CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II SINGLE ARM TRIAL OF ELECTIVE VOLUME ADJUSTED DE-ESCALATION RADIOTHERAPY (EVADER) IN PATIENTS WITH LOW-RISK HPV-RELATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

CCTG Protocol Number: **HN.10**

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CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to CCTG.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: CCTG HN.10

CENTRE: _____

TREATMENT SCHEMA

This is a phase II, single arm, open-label, multi-centre cooperative group trial of elective volume adjusted de-escalation radiotherapy in patients with low-risk human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC).

<table>
<tr><td rowspan="3">Pathologically-proven OPSCC

p16+ or HPV+

Clinical stage
T1-3 N0-1 M0
(UICC/AJCC 8th Ed.)

No prior radiotherapy or chemotherapy</td><td rowspan="3">REGISTER</td><td>Treatment Option #1
→</td><td><u>Radiotherapy (Standard Fractionation)</u>:
Reduced ENI Volumes
35 fractions, 5/wk, 7 wks
70Gy/56Gy

<u>Cisplatin</u>:
100 mg/m^2 on day 1, 22, and 43
or
40 mg/m^2 /wk for 7 wks

(Allowed for T3 N0-1, T2 N1, and T1 N1 with single node >3cm or multiple ipsilateral nodes)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Treatment Option #2
→</td><td><u>Radiotherapy Alone (Accelerated Fractionation)</u>:
Reduced ENI Volumes
35 fractions, 6/wk, 6 wks
70Gy/56Gy

(Mandatory for T1-2 N0 and for T1 N1 with single node ≤ 3 cm; allowed for other patients who are not eligible for cisplatin)</td></tr>
</table>

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the efficacy of primary definitive radiotherapy (RT) or chemoradiotherapy (CRT) utilizing volume reduced elective nodal irradiation (ENI) as measured by 2-year event-free survival (EFS) in patients with low-risk HPV-related OPSCC.

1.2 Secondary Objectives

To evaluate overall survival, local control, regional control, local-regional control, out-of-field regional control, distant metastasis free survival, early and late toxicities of treatment, subjective swallowing functions, quality of life (QOL), utilization of healthcare resources, work productivity, and prognostic biomarkers.

1.3 Tertiary Objectives

To assemble an imaging and biospecimen bank for future research that could improve risk stratification and patient selection for volume-reduced ENI.

2.0 BACKGROUND INFORMATION AND RATIONALE

Oropharyngeal squamous cell carcinoma (OPSCC) that is related to human papillomavirus (HPV) infection is increasing in incidence within Canada and worldwide and is now the most common category of head and neck squamous cell carcinoma (HNSCC) in Canada *[Canadian Cancer Statistics 2016]*. Standard treatment of HPV-related OPSCC includes radiotherapy (RT) often with concurrent chemotherapy (CRT). These treatments are highly effective but cause significant short- and long-term toxicities. Several de-escalated treatment strategies are now being investigated in favourable prognosis patients. One approach that has not been sufficiently evaluated is reducing the regions of the lymph nodes in the neck that are treated with RT.

Definitive treatment of OPSCC: Curative treatment strategies involving RT for OPSCC are associated with significant morbidity due to the intensity of the treatment and the anatomic location of the disease *[Beetz 2012; Christianen 2012; Goepfert 2017; Kelly 2016; Lagendijk 2008; Machtay 2008; Ward 2016]*. Efforts to reduce dose to normal tissues involved in swallowing and salivary function, such as the implementation of parotid-sparing and pharyngeal-sparing intensity-modulated radiotherapy (IMRT) have helped to reduce these risks to a moderate degree, but many patients still endure significant toxicities that impair their objective swallowing and salivary functions to an extent that impacts quality of life (QOL), utilization of healthcare resources, and work productivity *[Beetz 2012; Kohler 2013; Roe 2014; Yong 2012; Sturgis 2011; Chen 2017; Chera 2015; Lee 2016]*. Therefore, new and creative approaches for reducing toxicity and improving QOL while maintaining high cure rates are needed.

