozen until ready to ship. Forms: Study-Specific ST form	Ship on Dry Ice by Overnight Courier to NRGBB-SF
ON ALL CONSENTING PATIENTS: Whole Blood- EDTA tube for DNA	Pre-treatment: (Before or on the day of surgery)	Collect blood, mix and aliquot a minimum of 1 ml of whole blood per vial into three (3) 2 ml cryovials. Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice. Forms: Study-Specific ST form	Ship on Dry Ice by Overnight Courier to NRGBB-SF

*The NRGBB-SF can embed the punches for sites without the facilities to embed punches into blocks.

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Imaging

This imaging section includes procedures for ^{18}F FDG PET/CT, an integral imaging marker for this study, as well as lymphoscintigraphy (part of the surgical procedure) and SLN SPECT/CT.

11.1.1 ^{18}F FDG PET/CT Imaging

Recommended FDG-PET/CT Imaging Sequence and Details

- FDG PET/CT must be performed prior to step 2 registration. Note: FDG PET/CT done prior to step 1 can be submitted for central review.

- All FDG PET/CT scans must be performed on a certified clinical PET/CT scanner, accredited by the American College of Radiology (ACR) or similar accrediting organization, and follow the FDG PET/CT protocol outlined in this section. The scans will be quality checked by the IROC Philadelphia staff and submitted for central review, if quality is acceptable. Otherwise, a repeat whole-body PET/CT will be required prior to Step 2 Randomization on an accredited clinical PET/CT scanner following the protocol.
- All female participants of child bearing potential will have a negative pregnancy test within 72 hours prior to administration of 18F FDG or have been surgically sterilized or post-menopausal at least one year
- ***Scanner:*** A PET/CT scanner with current clinical accreditation by American College of Radiology or other professional /accrediting organization.
- **Patient preparation:** Patients should be NPO except water for at least 4 to 6 hours prior to injection of FDG. Patients with IV lines should not have glucose solutions for 4 to 6 hours before the test.
- Immediately prior to FDG injection, finger stick blood sugar should be <200mg/dL to proceed. If the blood sugar is >200 mg/dL, insulin may be administered according to institutional standard operating procedure (SOP), followed by re-measurement(s) of blood sugar. If post-insulin blood sugar is < 200 mg/dL, FDG PET study can proceed. Otherwise, test should be rescheduled.
- **FDG injection and post-injection uptake period:** FDG should be injected 55 to 70 minutes before PET scan. Once injected with FDG, the patient is be instructed to rest quietly prior to PET scanning.
- **Use of oral CT contrast material:** Oral contrast used (or not) according to institutional standard operating procedures
- It is recommended that patients be imaged from the orbits through the upper thigh.
- A dedicated head and neck imaging acquisition (orbits to upper thorax) with the patient's arms down is recommended given the higher sensitivity of this exam. The remainder of the body is to be scanned with the patient's arms raised over the patient's head. If patients cannot tolerate these positions for the PET/CT scan, investigators can use different patient positioning.
- A non-iodinated low-dose CT scan is required for attenuation correction and anatomical localization of findings in the PET scan. The radiation dose of this CT scan as assessed by the CTDIvol would be nominally 10 mGy or lower – this radiation dose level is lower than (typically by a factor of 2 or more) the radiation dose associated with diagnostic quality CT scan. The same CT acquisition can most often be used for both attenuation correction and anatomical localization.
- The typical acquisition parameters for the low-dose CT scan as follows: kV = 110-130; effective mAs = 50–100 (patient dependent tube-current modification recommended); gantry rotation time < 0.5 sec; maximum reconstructed width = 3–5 mm without overlap; standard reconstruction algorithm, minimum reconstruction diameter = outer arm to outer arm; and without iodinated contrast.
- The longitudinal field of view of the CT scan for attenuation correction will range from the mid thighs to the base of the skull. Arm positioning will be the same as for the PET scan (see above).
- The CT scan will be performed during the patient's normal breathing. No respiratory

gating is needed.

- As part of the dedicated head and neck PET/CT scan with arms down, the acquisition parameters for this dedicated head and neck CT, low-dose CT scan must be approximately as follows: kV = 110 -130; effective mAs = 90 -150 (patient dependent, tube current modification recommended); gantry rotation time < 0.5 sec; maximum reconstructed slice width = 2.5 mm (overlap acceptable); standard reconstruction algorithm, maximum reconstruction diameter = 30 cm; and without iodinated contrast.
- After the CT scan, a 3D PET scan covering the same axial field of view will be performed. The number of bed positions and the acquisition time per bed position will be scanner specific. Typical parameters are 6 bed positions and an acquisition of 2 to 5 minutes per bed position.
- The dedicated head and neck PET/CT will typically follow the body exam. Two bed positions will often suffice for orbits to upper thorax (top of aortic arch), and acquisitions must be at a minimum of 5 minutes per bed position and be reconstructed into a 30 cm field of view (FOV) with at least a 256 x 256 matrix.
- **Use of intravenous CT contrast material:** Attenuation correction of PET data using CT scans enhanced by intravenous (IV) CT contrast has a minor effect upon PET standard uptake value (SUV) measurements (compared to SUV measurements derived from FDG PET scans that use non-contrast CT scans for attenuation correction). Therefore, IV contrast use is permitted as per local institutional SOP.

FDG-PET/CT Image Reconstruction

The PET/CT data will be corrected for dead time, scatter, randoms, and attenuation using standard algorithms provided by the scanner manufacturers. For the dedicated head and neck views, a post-filter with a full-width at half maximum (FWHM) in the range of 5 mm is recommended.

Submission of FDG-PET/CT Image

Following the completion of PET/CT imaging at the site, the institution will submit images in DICOM format via TRIAD to IROC Imaging; see Sections 11.1.2 and 8.2.1 for details regarding TRIAD.

If an outside FDG PET/CT scan is performed, it will be submitted for central review via TRIAD to IROC (Philadelphia). The scan will undergo a quality check for compliance with the protocol and scanner accreditation as described above. If acceptable standard, as per above protocol, then the scan will undergo central review within 3-5 business days.

11.1.2 FDG-PET/CT Central Interpretation

- Please submit the FDG PET/CT scans (acceptable quality) to ACR via TRIAD. Images will be quality checked by the IROC Philadelphia staff (within 1-2 business days). A query will be issued in Medidata Rave if additional information is required on the images. If the images are submitted in correct DICOM format and are query-free, they will be interpreted ‘live’ (within 2-3 business days) by a team of three experienced nuclear medicine physicians / radiologists. Each PET/CT will go through a single read according to the central read schema described below

culminating in positive or negative for each side of the neck and overall for the patient before randomization. The central overall interpretation is the final read for eligibility.

- The confirmation/decision of patient eligibility per the central imaging review will be returned to the submitting site via an email within 3-5 business days of submission of query free imaging studies to ACR. Findings from the central read will take priority over site read regarding subject qualification for trial participation. Site investigators and study chairs may discuss potential issues with the central reviewers in order to resolve potential discrepancies.

- The schema for central read includes both *a priori* SUVmax cutpoints used in ACRIN 6685 (SUVmax 2.5 or 3.5, corrected for body weight, standard ordered subset expectation maximum – OSEM- reconstruction), as well as a structured qualitative visual analysis used in ACRIN 6685. Although the NPV for SUVmax cutpoints (SUVmax 2.5 or 3.5) was higher than for the overall visual read in ACRIN 6685 (0.94 versus 0.87, respectively), we will use both methods.

- The central read definitions will be:
  Negative PET: FDG uptake equal or less than blood pool (visual analysis) and SUVmax < 3.5
  Positive PET: FDG uptake greater than blood pool (visual analysis) or SUVmax ≥ 3.5.

11.2 Sentinel Lymph Node Radiotracer Administration

Approved radiotracers: 99mTc sulfur colloid or 99mTc tilmanocept

- **Sites in Canada are permitted to use only 99mTc-sulfur colloid.**

The total injected activity recommendation for sufficient remaining activity during intraoperative detection via gamma probe is 0.5-1 mCi for a single day SLN + surgery procedure (recommended) and 2-4 mCi for 2-day SLN + surgery procedure (on the 2nd day). In the situation where there may be a longer time delay (greater than 36-48 hours) between SLN imaging and surgery (e.g., surgery on Monday that may preclude Sunday radiotracer injection), a second radiotracer administration on day of surgery at activity levels for single day SLN + surgery procedure (0.5-1 mCi) is recommended; this scenario is however discouraged.

The technique of injection is crucial to obtain good distribution of the radiotracer and may vary depending on the location of the primary tumor. The radiotracer is to be administered as two to four superficial (submucosal) peritumoral injections, depending on the size and localization of the tumor, at each quadrant around the primary tumor. The activity might be diluted in a total volume not exceeding 0.4–0.5 mL (0.1–0.2 mL each syringe) of solution. The injections would be within 1 cm of the tumor edge. The injection should be performed with a 27-gauge, metal hub hypodermic needle.

Radiotracer injection should be performed by either the head and neck surgeon or nuclear

medicine personnel depending upon expertise, experience and level of comfort. Each institution will determine appropriate training for oral cavity injection of the radiotracer.

Immediately after injection, the injection site can be blotted with a sponge to remove saliva and secretions or the patient should rinse the oral cavity without swallowing in order to reduce radioactive contamination of oral cavity and saliva.

11.2.1 Sentinel Lymph Node Planar Imaging (scintigraphy)

Patient preparation:

- There are no dietary or medication restrictions for the procedure. Patients should follow preoperative restrictions if the procedure is performed on the same day as surgery.
- Adequate anterior hyper-extension of the neck is required, as long as tolerated by the patient, in order to accurately evaluate the neck levels, especially level I.