Treatment de-escalation for HPV-related OPSCC: Standard treatment for HPV-related OPSCC includes RT or CRT. These treatments are highly effective at curing most patients with HPV-related OPSCC. Short- and long-term toxicities from treatment can be significant, however, leading to the recognition that de-escalated treatment strategies should be investigated for a subset of favorable prognosis patients *[Marur 2016]*. Several de-escalation clinical trials for low-risk HPV-related OPSCC are currently ongoing or recently completed *[Kelly 2016; Woody 2016; Nevens 2017; Nuyts 2013; Sanguineti 2014; Kjems 2016; Huang 2017; O'Sullivan 2001]*. These trials are investigating the impact of (1) reduced RT dose or (2) reduced chemotherapy dose or intensity. In contrast, few studies are investigating the impact of reducing the volume of RT.

Rationale for volume de-escalation for low-risk HPV-related OPSCC: Definitive RT for OPSCC typically includes prophylactic elective nodal irradiation (ENI) of uninvolved cervical nodal levels on one or both sides of the neck. Comprehensive ENI involves treatment of bilateral cervical lymph node chains from the retropharyngeal lymph node regions cranially to just above the clavicles caudally. ENI is intended to treat microscopic tumour deposits and reduce the risk of regional recurrence. Comprehensive ENI treatment fields likely result in overtreatment of most OPSCC patients. Eliminating regions with very low likelihood (< 5%) of subclinical tumour involvement *[Li 2013; Seol 2016]* from the ENI fields is a creative strategy for reducing toxicity of treatment while maintaining high rates of disease control. Volume-reduced ENI for HPV-related OPSCC has been evaluated in retrospective studies; for example omission of the contralateral cervical lymph node regions from the standard ENI treatment fields has been shown to be safe and effective in carefully selected patients with lateralized OPSCC *[Villaflor 2016; de Almeida 2016]*. Prospective studies have demonstrated safety and lower toxicity when using volume-reduced ENI in patients with nasopharynx cancer *[Moore 2012; Pearce 2015]* or when treating only involved lymph nodes in patients with OPSCC who respond to aggressive multi-drug induction chemotherapy *[Caparrotti 2017]*.

Rationale for QOL and resource utilization studies: Recent interest in de-escalation protocols for low-risk HPV-related OPSCC stems from the recognition that: 1) standard treatments result in overtreatment of most patients; and 2) HPV-related OPSCC afflicts generally younger and healthier individuals in the prime of their working years *[Marur 2016]*. Overtreatment leads to unnecessary toxicity, reduces QOL, increases resource utilization, and results in lost productivity *[Machtay 2008; Kohler 2013; Yong 2012; Chen 2017; Chera 2015; Ringash 2017; Vainshtein 2015]*. OPSCC patients often require increased medical and/or surgical management of osteoradionecrosis, esophageal stricture, trismus, and xerostomia *[Aerts 2014; Leijenaar 2015]*. Furthermore, ~30% of patients require emergency care during treatment, and ~40% report a change in work status after treatment *[Kohler 2013]*. The impact of overtreatment on QOL has been reported to differ between HPV-related and HPV-unrelated OPSCC *[Gross 2014]*. The long-term impact of OPSCC treatment on QOL is thought to stabilize by 2 years post-treatment *[Bratman 2016]*, suggesting that this duration of follow up is sufficient for prospective studies.

Rationale for correlative studies: The goal of personalized cancer medicine is to deliver the appropriate intensity of treatment to each individual patient in order to maximize the likelihood of cure while minimizing side effects. De-escalated treatment approaches are best suited for patients with the most favorable prognosis, for whom the reduced intensity treatment is still sufficient for cure. Based on clinical stage and HPV-driven tumour biology, this study will select a group of low-risk patients with high EFS with inclusion criteria that are similar to other de-escalation studies *[Kelly 2016; Woody 2016; Nevens 2017]*. However, the identification of additional biomarkers for more refined risk stratification remains an important research objective. Multiple putative prognostic biomarkers are suitable for validation in the context of de-escalated therapy. For example, quantitative radiomic analysis of primary tumours in lung cancer and head and neck cancer patients has identified a 4-feature signature that consistently predicts adverse outcomes *[Goodman 2015; Cancer Genome Atlas Network 2015; Kwan 2018]*. Other studies have demonstrated the poor prognostic association of HPV genotype and of *TP53* mutation with concurrent chromosome 3p deletion *[Wan 2017; Bratman 2015; Lin 2004; Ahn 2014]*. Circulating tumour DNA is an established risk marker across all cancers *[Cao 2012; Dahlstrom 2015]*, with robust data from nasopharynx cancer demonstrating the poor prognostic association of elevated baseline plasma EBV DNA levels *[Chaturvedi 2013]*. Thus, it is likely that plasma HPV DNA levels in this population will also identify patients who are not suitable for treatment with de-escalated therapy.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Radiotherapy

Radiotherapy is a standard treatment option for patients with OPSCC, either alone or in combination with systemic therapy (https://www.nccn.org/professionals/physician_gls/default.aspx).

See Section 7.2 for permitted radiotherapy schedules.

3.2 Systemic Therapy

Systemic therapy given concurrently with radiotherapy is a standard treatment option for patients with OPSCC clinically staged: T3 N0-1 M0; T2 N1 M0; and T1 N1 M0 with either a single node > 3 cm or multiple ipsilateral nodes (NCCN Guidelines V2.2018). The systemic therapy on this study will be cisplatin.

3.2.1 *Cisplatin*

Cisplatin has biochemical properties similar to those of bifunctional alkylating agents producing inter-strand and intra-strand cross-links in DNA. It is apparently not cell-cycle specific.

Cisplatin in administered as intravenous injection (1 mg/ml).

The major toxic effects are gastrointestinal, haematopoetic, otologic, neurologic and renal.

Serious toxic effects include anaphylaxis, infections, myelosupression, neuropathy, leukoencephalopathy, posterior reversible encephalopathy, renal failure and venous or arterial thromboembolism.

See Product Monograph May 30 2017 for additional information.

Cisplatin will be administered on trial according to institutional practice.

Cisplatin is commercially available and will not be supplied for this study.

See Section 7.0 for permitted dose administration schedules.

4.0 STUDY POPULATION

This is a phase II, single arm, open-label, multi-centre cooperative group trial of elective volume adjusted de-escalation radiotherapy in patients with low-risk HPV-related oropharyngeal squamous cell carcinoma.

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

4.1 Eligibility Criteria

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy and to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

These eligibility criteria are expected to be followed. Any proposed variance must be discussed with CCTG prior to patient enrollment:

4.1.1 Patients with pathologically proven diagnosis of HPV-related OPSCC. HPV association will be determined locally by either p16 immunohistochemistry (> 70% of tumour cells demonstrating strong diffuse staining) or direct detection of HPV DNA sequences (e.g. by PCR or in situ hybridization), and must be performed on a core needle or surgical biopsy specimen of the primary tumour or involved cervical lymph node.

4.1.2 Clinical stage T1-3 N0-1 M0 (UICC/AJCC 8th Ed.)

4.1.3 Patients must be eligible for definitive RT or CRT.

4.1.4 Must be ≥ 18 years of age.

4.1.5 Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

4.1.6 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life and health economics questionnaires in either English or French. The baseline assessment must be completed within required timelines, preferably prior to registration, but must be done prior to treatment after enrollment. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

4.1.7 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

4.1.8 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.1.9 In accordance with CCTG policy, protocol treatment is to begin within 3 weeks of patient registration.

4.1.10 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

4.1.11 The following radiological investigations must be done within 8 weeks of registration:

- CT or MRI of head and neck (MRI is recommended for base-of-tongue primary tumours);
- PET-CT scan.