Planar Imaging Acquisition protocol:

- Place gamma camera heads in an anterior and posterior orientation about the patient's head and neck region and minimize the neck to collimator distance (to improve image spatial resolution).
- Immediate dynamic acquisition: This is not required but may be performed at the discretion of the nuclear medicine physician according local site clinical practice. Acquire immediate dynamic images of the neck in anterior view (within 2 min post-injection); the dynamic study typically encompasses the first 10-15 min. This part of the imaging process may be used to identify lymphatic vessels that drain the tumor. Recommended dynamic imaging parameters are provided below.
- Place a Cobalt-57 (Co-57) radioactive sheet source on the lower (posterior) gamma camera head so as to concurrently acquire the transmission and emission scan to help visualize the body contour.
- Static image acquisitions: anterior/posterior (AP) views should be acquired shortly (typically 3-5 min) after completion of all injections. This part of the imaging process is used to identify the LNs that receive direct drainage from the tumor. Recommended planar imaging parameters are provided below. Repeat planar imaging till tumor drainage and SLN is visualized (this may take 15 min to 30 min in some cases).
- Static planar images should be acquired from vertex to a region that extends below the clavicle to completely explore all possible regions of potential drainage.
- Once tumor drainage and SLN is visualized on the AP images, then acquire a lateral (LAT) view image on the side of the drainage, again with the Co-57 sheet source to concurrently acquire the transmission scan is acquired. Then proceed to mandatory SPECT/CT imaging (Section 11.2.3).
- If tumor drainage and SLN is NOT visualized on the AP images up to 30 min post injection, then terminate the static image acquisitions (no need to perform the LAT images) and proceed directly to mandatory SPECT/CT imaging (Section 11.2.3).
- Recommended parameters for Planar image acquisition:
    - Acquisition – Image 10 min after injection of radiotracer
    - Positioning – Minimize neck to collimator distance

- Photopeak Center Energy – 140 keV
- Photopeak Width – 15% to 20%
- Matrix – 256 x 256
- Preset time – 180-300 sec
- Zoom factor - 1.5 (optional)
- Collimator – MELP or equivalent preferred (LEAP or LEHR allowed only if ME not available)

- Recommended Dynamic Imaging parameters: Same parameters as planar image acquisition except for the stop time. Acquire 1 minute dynamic frames; start immediately after completion of all injections for 5-10 frames.

11.2.2 Sentinel Lymph Node SPECT/CT Imaging

SPECT/CT Imaging Acquisition protocol:

- A one bed SPECT/CT must be performed immediately after the late static images in the same patient position as the planar scintigrams. The typical longitudinal SPECT field of view (FOV) is about 38 cm. The injection location and drainage sites seen in Planar images should be central in the SPECT FOV.

- Recommended parameters for SPECT acquisition of SPECT/CT are:
  - Acquisition – Image immediately after late static images
  - Photopeak Center Energy – 140 keV
  - Photopeak Width – 15% to 20%
  - Scatter window – same as photopeak window width adjacent and lower to the photopeak energy window (109-130 keV for 15% photopeak window and 98-126 keV for 20% photopeak window)
  - Orbit – Step and Shoot with body contour
  - Angle step – 3 degrees
  - View – 120 over 360 degrees (60x2 dual head camera)
  - Pixel matrix – 128 x 128 (3-5 mm voxels)
  - Time per view – 20 to 30 sec per view
  - Collimator – MELP or equivalent preferred (LEAP or LEHR allowed if ME not available)
  - Reconstruction – SPECT images will be reconstructed with OSEM (or other SPECT/CT vendor provided) iterative reconstruction engine with scatter correction, CT-based attenuation correction, and collimator resolution compensation (if available). Typical iterative reconstruction parameters are: 8 iteration and 16 subsets and a post reconstruction Gaussian filtration with full-width at half maximum (FWHM) of 5 mm.

- Recommended parameters for CT acquisition of SPECT/CT
  - A non-iodinated CT scan is required for attenuation correction and anatomical localization of findings in the SPECT scan. The radiation dose of the CT scan as assessed by the CTDIvol would be nominally around 10 mGy – a radiation dose level that is lower than (typically by

a factor of 2 or more) the radiation dose associated with diagnostic quality CT scan. The same CT acquisition can be used for both attenuation correction and anatomical localization.

- The longitudinal FOV of the CT scan should be the same as the SPECT scan range with similar arm positioning (arms down and not over the head). The CT scan will be performed during the patient's normal breathing. No respiratory gating is needed.
- The typical acquisition parameters for the low-dose CT scan as follows: kV = 110-130; effective mAs = 50–100 (patient-specific automatic tube-current modification recommended); pitch = 1.2; gantry rotation time <= 1 s.
- CT images are reconstructed using FBP with reconstructed image thickness of 1.5 to 3 mm with 0.5 to 1 mm overlap between images; standard (sharper preferred) reconstruction algorithm, minimum reconstruction diameter.

o Generate secondary captures of fused SPECT and CT images as per institutional practice for archive on institutional PACS.

11.2.3 SPECT/CT System Requirements

The SPECT/CT scanner with current clinical accreditation by American College of Radiology (ACR) in NM subspecialty or the Intersocietal Accreditation Commission (IAC) in Nuclear/PET. Acceptability of accreditation by other organizations will be decided by the Co-Chairs on a case-by-case basis.

11.3 Patient-Reported Outcomes (PROs) and Quality of Life (QOL)

11.3.1 Description of QOL Instruments

Neck Dissection Impairment Index (NDII)

Neck- and shoulder-related dysfunction and effect on disease-specific QOL have been described after neck dissection using the Neck Dissection Impairment Index (NDII), a validated Patient-Reported Outcome (PRO) instrument, developed by Taylor et al., 2002. This PRO instrument was specifically designed to measure neck- and shoulder-related QOL in the head and neck cancer population after a neck dissection. The rationale for selection of the NDII to measure patient reported neck and shoulder impairment was selected with input from The Head and Neck Cancer Patient and Family Advisory Council at Henry Ford Hospital, supported by AHRQ and PCORI funding mechanism. This was formed through engaging a broad coalition of stakeholders including cancer survivors, caregivers, support groups and clinicians. The NDII is a multidimensional instrument which measures the impact of neck and shoulder dysfunction from the patient's perspective and has 10 questions related to physical (pain, discomfort, stiffness), how the patient is bothered by functional limitations (bother by difficulty in self-care, limitations in lifting light, heavy objects, reaching, bother by activity level), and impact of neck treatment on social (recreational, work) domains. NDII is a neck- and shoulder-related QOL tool, and not an objective functional assessment of shoulder function, but does measure patient perceived neck and shoulder dysfunction primarily related to injury to the spinal accessory nerve after neck dissection. The NDII can be completed in under five minutes. Taylor et al (2002), originally

validated the NDII in a cohort of 54 patients in a cross sectional study, (a total of 32 accessory nerve spared modified radical (MRND) and 32 selective neck dissections (SND) were performed). The mean score after neck dissection is 67.8 ± 17.4 (range, 7.5-100.0). The mean time to PRO assessment was 33.7 months after surgery, with a minimum of 11 months after surgery. The NDII test and retest correlation was 0.91 ($p<0.001$) with an internal consistency Cronbach α coefficient of 0.95. Convergent validity was assessed using the Constant's Shoulder Scale ($r=0.85$, $p<0.001$), a validated clinical assessment of shoulder function (Chepeha 2002) and the SF-36 domains (role-physical and physical functioning domains). In a double blinded randomized trial by Parikh et al, comparing level IIa versus level IIb elective supra-omohyoid neck dissections in oral cancer patients, the NDII was able to detect changes in shoulder related QOL from injury to the spinal accessory nerve. Furthermore, objective functional endpoints including range of movement, electromyography (EMG) and nerve conduction studies (NCS) of the trapezius muscle at baseline, 6 weeks and 6 months after surgery showed that NCS and EMG findings were supported by NDII. The change in trapezius motor amplitude fell in both groups although more so in patients undergoing IIb dissections. Correlations were stronger with the NDII questionnaires compared to the range of movement physical therapy assessments measuring range of motion. Gallagher et al, demonstrated in a cross sectional single institutional study that the NDII was able to distinguish between a modified radical neck dissection from a selective neck dissection. Patients with modified radical neck dissection reported lower scores than those with selective neck dissection (85 [10-100] vs. 92 [30-100]; P = .01. These data support the use of the NDII to distinguish the impact of the type of neck dissection on patient reported shoulder QOL. There is also evidence that the NDII can distinguish between a sentinel node biopsy and an elective neck dissection. Non-randomized data from Murer et al in a cross-sectional analysis of 62 patients undergoing SLN or END, demonstrated that NDII was significantly higher (indicating higher QOL) in the SLN arm (mean score, 99.7 (range, 90-100) compared to the END (94.3 (range, 32.5-100) arm (Murer 2011). This corresponded to objective shoulder function measures with a higher Constant Shoulder Scale Score range, 97.3-100% for SLN vs 65.3-100% for END.

Determination of the Minimum Important Difference (MID) for the NDII

The minimum important difference (MID) of the NDII is estimated to be in the range of 5-10 points. The granularity of the scale is such that a 5-point change for an individual translates to a change in impairment by one unit (e.g., from "a little bit" to "a moderate amount") across two items or by two units (e.g., from "a little bit" to "a lot") in a single item or a 7.5 point change is a one unit change across three items, or by three units in a single item. Neck Dissection Impairment Index (Questionnaire). The NDII has 10 items each with a 5-point Likert response. Scoring was achieved by rating response items from 1 to 5 (5 ''not at all,'' 4 ''a little bit,'' 3 ''a moderate amount,'' 2 ''quite a bit,'' 1 ''a lot''). Standardization for score of 100: [(raw score - 10)/40] x 100. The lower the patient scores, the greater the impairment. For this study, a 7.5-point difference (Minimum Important Difference; MID) in the mean individual NDII scores between arms for the all-risk patients in an ITT analysis at the 6-month post-surgery time point is defined as clinically meaningful (Ringash 2007), as there is lack of prior data on the MID in this patient population with early-stage oral cavity cancer for the NDII. The common standard deviation (SD) of 20 points was based on a psychometric evaluation of the NDII instrument in 170 head and neck cancer patients (Stuiver 2016). In that study, the SD for the NDII scores were 21 and 19.1 points at 1-3 months after surgery (1st assessment) and 3 months

after the first assessment, respectively. The NDII has demonstrated excellent reliability, validity and correlation (Gallagher 2015, Stuvier 2016) with the objective Constant Shoulder Scale (CSS), which objectively measures shoulder function (Constant 1987). When considering a distributional approach to determine MID (Yost 2005), the standard deviation (SD) at 7 weeks was 21.0, suggesting a MID of the NDII ranges from 7.0 (SD/3) to 10.5 (SD/2). From these observations, we expect the MID range to be from 7 to 12. This is the best support we have for our rationale for selected the MID of the NDII. The MID selected, also considers that patients with intermediate-risk pathological features who receive radiation therapy will have reduced NDII scores, but that this will affect both arms.

Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH)
The Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) is an 11-item tool addressing patient-reported disability in relation to performing specific tasks involving the upper limb, including arm, shoulder and hand, and measures physical function and symptoms related to upper-limb musculoskeletal disorders (Beaton 2005). The QuickDASH instrument covers functional domains, social domains and pain. While there is some overlap with the NDII, this instrument also asks questions specific to the hand and arm, which are not included in the NDII. Compared to the NDII, the QuickDASH also focuses more on ability to perform specific tasks, rather than the patient's perception of "bother". The QuickDASH is therefore focused primarily as a disability assessment of any upper extremity musculoskeletal disorder and is not specific to disabilities after neck dissection. It has strong psychometric properties and been widely used across multiple populations, particularly in orthopedic populations, but less used in the head and neck cancer population (Eden 2014).

The summative score is on a 100-point scale, with 100 indicating the most disability and 0 indicating no disability. Only one missing item can be tolerated to calculate the score. Each question has 5-point responses, and takes less than five minutes to complete. The QuickDASH was also selected with the input from the patient advisory council from Henry Ford Hospital.

Survey validity: The QuickDASH has been shown to have good psychometric properties across 14 studies of injury and surgery of the upper limb (Mintken 2009). A study of the NDII and DASH found that their scores are correlated in rank (Spearman's correlation coefficient: -0.86 [Eden 2014]), though impairment, measured by NDII, need not result in disability, as measured by QuickDASH. For instance, while the patient may experience stiffness in the left shoulder (impairment), they may not perceive disability washing their back because the right shoulder is fully functional.

Clinical validity: The MID of QuickDASH was estimated to be 8%, in a shoulder pain population, with 80% sensitivity and 77% specificity to discriminate "improved" from "stable" pain scores after 2-4 weeks of physical therapy (Mintken 2009). In a cross sectional study of 89 patients, at a median time of 3 years since head and neck surgery (with selective, modified neck dissection, unilateral and bilateral), patient reported upper limb and neck dysfunction were reported using the QuickDASH instrument (Gane 2017). In this study, patients undergoing neck dissection experienced both neck and upper limb dysfunction. Worse Quick-DASH scores were found with longer time since surgery, undergoing post-operative radiation, and patients reporting shoulder pain. Median scores for the whole cohort, 11 (quartile-Q1-Q3, 3-32), after unilateral

selective ND were 11 (Q1-Q3, 5-28), unilateral MRND was 5 (Q1-Q3, 0-34), and bilateral ND was 17 (Q1-Q3, 2-50) (Scores range from 0 = no functional impairment to 100 = total functional impairment). Corresponding median score for shoulder pain, and neck pain on a visual analogue scale (VAS), was 5, 3, 3, 16 and 11, 11, 9, 9, where 0 mm = no pain, and 100 mm = worse imaginable pain). This study suggested that patients experience loss of function at the both the neck and upper limb level following a neck dissection. While the levels of dysfunction were low, the range of responses suggests that a portion of patients have high levels of upper limb and neck disability.

Hence use of the NDII and Quick-DASH will be a complementary patient reported evaluation of neck and shoulder dysfunction and QOL, and disability of the upper extremity after SND and END.

Functional Assessment of Cancer Therapy - Head and Neck, Version 4
In this trial we will use a head and neck specific QOL instrument, the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) to capture PRO specific to multimodality management of head and neck cancer including surgery and post-operative radiation (PORT) with or without chemotherapy, based on pathological risk factors. The FACT-H&N will allow calculation of the FACT-Trial Outcome Index (TOI) which removes emotional and social wellbeing as these are not as likely to change as quickly longitudinally in response to therapy (http://www.facit.org/). This instrument measures the multidimensional QOL and will capture the effects of treatment (including RT and chemotherapy depending on PORT indications). The hypothesis is that the SLN biopsy arm compared to END arm, will have higher FACT-TOI scores, as patients who are node negative will be spared a completion neck dissection and will not require additional multimodality therapy, including radiation or chemotherapy. FACT scoring and information may be found at https://www.facit.org .

NRG Oncology has obtained permission to use the FACT-H&N for this study in English only.

Quality-Adjusted Survival, EuroQol (EQ-5D-5L)
The EQ-5D™ is a trademark of the EuroQol Group, it is a well-accepted instrument to measure general QOL and patient preference or health utilities (EuroQol Group 1990). Patient preference or health utilities, allow calculation of quality-adjusted life years (QALYs). QALYs are calculated by multiplying life years by the utility of the given health state. EQ-5D will also allow us to perform a comparative effectiveness evaluation between the SLN biopsy and END arm as an exploratory analysis (https://euroqol.org/). It is a 2-part questionnaire that the patient can complete in approximately 5 minutes and has been translated into multiple languages. The first part consists of 5 items covering 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is graded on 5 levels: 1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, and 5-unable to perform/extreme problems. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. Either the index score or the VAS score can be used in the quality-adjusted survival analysis. The benefit of measuring quality-adjusted survival is that the product, quality-adjusted survival, can be compared to the outcomes of other interventions across disease sites and can be used by health policy makers to rank interventions. The EQ-5D-5L is available in over 125 languages.

NRG Oncology has obtained permission to use the EQ-5D-5L for this study in English.

11.3.2 Administration of NRG-HN006 Patient-Completed Questionnaires

Quality of Life Patient Population
All patients enrolled in NRG-HN006 who are English speaking will be required to complete the NDII at baseline and participate in the QOL study. Patients who cannot read and understand English cannot participate on this study. The questionnaire may not be translated in written format. Since the NDII is the primary endpoint for the phase II study and co-primary endpoint for the phase III study, completion of the NDII is required at baseline and at 6 months, although permitting for missing data and /or compliance issues. Completion of the remaining PROs are strongly encouraged. For time points of administration, see Section 4.

Administration Instructions
Questionnaires are to be administered per Section 4. For patient opting out of ePRO, the PRO forms should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. The completed forms will be data entered in Medidata Rave.

Patients who never initiate NRG-HN006 study therapy or who experience disease progression should continue participating in the PRO study. If a patient does not come in to clinic, the questionnaires will either be mailed to the patient or the research assistant will call the patient to complete the forms. If the patient does not return the forms within two weeks the patient will be called and either another set will be sent or the patient will complete the questionnaires over the phone with the research assistant.

If a patient declines to complete a scheduled PRO forms or if the questionnaire is not completed for any other reason (and cannot be completed by phone or mail), the QOL coversheet must be completed in Rave. For patients who agree to use ePRO for PRO collection please refer to Appendix III.

12 MODALITY REVIEWS

12.1 Surgical Quality Assurance Reviews

The Principal Investigator Dr. Stephen Lai, Surgical Oncology Co-Chair Dr. Steven Chang, and members of the SQAWG will perform a surgical quality assurance review of all patients enrolled onto this trial. The goal of the review is to evaluate protocol compliance related to the node acquisition via SLN biopsy and neck dissection. The review process is contingent on timely submission of surgical treatment data and will be performed on an ongoing basis once complete data of each case is received.

Surgical Protocol Compliance Criteria
Deviations Unacceptable:
Those deviations that affect patient safety/outcome, which will result in the surgeon being

suspended from further participation in the study, such as:

- Positive margin rate exceeding 20% (assessed every 5 cases accrued);
- Close margin rate exceeding 40% (assessed every 5 cases accrued);
- Inadequate nodal dissection (<15 nodes removed) exceeding 20% (assessed every 5 END/CND cases accrued);
- Bleeding required return to the operative control exceeding 20% (assessed every 5 cases accrued);
- Inability to identify SLN intraoperatively exceeding 20% (assessed every 5 cases SLN Biopsy accrued).

The SQAWG in conjunction with the NRG Oncology Statistics & Data Management Center (SDMC) will monitor the cases by surgeon. In the event that the surgical quality assurance review identifies unacceptable deviations on 5 cases enrolled on the study, then the surgeon will be removed from the pre-requisite module in the OPEN registration system. The site will be notified by either the SQAWG or the NRG Data Manager with instructions on how to be reinstated. Reinstatement will be dependent on the recommendations from the overall Study Chair in consultation with the surgery co-chair and SQAWG and receipt of a revised corrective action plan or training.

For more details see Appendix IV.

12.2 Pathology Quality Assurance Review of the SLN Biopsies

The Pathology Co-Chairs, Dr. Diana Bell and Dr. Cheng Z. Liu will conduct central pathology quality assurance review on all cases. The review may include both SLN biopsies, non-SLN neck dissections and the primary tumors.

Local pathologists should follow the guidelines for SLN biopsy outlined in Section 10.1. The Pathology Co-Chairs can provide consultation on ambiguous or challenging individual cases if requested by site local pathologist.

There are interpersonal discrepancies and a learning curve in the histological interpretation of SLN biopsies by individual pathologists, especially for micrometastases and isolated tumor cells. For these purposes, stringent quality assurance measures are required. The local pathology review will recognize the potential pitfall and apply stringent QA.

- Sites must submit the pathology reports for central pathology review. The pathology reports will be uploaded in Medidata Rave (refer to data submission table on the CTSU website). The pathology reports must document the following SLN biopsy features: laterality, neck levels positive vs. negative, giving the details of numbers of positive/negative nodes; location of metastasis subcapsular versus parenchymal; size of the metastasis (semiquantitatively reporting in macrometastasis, micrometastasis, and isolated tumor cells, following the consensus established on breast lymph node reporting); and testing methods - H&E and/or IHC (with description of antibodies).
- Discrepancies between central review diagnosis and original pathology diagnosis will be communicated to the local pathologist. If the diagnosis between central review and original review is different, the Pathology Co-Chair will contact the site pathologist in order to adjudicate any such discrepancy.

13 DATA AND RECORDS

13.1 Data Management/Collection

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
- Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
    - Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
    - Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

Summary of All Data Submission: Refer to the data submission table on the CTSU website.

Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 8.2.1 for TRIAD account access and installation instructions.)

<table>
<tr><td rowspan="5">DICOM DIGITAL DATA</td><td>DICOM CT IMAGE SET</td><td rowspan="9">TRIAD submission time point = RT DIGITAL PLAN

Due within 1 week of the start of RT</td></tr>
<tr><td>DICOM RT STRUCTURE</td></tr>
<tr><td>DICOM RT DOSE</td></tr>
<tr><td>DICOM RT PLAN</td></tr>
<tr><td>*DICOM pre-operative diagnostic CT (Required when applicable)
*DICOM PET/CT (Required when applicable)
*DICOM MRI (Required when applicable)</td></tr>
<tr><td colspan="2">*All image data sets used for structure delineation must be submitted with RT data (Section 5.3.2).</td></tr>
<tr><td colspan="2">All required structures MUST be labeled per the tables in Sections 5.3.2 and 5.3.3.</td></tr>
<tr><td colspan="2">Upon submission of the Digital Data via TRIAD, complete an online Digital Data Submission Information Form (DDSI)
https://www.irocqa.org/Resources/TRIAD-for-RT-QA</td></tr>
<tr><td colspan="3">NOTE: ALL SIMULATION AND PORTAL FILMS AND OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.</td></tr>
</table>

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 Global Reporting/Monitoring

This study will be monitored by the Data Mapping Utility (DMU).