4.1.12 Patient must consent to provision of, and investigator(s) must confirm location and commit to obtain a representation of formalin fixed paraffin block of non-cytology tumour tissue in order that the specific correlative marker assays described in Section 12 (Correlative Studies) may be conducted. Please see the Correlative Manual for details.

4.1.13 Patient must consent to provision of samples of blood and plasma (for circulating cell free DNA) in order that the specific correlative marker assays described in Section 12 (Correlative Studies) may be conducted.

4.1.14 *Prior or Concurrent Malignancies*

Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Previous chemotherapy or radiotherapy treatment for head and neck cancer.

4.2.2 Patients with an unknown primary.

5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

Required Investigations	Pre-study	During Protocol Therapy *(start of treatment until the end of RT)*	After Protocol Therapy until Recurrence/Progression	Post Recurrence or Local, Regional or Distant Progression[1]
History and Physical Exam				
Including: height[2], weight, BSA, tobacco use, performance status, mucosal clinical assessment	≤ 28 days	Weekly	1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36 months post RT then q6 months until 60 months post RT	q6 monthly from the date of first failure[3]
Direct or indirect visualization of tumour and surrounding area per local standards	≤ 8 weeks		3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36 months post RT then q6 months until 60 months post RT	At discretion of the investigator
Laboratory Procedures/Assessments				
CBC with differential, creatinine, bilirubin, AST, ALT, ALP, LDH, albumin, total protein, glucose, magnesium, calcium, sodium, potassium, chloride, PTT, PT/INR	As clinically indicated			
TSH *(Free T4 will be measured if TSH is abnormal)*	≤ 14 days	As clinically indicated	12 and 24 months post RT	As clinically indicated
Radiology				
CT or MRI of head and neck (MRI is recommended for base-of-tongue primary tumours)	≤ 8 weeks	Full staging required if failure documented during treatment	At 3 and 6 months post RT, and as clinically indicated	At the discretion of the investigator
Chest CT or chest X-ray	As clinically indicated		As clinically indicated	
PET-CT scan	≤ 8 weeks	At the discretion of the investigator		
Adverse Events				
Adverse event assessment[4]	≤ 14 days	Weekly	1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36 months post RT then q6 months until 60 months post RT[5]	As clinically indicated
PRO-CTCAE selected items	≤ 14 days	Last week of RT	3, 6, 12, 24, and 36 months post RT	
Other Investigations				
Pregnancy Test[6]	≤ 14 days			
Audiogram[11]	≤ 8 weeks		6 months post RT	
Tumour HPV status by IHC, PCR, or ISH[7]	For all patients			
Biopsy[8]		Recommended for confirmation of first recurrence, first distant metastases or first local/regional progression.		
Phone contact follow-up[9]			Annually after 60 months post RT	

footnotes on next page …

Required Investigations	Pre-study	During Protocol Therapy *(start of treatment until the end of RT)*	After Protocol Therapy until Recurrence/Progression	Post Recurrence or Local, Regional or Distant Progression[1]
Correlative Studies				
Archival Tumour Tissues (for HPV genotyping and mutation testing)	Submit ≤ 4 weeks after registration			
Whole blood and plasma (for circulating cell free DNA [cfDNA])	After patient consent, prior to start of treatment		1 month post RT	
Radiomic analysis of protocol-mandated imaging	No additional investigations are required other than collection of protocol-mandated imaging (diagnostic, simulation/planning and relapse CT and/or MRI).			
Quality of Life				
FACT-H&N[10]	≤ 14 days	Last week of RT	3, 6, 12, 24, 36 months post RT	
Swallowing Related Quality of Life				
MDADI	≤ 14 days	Last week of RT	3, 6, 12, 24, 36 months post RT	
Economic Analysis				
Health Utilities Index (EQ-5D-5L)	≤ 14 days	Last week of RT	3, 6, 12, 24, 36 months post RT	
Resource Utilization Assessment		Last week of RT	6, 12, 24, 36 months post RT	
Lost Productivity Questionnaire		Last week of RT	6 and 12 months post RT	
Swallowing Status				
FOIS	≤ 14 days	Last week of RT	3, 6, 12, 24, 36 months post RT	
PSS-HN	≤ 14 days	Last week of RT	3, 6, 12, 24, 36 months post RT	