For studies assigned Demography monitoring and enrolling patients via OPEN: Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

14 STATISTICAL CONSIDERATIONS

14.1 Study Design

This study is designed as a randomized, phase II/III trial aiming at comparing Elective Neck Dissection (END) and Sentinel Lymph Node (SLN) Biopsy in terms of shoulder related-quality of life (QOL) and disease-free survival (DFS) in patients with early-stage oral cavity squamous cell carcinoma (OCSCC) (cT1-2N0). The phase II uses a superiority design with shoulder-related quality of life (QOL), as measured by the Neck Dissection Impairment Index (NDII), as the primary endpoint. The phase III portion is a non-inferiority trial with DFS as the primary endpoint. The NDII is a hierarchical co-primary endpoint for the phase III. Patients enrolled to the phase II will be included in the primary endpoint analysis of the phase III based on 618 randomized patients. In phase II, 194 randomized patients are required for the analysis after accounting for QOL non-compliance, so 228 patients will be randomized.

With this trial, the difference in 6-month NDII scores between arms in the phase II will determine if the study should proceed to a phase III study ("Go/No-Go" decision) to evaluate DFS and NDII. The phase II portion will also determine the feasibility for conducting a SLN biopsy-related study in the NCTN setting. While sufficient DFS events will not be available during the phase II portion of the study, evaluation of the NDII scores between arms in the intermediate (6 month) period, will allow for moving into a phase III study based upon shoulder-related QOL for patients treated with SLN biopsy compared to END, potentially shortening the overall duration of the study if no shoulder-related QOL difference between the surgical arms is detectable.

Enrolled OCSCC patients with FDG PET/CT negative result will be stratified by clinical and radiographic T-stage (T1 vs. T2) and Zubrod performance status (0 vs 1-2) before being randomized to receive either SLN biopsy or END in a 1:1 ratio. Enrolled OCSCC patients with FDG PET/CT positive result will go off study and their pathology findings will be collected into a neck registry.

This trial implements a permuted block randomization to randomize patients within each strata cell.

14.2 Study Endpoints

14.2.1 Primary Endpoint

Phase II: Patient-reported neck and shoulder function and related QOL, as measured by NDII.

Phase III:

- Disease-Free Survival (DFS) – *(Failure: local/regional recurrence, distant metastasis, or death due to any cause).*
- Patient-reported neck and shoulder function and related QOL, as measured by NDII.

14.2.2 Secondary Endpoints

- Overall Survival (OS).
- Locoregional failure and distant metastasis.
- Toxicity, as measured by the CTCAE v5.0.
- Patient-reported shoulder-related QOL, function impairment and disability using QuickDASH, and patient-reported general QOL using the FACT-H&N.
- Nodal metastasis detection rate.
- Pathologic false omission rate (FOR) in the SLN biopsy arm.
- Length of hospitalization, post-operative drain placement, and operative morbidity.
- NDII for low-risk patients.
- Negative predictive value (NPV) of FDG PET/CT in T1 and T1-2 patients in the END arm.

14.2.3 Exploratory Endpoints

- Quality of life, as measured by EQ-5D.
- DFS for low-risk patients.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

Phase II: SLN biopsy will have superior patient-reported neck and shoulder function and quality of life (QOL), as measured by the Neck Dissection Impairment Index (NDII), compared to elective neck dissection (END), at 6 months post-surgery.

Phase III: SLN biopsy will achieve non-inferior disease-free survival (DFS) compared to END, and will have superior patient-reported neck and shoulder function and quality of life (QOL), as measured by the NDII, for early-stage (clinical T1-2N0) oral cavity squamous cell carcinoma (OCSCC).

14.3.2 How Primary Endpoints Will Be Analyzed

Phase II

The primary endpoint for the phase II is the NDII score change from baseline to 6 months post-surgery. Descriptive statistics on the NDII scores at baseline, at 6-month post-surgery time point and change scores will be calculated. An ANCOVA model with the baseline NDII and treatment factor will be used to assess the between-arm difference in mean NDII scores at 6 months (Liu et al 2019; Tsiatis et al 2008). The benefit of the SLN biopsy arm against the END arm at 6 months is denoted by δ. The NDII scores range from 0 to 100 and higher scores indicate better shoulder functioning and shoulder-related quality of life. Thus, H_0:$\delta \leq 0$ will be tested against the alternative hypothesis: H_a: $\delta > 0$. The minimum importance difference (MID) for the NDII is 7.5 points. The hypothesis of no between-arm difference in 6-month NDII scores will be tested using the ANCOVA model at one-sided significance level of 0.10. Point estimates and 95% confidence intervals (CIs) for the mean NDII scores at 6 months for each treatment arm and for the between-arm difference at 6-months based on the proposed model will be provided.

All patients according to the randomized treatment assignment will be used for the primary NDII analysis (i.e. ITT analysis). However, given that patients with a SLN positive will undergo completion neck dissection (CND), a sensitivity analysis is proposed using two approaches:

- *"Per-protocol" approach*: Patients who undergo a CND in the SLN biopsy arm will be excluded from the analysis.
- *"As-treated" approach*: Patients who undergo a CND in the SLN biopsy arm will be included in the END arm for this analysis. Patients with SLN positive will undergo a CND. The expected nodal metastasis rate detected by the SLN biopsy is expected to be around 20%. Note that these patients will receive both SLN biopsy and END. However, these patients will be included in the END arm for purposes of this analysis.

Phase II "Go/No-Go" Decision

If the phase II analysis indicates that the mean change NDII score from baseline at 6 months is improved for the SLN biopsy arm compared to the END arm, the study will continue with accrual to the phase III. A summary of the decision algorithm is given in the table below. The model-based results will be used for the "go/no-go" decision.

"Go/No-Go" Decision Algorithm Regarding Phase III Trial Primary Endpoint Analysis (Phase II)	**Decision Rule**
Mean change NDII score from baseline at 6 months between arms (SLN vs. END) is statistically significant (one-sided alpha of 0.10) and difference ≥ 7.5 (MID) – ITT analysis	Proceed to phase III
Otherwise	Do not proceed to phase III

Accrual will be suspended at least 6 months until the primary endpoint completion of phase II. Following the CTEP policy guidelines for go/no-go decision implementation in phase II/III trials, the protocol-specified phase II decision-rule analysis will be performed within 6 weeks from the date the last enrolled patient has completed the 6-month follow up to assess the NDII. If the decision rule is used as specified above then NRG Oncology will notify the NRG Oncology DMC, the Chief, CIB, and DCP of the status of the trial (i.e. continuing or stopping). Otherwise, the study team will follow the procedures specified in the CTEP policy guidelines (see more details in *Part 4, Appendix VIII, DMC Policy, NCTN Program Guidelines*).

At the time of the go/no-go decision, the minimum acceptable compliance rate for 6-month NDII analysis is 80% (see Section 14.4). If the compliance rate in the phase II is below 80%, the study team will discuss with NCI/DCP before doing the analysis of the phase II data. The statistical power based on the actual compliance will be part of this discussion.

Analysis of Potential "Confounders"

Some studies in multimodality neck treatment have shown that advanced stage-disease and more aggressive treatment in the form of surgical dissection and/or adjuvant radiation and chemotherapy, are associated with worse quality of life and shoulder function (Taylor 2002, Gallagher 2015). Use of pain medications and physical therapy, change in work status and leisure activities after surgery have shown association with the NDII (Gallagher 2015). It is worth pointing out that the latter factors are measured after surgery so they could also be related to treatment as potential mediators (Fairclough 2010). For instance, the result of the extent of damage in the surgical procedure could have an influence in the use of pain mediation, which, in turn, could lead to greater shoulder impairment (Gallagher 2015).

In this trial, data on factors such as the pathological T-stage and N-stage, risk group (based on adverse features) and use of adjuvant therapy (radiation and chemotherapy) will be collected post-surgery. The clinical T-stage (1 vs. 2) and the Zubrod performance status (0 vs. 1-2), both measured at the baseline, are used as stratification factors. Particularly, the Zubrod performance status captures the effect of other prognostic factors, and has been found to be an important factor in predicting how a patient is likely to respond to cancer therapy (West 2015). No additional baseline characteristics were included as stratification (confounding) factors in the design due to the lack of strong evidence on their association with the NDII scores, or due to the small proportion of

patients expected in one of the categories of the potential stratification factor (for instance, about 3-5% of patients are expected to have previous shoulder surgery, injury or trauma).

A series of analyses are proposed to detect potential confounders and facilitate the interpretation of the NDII results at the end of the phase II and phase III when reporting the primary endpoint results. Baseline characteristics are expected to be balanced between treatment arms due to randomization. Therefore, the analysis is more focused on the post-surgery variables, although some key baseline characteristics, such as handedness, will be included in the analysis. These variables were selected based on the existing data and experts' input. The table below shows a list of variables that will be considered in these secondary analyses.

Baseline characteristics	**Post-surgery covariates**
• *cT-stage (1 vs. 2)** • *Zubrod performance status (0 vs. 1-2)** • Handedness • Previous shoulder surgery, injury or trauma	• pN-stage • Risk group (low, intermediate, high) • Chemotherapy • Radiotherapy • Rehabilitation/Physical therapy** • Use of shoulder/oral cavity pain medication**

*Stratification factors
**Time points: baseline, 3 weeks, 3, 6 and 12 months post-surgery.

The secondary analyses proposed for the NDII scores envision the following steps:

1. Comparisons of the distributions of all covariates between arms. Tables with appropriate descriptive statistics by arm will be reported. A chi-square test will be used to test for between-arm differences for a nominal covariate and a Mann-Whitney test for ordinal variables. For all these analyses, an alpha level of 0.10 will be used in the phase II and 0.05 in the phase III. These bivariate analyses will include all the variables in the table above.
2. Fitting separate models including the treatment factor and covariates in the table above. These models will provide adjusted treatment effect estimates after accounting for these potential confounders individually.
3. A stepwise procedure with the BIC criterion to determine which effects enter and/or leave the model at each step and to select the final model will be implemented. The output from the final model will provide an adjusted treatment effect estimate after accounting for confounders deemed relevant as suggested by the model selection procedure.