1. As defined in Section 8.
2. Height is only required at baseline.
3. Weight and performance status only.
4. Adverse events will be recorded and graded according to the CTCAE v 5.0 (Appendix VI).
5. During the follow-up period, only treatment-related AEs will be collected.
6. For women of child-bearing potential. May be urine or serum. Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
7. HPV testing will be done locally. Reports showing positive immunostaining for p16 or positive HPV detection using PCR or in situ hybridation (ISH) must be submitted for each patient.
8. Must be a needle core biopsy; FNA is not acceptable.
9. Annual contact by phone or equivalent means to verify patient status, disease status and adverse events related to protocol treatment.
10. The FACT-H&N questionnaire should be completed before the MDADI, EQ-5D-5L and PRO-CTCAE.
11. Audiogram may be omitted at baseline and at the 6-month time point provided that this is aligned with institutional policy and there are no associated safety implications to the patient. If pre-registration audiogram is performed, it may be delayed until after enrollment but before commencement of therapy to accommodate delays in scheduling. The rationale for not ordering/delaying the test should be indicated in the source documentation

5.1 Follow-up for Ineligible Patients

For patients declared ineligible and/or who have received no protocol therapy, a Baseline Report and annual follow-up using the Short Follow-Up Report must be submitted.

Patients declared ineligible but who have received at least one dose of protocol therapy should be followed according to protocol to allow for treatment and adverse event assessments to be collected.

Note: The dates of objective progression and death must be reported for ineligible patients.

6.0 ENTRY/REGISTRATION PROCEDURES

6.1 Entry Procedures

All registrations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the HN.10 trial specific web-site. If sites experience difficulties accessing the system and/or registering patients, please contact the help desk (link in EDC) or the HN.10 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG HN.10);
- patient's initials (may be coded);
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed;
- tissue banking/optional consent version date;
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values;
- BSA, height and weight.

6.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a patient's surface area is greater than 2.2, the actual surface area or 2.2 may be used. CCTG BSA calculations are based on the Mosteller formula.

6.3 Registration

Registration will be provided electronically.

At the time of enrollment, all data reported within the Patient Enrollment folder must be accurate, complete and verifiable against source documentation. If a system query is issued indicating that the patient is not eligible, enrollment within the EDC system will not proceed. CCTG should be contacted for assistance if needed. Under no circumstances should inaccurate data be entered in order to permit enrollment.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration.

7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 3 weeks of patient registration.

7.1 Systemic Therapy Options

For patients with OPSCC clinically staged (AJCC 8th Ed.) as T3 N0-1 M0, T2 N1 M0, or T1 N1 M0 with either a single node > 3 cm or multiple ipsilateral nodes, systemic therapy may be administered concurrent with RT. For patients with clinical stage T1-2 N0 or T1 N1 with a single node ≤ 3 cm, no systemic therapy is permitted; these patients will be treated with accelerated fractionation RT alone.

Systemic therapy may consist of cisplatin given either once every 3 weeks or once weekly.

Patients with contraindication(s) to cisplatin will be treated with accelerated fractionation RT alone.

7.1.1 *Cisplatin Therapy*

Cisplatin will be administered (concurrent with conventional fractionation RT) according to one of the following treatment schedules:

Cisplatin: 40 mg/m^2/once weekly during RT, for a maximum of 7 doses.

Cisplatin: 100 mg/m^2 day 1, 22 and 43 of RT.

Dose adjustments will be based on institutional guidelines and Product Monograph.

Antiemetic, hydration (pre and post) and other supportive care will be administered according to institutional guidelines and Product Monograph.