When reporting the treatment effect estimates from all models, 95% CIs for the treatment effect will be also provided.

Missing Data

An important aspect in the assessment of the treatment effect on the NDII score change from baseline at 6 months is the handling of missing data due to non-compliance, and other various reasons. The study was powered to allow up to 15% of missing data for the NDII scores at 6 months. However, if more than 15% of the NDII scores at 6 months in both arms are missing then an imputation process using the procedures outlined in Section 14.6.2 will be implemented. As recommended by several authors, a sensitivity analysis comprising complete-case analysis, an analysis based on the MAR assumption after adding covariates associated with the missingness or dropout and the observed data to the analytic model, and an analysis based the MNAR assumption will be performed (Fairclough 2010, Verbeke 2000). In all these scenarios, the same analytic model proposed for the primary endpoint analysis will be used regardless of the imputation model being proposed.

Phase III

The primary endpoint for the phase III part of the study is disease-free survival (DFS), which is defined as the time from randomization to local/regional recurrence, distant metastasis, or death due to any cause, whichever comes first. Patients who have not experienced any of the events of interest at the time of analysis will be treated as censored observations. DFS rates for both treatment arms will be estimated using the Kaplan-Meier method (Kaplan 1958). The primary phase III endpoint will be tested using a two-sided confidence interval (CI) approach based on a Cox proportional hazards model including the treatment factor only. An ITT approach will be used to perform this analysis. However, a sensitivity analysis will be also done using the two approaches outlined above for the NDII primary analysis.

Multivariate analysis with the DFS will be also performed using the Cox proportional hazards model with treatment factor, gender, sex, age, T-stage, pN-stage, risk group, and adjuvant therapy. Adjusted hazard ratios and their respective 95% confidence intervals will be provided.

For the co-primary endpoint in the phase III, 6-month post-surgery NDII, similar analyses will be performed as in the phase II portion. However, the hypothesis testing will be performed using a one-sided alpha level of 0.025. This analysis will be done in a hierarchical manner. That is, the between-arm comparison of the PRO endpoint will be done only if the SLN biopsy arm is declared non-inferior with respect to DFS.

14.3.3 Sample Size and Power Calculations

Phase II Sample Size

For the primary endpoint analysis, the mean NDII score change from baseline at the 6-month post-surgery will be evaluated and compared between the two treatment arms. It is assumed that a 7.5-point between-arm difference (MID) in the 6-month post-surgery NDII scores is clinically meaningful. A standard deviation (SD) of 20 points is assumed for the NDII scores at 6 months. Stuiver et al (2016) reported a SD for the NDII scores at 6 months post-surgery was 19.1; a similar number was also reported elsewhere (Dziegielewski 2019). Therefore, a SD of 20 points is a conservative figure for purposes of power calculations. With a one-sided significance level of 0.10, 194 randomized

patients from both arms (97 per arm) will provide a statistical power of at least 95% to detect the projected effect size using an ANCOVA model as described in Section 14.3.2. This calculation assumes a correlation coefficient r=0.50 between the baseline and the 6-month NDII. If the correlation coefficient between these two assessments is lower, for instance, r=0.20, then the power for this analysis is 90% with 194 randomized patients.

Assuming that 15% of the randomized patients may not be evaluable for this endpoint due to reasons such as non-compliance, patient refusal, etc., 228 patients will be randomized to both arms. The assumption of 15% non-compliance rate at 6 months is reasonable given historical data on NRG Oncology trials and the relatively good prognosis in this population (Atherton 2016). For instance, NRG-RTOG 1008, a randomized phase II/III trial of adjuvant concurrent radiation and chemotherapy in resected high-risk malignant salivary gland tumors, has shown a compliance rate of 80% at 12 months from the end of RT for the FACT-HN. However, some strategies to reduce missing data will be implemented as described later in this document.

Phase III Sample Size

The primary endpoint for the phase III part of the study is DFS. All patients enrolled in the phase II portion of the study will be included in the phase III primary endpoint analysis. Based on historical data for this population from the RT+cisplatin arm of NRG/RTOG 0234 and RT alone arm of NRG/RTOG 0920, a 2-yr DFS of 54.8% and 78.3%, respectively, are assumed for high- and intermediate-risk patients in the END arm in this trial. Combining these estimates with a 2-yr DFS for low-risk patients (90.5%) and an expected distribution by risk group of 60%, 30%, and 10% in the low-, intermediate- and high-risk groups, respectively, it is assumed that the 2-yr DFS for all risk-patients in the END arm is 83.3%. Moreover, a retrospective cohort of 967 pT1-T2 and N0-Nx patients from Memorial Sloan Kettering Cancer Center and Princess Margaret Hospital informing AJCC TNM classification (8th edition) reported a 2-yr DFS of 80.5% (Lydiatt 2017). This figure is similar to the value used in the design of this trial. The SLN procedure is considered non-inferior to END if the 2-year DFS rate for the SLN arm if at most 5% (in absolute value) lower than the 2-year DFS rate for the END arm. For the SLN arm, under the null hypothesis, it is assumed that the 2-year DFS rate is 78.3% (5% non-inferiority margin), corresponding to a hazard ratio (HR) of 1.34 on DFS for the SLN arm with respect to the END arm; under the alternative hypothesis, it is projected that the 2-year DFS rate is 83.3%, corresponding to an HR of 1. With a one-sided significance level of 0.05, an accrual rate of 9 PET/CT negative patients/month, and an interim look for efficacy at 67% of the events based on an O'Brien-Fleming boundary, a total of 297 DFS events from 618 randomized patients from both arms, or 309 patients per arm, will provide 80% statistical power for the non-inferiority test on the primary endpoint, DFS. Patients enrolled in the phase II portion will be part of the DFS assessment in the phase III. Assuming that 228 patients are randomized in the phase II, 390 additional randomized patients are needed in the phase III (195/arm).

For the co-primary (hierarchical) QOL endpoint analysis in phase III, the mean NDII score change from baseline at the 6-month post-surgery will be evaluated and compared between the two treatment arms. With a one-sided significance level of 0.025, a common

SD of 20 points, and 525 randomized patients (assuming a 15% of non-compliance), the t-test for two independent samples will provide >95% statistical power to detect the projected effect size (MID=7.5) based on an ITT analysis.

If the SLN biopsy is declared non-inferior on DFS to the END, then the superiority of the SLN biopsy arm will be assessed. It is assumed that the 2-yr DFS rate for this population is 83.3% as before. With a one-sided significance level of 0.025, a log-rank test will provide 87% statistical power to detect a HR=0.70 (equivalent to an absolute difference in 2-yr DFS of 4.7%) in favor of the SLN biopsy arm.

14.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis in between regularly scheduled meetings. This study will be monitored by the Data Mapping Utility (DMU).

Monitoring of NDII Compliance

Completion rates of the NDII will be monitored quarterly, as is routinely done for PRO tools in all NRG Oncology trials. All time points will be used to monitor compliance. If the NDII non-compliance rate is > 15% at any of the time points up to 1 year, the study PI and QOL co-chair will work in collaboration with the NRG Oncology Statistics and Data Management Center to contact sites and RAs with delinquent data, assessments completed too early or too late, and assessments not completed due to institution errors. In particular, if the NDII non-compliance rate at 6 months is > 20%, the study will be presented to the NRG Oncology Data Monitoring Committee (DMC) for reassessment of feasibility or change in study design.

Since the phase II and III include a PRO primary and co-primary endpoint, efforts at minimizing missing PRO data include: utilization of electronic platform to collect PROs, minimization of patient burden to improve compliance (65 items in QOL instruments; 10 items in the NDII tool) and QOL e-mails reminders to the site research assistant prior to the due date and on the day the QOL is due. Additional reminders will be sent after the QOL due date.

If funded, a grant proposal will implement several strategies to reduce PRO non-compliance in this trial. Some of these strategies are: creation and distribution of patient centered education materials in conjunction with all stakeholders, to help patients understand the importance of timely survey completion with specific, culturally appropriate messages tailored for underrepresented minorities, highlighting the value of their participation; develop and deploy a standardized patient centered educational curriculum for both research assistants and surgeons, emphasizing the importance of survey completion and recruitment of underrepresented minorities; and integration of engagement approaches and survey completion options based on patient preferences (for example, texting surveys allows survey completion without a clinical visit which may reduce disparities related to patient transportation).

Monitoring of Accrual Rate

Patient accrual will be closely and continuously monitored throughout the entire trial. Once the study is activated, the study will be subject to CTEP's early stopping guidelines for slow accruing trials. Necessary adjustments will be made upon discussions with the NRG Oncology DMC and NCI/DCP.

Routine Interim Analysis to Monitor Study Progress

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events. The distribution of patients by risk group (low, intermediate and high) between surgical arms will be also included in these reports.

Significance Testing for Early Termination and/or Reporting

Early Termination in Phase III

Statistical monitoring for both efficacy (rejection of the null, establishment of non-inferiority) and futility (evidence that non-inferiority will not be satisfied) will be performed. At 33% of the information (98 DFS events), an interim futility analysis will be performed, and this is projected to occur around 68 months after study activation, or about 14 months prior to accrual completion for the phase III portion. At 67% of the information (199 DFS events), both an interim futility and efficacy analyses will be performed. An O'Brien-Fleming boundary is utilized for the efficacy monitoring. The interim futility analyses is be based on the non-inferiority monitoring rule developed by Korn and Freidlin (2018). At each monitoring time, the one-sided *p*-value will be calculated for testing the hypothesis HR = 1 versus the alternative HR > 1 (meaning the experimental treatment is doing worse than the standard treatment). If the *p*-value is <0.0394 at a monitoring time, then a recommendation of stopping the trial with the conclusion that non-inferiority cannot be claimed will be presented to the DMC.

At 67% of the DFS events the null hypothesis of inferiority will be rejected, in favor of the non-inferiority of the SLN biopsy arm, if the p-value based on the Cox model is ≤ 0.0166.

Analysis for Reporting the Initial Treatment Results

The analysis report will include: tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given, distributions of important prognostic baseline variables, the frequencies and severity of adverse events by treatment arm, compliance rate of treatment delivery, observed results with respect to the primary and secondary endpoints.

The primary analysis will be done once 297 DFS events have been observed. The required number of DFS events will be reached around 52 months after accrual closure.

After accounting for an interim efficacy analysis at 67% of the DFS events, the null hypothesis of inferiority will be rejected, in favor of the non-inferiority of the SLN biopsy arm, if the upper limit of the two-sided 91% CI for the HR (SLN biopsy/END) is below the non-inferiority margin 1.34. This is equivalent to rejecting the null hypothesis of inferiority if the p-value associated with the equivalent statistical test is ≤ 0.045 (*i.e.*, testing against the null hypothesis of HR ≥ 1.34). The DFS analysis will be based on an ITT approach.

14.5 Accrual/Study Duration Considerations

Phase II Timeline

It is projected that the accrual rate is 9 PET/CT negative patients/month in this trial. This figure is based on an expected accrual rate of 12 clinical T1-2N0 OCSCC patients per month, a conservative estimate from the internal survey, and a projection of 75% PET/CT negative patients. With minimal accrual expected for the first 6 months after study activation, it will take around 31 months (~2.6 years) to reach the target accrual for the phase II part of the study. Accrual will be temporarily stopped for at least 6 months for the assessment of the NDII at 6 months once the required number of randomized patients for the phase II primary endpoint analysis has been met. The study duration for the phase II portion is about 37 months (~3.1 years).

Phase III Timeline

According to the projected monthly accrual rate of 9 PET/CT negative patients/month, it will take approximately 43 months from study reactivation to the phase III to reach the target accrual of 618 PET/CT negative patients (including 228 patients enrolled in phase II; 390 additional patients need to be enrolled once the trial reopens to accrual to the phase III portion). The required number of DFS events will be reached around 52 months after accrual closure. So, the total study duration to primary endpoint completion in phase III is around 132 months (11 years) from study activation. A summary of the main elements in the current design is given in the table below.

Phase	Primary Endpoint	Eligible pts for QOL analysis	Randomized pts (PET/CT Negative)	Accrual Duration (months)	Follow-up Time (months)
II	NDII scores at 6 months post-treatment	194	228*	31	6
III	Disease-Free Survival (DFS)	---	390	43	52
Total (II/III)			618**	74	58
				132 (11 yrs)	

*Assuming a NDII non-compliance at 6 months of 15%.

**824 enrolled patients are expected to undergo a PET/CT exam before step 2 registration to get 618 PET/CT negative patients.

14.6 Secondary Endpoints (including correlative science aims)

14.6.1 Secondary Hypotheses and Endpoints:

- Overall survival (OS)
  Hypothesis: The OS rate will be different between arms.
- Loco-regional failure (LRF)
  Hypothesis: The LRF rate will be different between arms.
- Distant metastasis (DM)
  Hypothesis: The DM rate will be different between arms.
- Toxicity, as measured by the CTCAE v5.0.
  Hypothesis: The SLN biopsy would result in less adverse events associated to the surgical procedure than the END.
- Patient-reported shoulder-related QOL, function impairment and disability using QuickDASH.
  Hypothesis: The SLN biopsy arm will have lower scores (lower disability) after surgery compared to the END arm.
- Patient-reported general QOL using the FACT-H&N.
  Hypothesis: SLN biopsy arm compared to END arm, will have higher post-surgery FACT-TOI scores.
- Six-month post-surgery patient-reported outcome (PRO), as measured by NDII, in low-risk OCSCC patients.
  Hypothesis: The SLN biopsy arm will have better patient-reported neck and shoulder function and related quality of life (QOL) after surgery compared to the END arm in this subset of patients.
- Pathologic False Omission Rate (FOR) in the SLN arm.
  Hypothesis: The pathologic FOR in the SLN arm will be around 15%.
- Nodal metastasis detection rate.
  Hypothesis: The nodal metastasis detection rate will be similar between arms.
- Length of hospitalization, post-operative drain placement, and operative morbidity.
  Hypothesis: SLN biopsy arm compared to END arm, will have shorter hospital stay and lower rates of post-operative drain placement, and operative morbidity.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Except for PRO secondary endpoints, no multiplicity adjustments will be done for other secondary endpoints.

Time-to-Event Endpoints

The distribution of OS, defined as the time from randomization to *death due to any cause* will be estimated using the Kaplan-Meier method and between-arm differences compared using the log-rank test (Kaplan 1958). All other secondary time to event endpoints have precluding events that act as competing risks. Failure events and competing risks for local-regional and distant metastasis failure endpoints is outlined in the table below. Anything not explicitly in the table (e.g., second primary tumor) is not considered an event, and the patient will continue to be followed for failure.

First event	**Disease-Free Survival**	**Local-regional failure**	**Distant metastasis**

None	Censored	Censored	Censored
Local progression or recurrence	Failure	Failure	Competing risk
Regional progression or recurrence	Failure	Failure	Competing risk
Distant metastasis	Failure	Competing risk	Failure
Death due to study cancer or unknown causes	Failure	Failure	Competing risk
Death due to any other reason	Failure	Competing risk	Competing risk

Time to locoregional failure will be measured from the time of randomization to the date of failure, date of precluding event, or last known follow-up date. Time to distant metastasis will similarly be measured from the time of randomization to the date of distant metastasis, date of precluding event, or last known follow-up date. Definitions of locoregional and distant failure are provided in Section 4. The cumulative incidence estimator will be used to estimate time to event distributions for locoregional failure and distant metastasis with between arm differences tested using cause-specific log-rank test.

For all efficacy endpoints, Cox proportional hazards models will be used to determine hazard ratios (cause-specific hazard ratios in the case of endpoints with competing risks) and to assess the effects of covariates of interest mentioned in Section 10.3 (Cox 1972). The Fine-Gray subdistribution hazards model may be applied to further explore outcomes by treatment arm and other covariates for endpoints with competing risks (Fine 1999).

All efficacy endpoints will be reported at the time of the primary endpoint analysis. A two-sided significance level of 0.05 will be used to determine significance for these secondary endpoints. All the analysis for secondary time-to-event endpoints will be done in the intent-to-treat (ITT) population. The long-term analysis will be performed after initial reporting, if warranted, for the DFS and OS endpoints.

Toxicity

Adverse events (AEs) will be graded using CTCAE v5.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. The proportion of patients with at least 1 grade 3 or higher AE will be compared between the treatment arms. All comparisons will be tested using a chi-Square test, or Fisher's exact test if cell frequencies are < 5, with a significance level of 0.05.

The mean number of grade 3-4 adverse events between arms will be compared using a negative binomial regression. The mean toxicity ratio between arms and its 95% confidence interval (CI) will be reported.

All toxicity analyses will be conducted at the time of the primary endpoint analysis.

Patient-Reported Outcomes (PROs)

The NDII, Quick-DASH, FACT-H&N and EQ-5D-5L are collected at baseline, 3 weeks, 3, 6 and 12 months post-surgery. A disability/symptom score on a 0-100 scale will be computed from

the QuickDASH. A higher QuickDASH score indicates greater disability. The FACT-Trial Outcome Index (TOI) on a 0-96 scale will be assessed using the FACT-H&N. A higher FACT-TOI indicates better QOL. More details on the PRO tools are given in Section 11.3.

For purposes of interpretation of the PRO scores, the minimum importance difference (MID) for the NDII and QuickDASH tools are assumed to be 7.5 points and 8%, respectively. For the FACT subscales, changes of ≥ 2 points for PWB, FWB, HNCS, or ≥ 5 points for TOI will be considered clinically meaningful (Yost and Eton 2005).

For all scores, change from baseline will be summarized using mean and standard deviation at baseline, 3 weeks, 3, 6 and 12 months post-surgery. A longitudinal ANCOVA model incorporating the baseline, 3 weeks, 3, 6 and 12 months post-surgery time points will be conducted separately for the NDII, QuickDASH overall score, and FACT-TOI using mixed effects models with the effect of time, treatment and its interaction. Adjustment for additional covariates such as T-stage, gender, sex, adjuvant therapy, pN-stage, and other clinical variables will be done if it is deemed necessary based on missing data patterns. A two-sided significance level of 0.05 will be used to determine significance for these secondary endpoints.

Due to the multiple tests involving treatment by time interaction terms across PROs, a multiplicity adjustment based on Bonferroni method will be performed when testing these hypotheses.

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If > 15% of the data is missing at any time point for the PROs, patient characteristics will be compared between patients with completed assessments and those with missing assessments using, for instance, a logistic model. If any are found to differ significantly, they will be included in the mixed effects model, which assumes that the data is MAR. If the missingness is determined to be non-ignorable, other methods may be applied. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

NDII for the low-risk subgroup

The low-risk subgroup is defined in Section 2.7. These low-risk patients will not receive adjuvant radiation therapy or chemotherapy. Therefore, the shoulder function and QOL comparison between arms will be able to be done without the potential confounding effects of adjuvant therapy by doing the analysis in this subpopulation. Moreover, these adverse features defining the risk groups are unknown at the randomization step, so the risk group cannot be considered as a stratification factor in this trial. In this cohort, the 6-month NDII scores between arms will be compared using an ANCOVA model. This subgroup analysis will avoid the potential confounding effects of adjuvant therapy given to intermediate and high-risk patients. However, there could be other potential confounders given the nature of this analysis. Therefore,

the analytic model will incorporate additional covariates (see Section 14.3.2) for this subgroup analysis. The final model to estimate the treatment effect for the low-risk group will be selected using the BIC criterion. A comparative analysis of patient and tumor characteristics between arms for this subgroup will be also done.

With the same assumptions as for the sample size calculation for the primary endpoint in phase II (one-sided alpha level of 0.10, common SD=20, and r=0.5), the table below shows the statistical power to detect the MID of 7.5 points at 6 months between the treatments arms in the low-risk cohort in the phase II (194 evaluable patients).

% of low-risk patients (# of patients) with NDII data	**Statistical power to detect the MID=7.5 (Phase II)**
60% (116)	85%
65% (124)	87%

The NDII analysis at 6 months in this cohort of patients enrolled in phase III exhibits a higher power to detect the same MID, given that the target accrual is 618 randomized patients. Assuming the same non-compliance rate of 15% from phase II, the table below shows the statistical power to detect a MID of 7.5 points between arms in this cohort in phase III. A one-sided alpha level of 0.025 will be used to perform this comparison. In a less favorable scenario of a non-compliance rate of 30% and 60% low-risk patients, which translates to 260 patients available for the analysis, there will be 85% power to detect such MID.

% of low-risk patients (# of patients); Non-compliance rate	**Statistical power to detect the MID=7.5 (Phase III)**
60% (315); 15%	97%
65% (341); 15%	98%
60% (260); 30%	93%

Negative predictive value of FDG PET/CT for T1 and T1-2 patients in the END arm

One of the secondary objectives of this trial is to estimate the negative predictive value (NPV) of FDG PET/CT for T1-N0 neck patients in the END arm. After central review, the PET/CT will be dichotomized into node positive or negative using the central read definition outlined in Section 11. This definition is based on the combination of both SUVmax cutpoint and visual read. The true N0 negative neck cases will be identified using the histopathology reports. The NPV will be estimated using binomial distributed sample with a 95% CI based on normal approximation. It assumed that 75% of the enrolled patients are PET/CT negative and that the expected NPV of PET/CT is around 95%. This is based on the assumption that 75% of the patients accrued for this study would have T1 and 25% would have T2 oral cavity tumors. This distribution calculation is based on ACRIN 6685 data (which included T2 -T4 tumors) and 53% of clinical N0 neck had a negative PET/CT read. The prevalence of neck nodal metastasis in T1 and T2 tumors in this trial

is expected to be lower than ACRIN 6685, which did not include T1 tumors and hence the negative PET/CT reads would be estimated around 75%.

Two hundred and twenty eight PET/CT negative patients are expected to be randomized to both arms in the phase II, thus 171 patients are expected to have T1 stage. From these 171 patients, about 85 patients will be randomized to the END arm in phase II. The NPV of PET/CT in both phases along with a 95% CI based on the normal approximation will estimated. If the true NPV is assumed to the 90% and 92% then the 95% CI half-width for the NPV in the phase II will be 6.4% and 5.8%, respectively. For the phase III with 232 T1 patients expected to be enrolled to the END arm, the 95% CI half-width will be 3.9% and 3.5% if the true NPV is assumed to the 90% and 92%.

The 95% CI half-width for the NPV of the PET/CT for T1-2 patients in the END arm in the phase II (114 patients) and phase III (309 patients) will be 5.5% and 3.3%, respectively.

Nodal metastasis detection rates

Nodal metastasis rate, defined as the proportion of patients with pathologic positive nodes, will be assessed for each arm using the pathology results. Nodal metastasis detection rates in both arms, along with 95% CIs, assuming a binomial sample and normal approximation will be estimated. A 95% CI for the difference of rates between the SLN biopsy arm and the END will be computed. For a given arm, the 95% CI half-width for the nodal metastasis detection rate is 7.3% and 4.5% in the phase II and III, respectively, assuming a true rate of 20%. The 95% CI half-width for the rate difference is 9.8% and 6.0% in the phase II and III, respectively, assuming true rates of 20% and 15% for the treatment arms.

Pathologic False Omission Rate (FOR) in the SLN Biopsy Arm

Sentinel lymph nodes (SLN) will be classified as positive or negative based on the local review. Negative SLNs, as determined by the local review, will be centrally reviewed. Patients will be classified as positive or negative SLN biopsy according to the local and central review separately. The false omission rate (FOR), defined as the proportion of patients with false negative results among negative SLN biopsy patients, as determined by local review, will be estimated in this trial. A 95% confidence CI for the FOR will be computed using a normal approximation. A pathologic FOR of 15% is expected in this trial. The 95% CI half-width for the FOR is expected to be 7.3% and 4.4% in the phase II and III, given that the expected sample size is 91 and 247 negative SLN biopsy patients, respectively. In the previous calculations, it is assumed that 80% of patients will have a negative SLN biopsy based on the local review.

Length of hospitalization, post-operative drain placement, and operative morbidity

Morbidity associated to surgical procedures will be assessed using the length of hospitalization (days), the Clavien-Dindo Classification scale (CDC) (Dindo 2004), and a list of pre-specified surgical complications (see Section 5.1.4). The CDC is a 7-item scale with five grades (I-V) to measure post-surgery complications (see Section 5.1.2 for more details on the CDC scale). Surgical complications will be assessed at several time points according to the follow-up tables in Section 4. The distribution of grades for each complication will be reported. The overall proportion of patients with grade II-V surgical complications will be estimated and compared between arms using a chi-square test. Assuming that 15% of patients in the END arm have grade

II-V complications, the chi-square test will have 90% (94%) power to detect a reduction of 10% (8%) in the SLN biopsy arm in the phase II (III) with 228 (618) randomized patients. A one-sided alpha of 0.10 and 0.05 will be used for all the secondary endpoints in this section in the phase II and III, respectively.

Length of hospital stay due to the surgical procedure will be compared between arms using the Mann-Whitney test. Cramer et al (2018) reported a median LOH of 3 days (SD=7.3) for END. The statistical power to detect a 2-day difference is 79% and 96% in the phase II and phase III, respectively.

The rates of post-operative drain placement for each treatment will be estimated using a binomial sample and the 95% CIs will be computed using a normal approximation. The rate difference between arms and a 95% CI for this difference will be computed using the same method. The 95% CI half-width for the rate difference is 8.6% and 5.2% in the phase II and III, assuming true rates of 15% and 90% for the SLN biopsy and END arms, respectively.

14.7 Exploratory Hypothesis and Endpoints

Cost effectiveness

The EQ-5D-5L is collected at baseline, 3 weeks, 3, 6 and 12 months post-surgery. The VAS and index scores will be assessed with higher scores indicating better QOL. Missing data will be assessed as described in Section 14.6.2. The change from baseline will be calculated at 3 weeks, 3, 6 and 12 months post-surgery and compared between arms using a t-test. A longitudinal analysis incorporating all the time points will be conducted for the EQ-5D index score using mixed effects models, adjusting for treatment arm. A treatment by time interaction will also be assessed in each model.

The following analysis will only be conducted if the SLN biopsy arm is shown to be non-inferior to the END arm for DFS and has at least 1 significant difference in index change score. Quality-adjusted life years (QALYs) is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. A Markov model will be used to model cost for this analysis. The Medicare reimbursement in dollars/QALY will be calculated as a function of the monetary cost per relative value of each health state and its duration. The EQ-5D-5L index score at 3 weeks, 3, 6 and 12 months post-surgery will be used for the cost-utility analysis. The z-test will be used to test the hypothesis that the cost-utility in the two treatment arms is the same with significance level of 0.05. The cost-utility using the Medicare reimbursement in dollars/QALY will be compared between the two treatment arms after adjusting for baseline variables.

DFS for the low-risk subgroup

The low-risk cohort of OCSCC patients is defined in Section 2.7. About 60-70% of patients are expected to be low-risk. That implies that 370 low-risk patients are expected in the phase III if a prevalence of low-risk patients 60% is assumed. For this subgroup of patients, exploratory analyses will be done using the Kaplan-Meier method to estimate the DFS distribution in both arms. Cox proportional hazards models with the treatment arm only and with treatment arms and relevant patient and tumor characteristics will be fitted. 95% CIs for the treatment effect from both models will be also reported.

14.8 Gender/Ethnicity/Race Distribution

The expected gender/ethnicity/race distribution is based on the data from NRG-RTOG 0920, a phase III trial of post-operative radiation therapy for locally-advanced resected head and neck cancer, and 85% of domestic enrollment (randomized patients) vs. 15% international (including Canadian participants) enrollment.

Phase II/III

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	2	0	0	2
Asian	6	12	0	0	18
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	11	35	0	0	46
White	128	300	7	21	456
More Than One Race	0	0	2	0	2
Total	146	349	9	21	525

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	5	8	0	0	13
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	13	65	0	2	80
More Than One Race	0	0	0	0	0
Total	18	73	0	2	93

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APPENDIX I: RECOMMENDED CISPLATIN GUIDELINES

Cisplatin should only be given with concurrent radiation on the following schedules:

1. Bolus cisplatin every 3 weeks, or;
2. Weekly cisplatin.

Drug Information

Cisplatin: a cytotoxic chemotherapy that is routinely used for the treatment of head and neck cancer. Commercially available cisplatin will be administered to patients, it will not be provided by the study.

Other Names: cis-platinum, Platinol

Mechanism of Action: cisplatin inhibits DNA synthesis by the formation of DNA adducts across the same DNA strand or adjacent strand. This denatures the DNA double helix and disrupts its DNA function.

Route of Administration: Cisplatin is only given intravenously (through a peripheral I.V or a port-catheter) not by rapid infusion or bolus. Maximum rate is 1 mg/minute - adjust rates accordingly. Note: Needles or intravenous sets containing aluminum parts should not come in contact with cisplatin injection should not be used for preparation or administration. Aluminum reacts with cisplatin injection, causing precipitate formation and a loss of potency.

Parameters to use:

- Absence of pre-existing grade 2 neuropathy or hearing loss
- Creatinine clearance $\geq$ 50 mL/min
- ANC $\geq$ 1000 mm^3
- Hg $\geq$ 10 g/dL
- Platelets $\geq$ 100 K/mm^3

Recommended pre-medications (by drug class) or per institutional standard

Low Dose: (< 50 mg/m^2)

- *Low-dose Cisplatin anti-emetic administration guidelines*: 5-HT_3 antagonists (e.g. ondansetron 8 mg IV/PO +. Dexamethasone 10-20 mg IV 30 minutes prior to chemotherapy. (*Note if choose to use PO route administer 60 minutes prior to chemotherapy) Continue ondansetron 8 mg PO twice a day for three days then as needed. Rescue antiemetic such prochlorperazine 10 mg PO up to four times a day should be provided. Use of other anti-nausea meds such as aprepitant, metoclopramide, or olanzapine is left to the discretion of the investigator.
- *Low-dose Cisplatin pre-hydration guidelines*: Pre-hydration with 0.9% sodium chloride 500 mL with 16 mEq magnesium sulfate infused over 1 hour prior to cisplatin.
- *Low-dose Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional give 0.9% sodium chloride 500 mL with 20 mEq potassium chloride and 16 mEq magnesium sulfate infused over 1 hour. Patients should be encouraged to self-hydrate throughout the week with frequent fluid intake. Patients

unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

High Dose: ($\geq$ 50 mg/m^2)
High-Dose Cisplatin Anti-Emetic Administration Guidelines: NK-1 antagonist (e.g. fosaprepitant 150 mg IV), 5-HT$_3$ antagonists (e.g. ondansetron 8 mg IV +. Dexamethasone 10 mg IV/PO 30 minutes prior to chemotherapy.(*Note if choose to use PO route administer 60 minutes prior to chemotherapy). Continue ondansetron 8 mg PO twice a day for three days then as needed. Rescue antiemetic such prochlorperazine 10 mg PO up to four times a day should be provided. Use of other anti-nausea meds such as metoclopramide, lorazepam, or olanzapine, is left to the discretion of the investigator.

- *Cisplatin Pre-Hydration Guidelines*: Pre-hydration with 0.9% sodium chloride 1L with 16 mEq magnesium sulfate infused over 2 hour prior to cisplatin.
- *Cisplatin Post-Hydration Guidelines*: Following the end of the cisplatin administration, an additional give 0.9% sodium chloride 1L with 20 mEq potassium chloride and 16 mEq magnesium sulfate infused over 2 hour. Patients should be encouraged to self-hydrate throughout the week with frequent fluid intake. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

Recommended Dose modifications (based on organ function; toxicity)
Dosage with renal impairment:

Creatinine clearance	**% previous dose**
46-60	75%
30-45	50%
<30	Avoid if possible

Dosage with hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling. Dosage adjustment is likely not necessary as cisplatin is believed to undergo spontaneous degradation in the bloodstream and is not hepatically metabolized. Cisplatin is predominantly eliminated by the kidneys.

Dosage with toxicity:

Grade 2 neurotoxicity/ototoxicity	Reduce dose by 20%
Grade 3 or 4 neurotoxicity/ototoxicity	Discontinue
Other grade 3 non-hematologic/organ toxicity	Reduce dose by 25%
Other grade 4 non-hematologic/organ toxicity	Discontinue
Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions, grade 3/4 increased LFTs	Discontinue
Grade 4 platelets, grade 4 ANC >/= 5 days, thrombocytopenic bleeding or febrile neutropenia	Reduce dose by 25%

Potential ADRs

- Adverse effects include myelosuppression, nausea/vomiting, peripheral neuropathy, nephrotoxicity, ototoxicity, alopecia, and hypersensitivity. **For management please refer to institutional standard**

Hypersensitivity reactions include anaphylactic-like reactions.
Tachycardia, bronchoconstriction, hypotension, facial edema and erythema may occur and should be should be treated with antihistamine, corticosteroids, and epinephrine as per institutional hypersensitivity management protocol. These reactions typically occur in patients with prior exposure to cisplatin. If appropriate based on the discretion of the treating Physician to continue with treatment then desensitization required for future doses, pretreat with the same medications for at least 24-hour and at time of infusion.

Review of drug/drug interactions concomitant medications

- **Prohibited or restricted medications:** Caution with other renally excreted drugs or other nephrotoxic and ototoxic drugs**.**
- The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, a basic multivitamin , L-glutamine, or probiotics oral supplements will be permitted at long as at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed. Any additional supplements will need prior review and approval by Study Chair (Study chairs can send to the NRG Pharmacy Sub-Committee for guidance as needed).

APPENDIX II: RT SCHEMA

Radiation Schema for Intermediate/High Risk Patients (Lateralized Tumors)

Primary \ Neck	N0	N1	N2a	N2b	N2c	N3
No adverse	N (low risk)	N (low risk) or P + NI	P+NI	P+NI	P+NB	P+NB
Margin (close)	Re-resect	P+NI	P+NI	P+NI	P+NB	P+NB
PNI/LVSI	P+NI	P+NI	P+NI	P+NI	P+NB	P+NB
DOI > 10 mm	P+NI	P+NI	P+NI	P+NI	P+NB	P+NB
pT3	P+NI	P+NI	P+NI	P+NI	P+NB	P+NB
pT4	P+NI	P+NI	P+NI	P+NI	P+NB	P+NB
ECE	N/A	P+NB+C	P+NB+C	P+NB+C	P+NB+C	P+NB+C
Margin (positive)	Re-resect	P+NB+C	P+NB+C	P+NB+C	P+NB+C	P+NB+C

LATERAL (>1 cm from midline oral tongue or alveolar ridge, buccal mucosa, retromolar trigone)

Radiation to none (N), primary (P) neck-ipsilateral (NI), neck-bilateral (NB), +C (with concurrent chemotherapy/cetuximab)

This is the radiation plan. The protocol will allow for margin (close/positive) re-section.

Radiation Schema for Intermediate/High Risk Patients (Midline Tumors)

Primary \ Neck	N0	N1	N2a	N2b	N2c	N3
No adverse	N (low risk)	N (low risk) or P + NI	P+NB	P+NB	P+NB	P+NB
Margin (close)	Re-resect	P+NB	P+NB	P+NB	P+NB	P+NB
PNI/LVSI	P+NB	P+NB	P+NB	P+NB	P+NB	P+NB
DOI > 10 mm	P+NB	P+NB	P+NB	P+NB	P+NB	P+NB
pT3	P+NB	P+NB	P+NB	P+NB	P+NB	P+NB
pT4	P+NB	P+NB	P+NB	P+NB	P+NB	P+NB
ECE	N/A	P+NB+C	P+NB+C	P+NB+C	P+NB+C	P+NB+C
Margin (positive)	Re-resect	P+NB+C	P+NB+C	P+NB+C	P+NB+C	P+NB+C

MIDLINE (includes any FOM)

Radiation to none (N), primary (P) neck-ipsilateral (NI), neck-bilateral (NB), +C (with concurrent chemotherapy/cetuximab)

This is the radiation plan. The protocol will allow for margin (close/positive) re-section.

APPENDIX III: MEDIDATA PATIENT CLOUD ePRO OPERATIONAL INSTRUCTIONS

Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

ePRO Application Download

Note that there are multiple versions of the Medidata Patient Cloud ePRO Application. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error if the wrong version is downloaded.

Patient Cloud ePRO

Patient Cloud

CRA SITE USERS

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.
To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

Patient Users

To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into Patient Cloud ePRO with their passwords or their PIN codes on the same device. **Refer to Appendix E on Setting the Patient Cloud ePRO App to Multi-User Mode.**

Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail,

and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you

completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks “Submit,” the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient’s email links the device (used) and (ePRO) account to where the data is stored. The patient’s email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

Site checklist for activities prior to consenting a patient

- ☐ Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO
- ☐ Accept study invitation at iMedidata.com

- Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO

- Verify the IOS or Android operating system is using the most current version
- Verify Patient Cloud ePRO app is using the most current version
- If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode
- Refer to Review Quick Reference Guides for videos and other procedural information

Patient withdraws study consent or withdraws consent from participating on ePRO

CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from being sent to the patient.

APPENDIX IV: SURGEON EDUCATION AND CREDENTIALING

Surgeon credentialing and education for SLN mapping and biopsy are a critical determinant for success of this trial, as previously demonstrated in the ACOSOG Z0360 trial. We have created teaching materials and included concepts and guidance from Dr. Francisco Civantos who organized the education efforts for ACOSOG Z0360 and Dr. Clare Schilling who has led educational efforts in the European Union for the SENT trial through Headstart: Sentinel Node Biopsy. Importantly, the training workshop in Europe encourages participation of a multidisciplinary team, including surgeon, pathologist and nuclear medicine physician, to ensure that all aspects of the SLN biopsy procedure are covered in training. NRG Oncology will follow this model for education and we have encouraged surgeons to begin engaging with their pathologist(s) and nuclear medicine physician(s) to determine their overall workflow. SLN biopsy course will be held in conjunction with the semiannual NRG Oncology meetings, AHNS annual meetings and also at other venues according to investigator interest and budgetary availability.

Surgeons must be credentialed by their local institutions to perform neck dissection and sentinel lymph node biopsy prior to enrolling patients on the trial. The Surgical Credentialing Checklist form can be accessed on the protocol-specific page of the CTSU website. Adequate experience must be demonstrated to ensure quality control. Requirements are as follows:

- Each participating surgeon must document that he/she has performed a minimum of 5 cases of neck dissections for oral cavity cancer as the primary surgeon (with at least 15 lymph nodes submitted for pathological evaluation) within the past 36 months;
- Each participating surgeon must document that he/she has performed a minimum of 5 cases of SLN biopsy within the past 60 months:
    - SLN biopsy for oral cavity cancer with at least 6 months of disease-free survival (outcome evaluation);
    - SLN biopsy for oral cavity cancer followed by an immediate completion neck dissection during the same surgical encounter (pathology evaluation); or
    - SLN biopsy for melanoma in the head and neck region will also be used to demonstrate surgeon experience with this surgical procedure. Surgeons with primarily melanoma SLN biopsy experience will be required to take the SLN biopsy course.
- Education will be available for surgeons who have not previously performed SLN biopsy for oral cavity cancer –SLN biopsy courses/continual quality assurance;
    - For next available training please contact (*NRG-HN006@NRGOncology.org).*
- Institutions should allow adequate processing time (7-10 days) before registering the first patient.

Surgical Quality Assurance Program

The Surgical Quality Assurance Working Group (SQAWG) will be comprised primarily of the HN006 study chairs with select members from the NRG Surgical Oncology and/or H&N Committees. The purpose of this working group is to provide support for continuing assessment of SLN biopsy and neck dissection quality as part of the quality assurance program for this trial. Each surgeon will provide operative reports, pathology reports and

imaging reports for 10 SLN biopsy cases with at least 6 months of follow up data or with immediate neck dissection for comparison. We will also accept SLN biopsy cases for management of oral cavity cancer, melanoma or breast cancer. Surgeons with limited or no experience with SLN biopsy for oral cavity cancers will participate in the education course. All surgeons will be subject to continuous auditing regarding node acquisition via SLN biopsy and neck dissection.

As stated in Section 12.1, In the event that the surgical quality assurance review identifies unacceptable deviations on 5 cases enrolled on the study, then the surgeon will be removed from the pre-requisite module in the OPEN registration system. The site will be notified by either the SQAWG or the NRG Data Manager with instructions on how to be reinstated. Reinstatement is at the discretion of the SQAWG and can include receipt of a corrective action plan or additional required training. Once the surgeon is reinstated, the surgical treatment data for the next case will be evaluated to ensure no issues are found. In the event of repeated unacceptable deviations from the protocol, the surgeon may be suspended from further enrollment to the trial. This suspension will be at the discretion of the overall Study Chair in consultation with the surgery co-chair and SQAWG. If a site has multiple surgeons in non-compliance, accrual at the site may be suspended per discretion of the overall Study Chair in consultation with the surgery co-chair and SQAWG.