7.2 Radiation Treatment Plan

Participating patients will be managed with RT at a dose of 70 Gy in 35 fractions to high dose regions and 56 Gy in 35 fractions to elective dose regions. Volume-reduced ENI will be used for all patients, with the extent of ENI determined by the subsite of the primary tumour within the oropharynx and by the number and distribution of involved cervical lymph nodes (Appendix II).

Treatment options will include:

- RT with conventional fractionation, 5 fractions per week over 7 weeks, and with concurrent cisplatin; or,
- RT alone with accelerated fractionation, 6 fractions per week over 6 weeks.

7.2.1 *Glossary for Radiotherapy Section*

Table 1: Glossary of terms and contoured structures:

IMRT	Intensity Modulated Radiation Therapy
VMAT	Volumetric Modulated Arc Therapy
CT	Computed Tomography
CTV	Clinical Target Volume
DRR	Digitally Reconstructed Radiographs
DVH	Dose Volume Histogram
ECE	Extracapsular Extension
ENI	Elective Nodal Irradiation
GTV	Gross Tumour Volume
MRI	Magnetic Resonance Imaging
OAR	Organs-at-Risk
PET	Positron Emission Tomography
PRV	Planning Organ-at-Risk Volume
PTV	Planning Target Volume
ROI	Region of Interest
QARC	Quality Assurance Review Centre

7.2.2 *Centre Credentialing for Delivery of Radiotherapy Technique*

All centres participating in the study will require credentialing for the delivery of IMRT or VMAT prior to local activation.

Radiation therapy credentialing for this study will be done by the Quality Assurance Review Centre (QARC) (www.qarc.org). The credentialing process will involve completion of a facility questionnaire in addition to the completion of a benchmark case provided by QARC. Facilities that have been previously credentialed to deliver IMRT and/or VMAT through active participation in CCTG HN6, CCTG HN9, EORTC 1219, NRG HN001 or HN002 will be exempt from the benchmark test case. Other previous credentialing may also be acceptable at the discretion of QARC. The facility questionnaire must be completed by all sites, including those previously credentialed. Procedures, information and forms for this credentialing process can be found at http://www.qarc.org.

7.2.3 *Patient Evaluation*

It is recommended that subjects undergo a complete dental evaluation. Any required dental work should be completed prior to radiotherapy. All subjects should undergo a nutritional evaluation prior to and during treatment. Prophylactic gastrostomy tube placement prior to treatment is not mandatory but encouraged particularly for patients being treated with concurrent cisplatin and should be performed if deemed appropriate. All patients should be reviewed by the treating radiation oncologist weekly during treatment for assessment of toxicity and treatment response. Patients with significant weight loss and/or response in bulky tumours may require replanning, if in the opinion of the treating radiation oncologist, delivery of the original plan may be compromised.

7.2.4 *Equipment and Treatment Delivery*

All patients will be managed with either IMRT or VMAT delivered on linear accelerators with photon beam energy of 4MV or greater.

7.2.5 *Treatment Planning*

CT-based treatment planning is mandatory for all patients. All planning should be volumetric with dose volume histogram (DVH) assessments to ensure PTV coverage and OAR and PRV exclusion within study specifications (see Section 7.2.8). Every effort should be made to limit dose to noncritical normal tissues where possible. Corrections must be made for tissue heterogeneity. The dose calculation grid resolution should be less than or equal to 3 mm on a voxel edge.

All plans will be generated by an inverse planning approach utilizing commercially available planning systems.

7.2.6 *Positioning and Immobilization*

Patients will be treated in the supine position with arms at their side. All patients will be immobilized in a thermoplastic mask at the time of CT simulation and treatment. Shoulder immobilization is required and can be achieved by inclusion in the mask or other methods.

7.2.7 *Simulation and Planning CT Scan*

CT-based simulation and planning is mandatory for all patients. Treatment planning CT scans will be acquired with the patient in the treatment position and immobilization device. All tissues to be irradiated must be included in the planning CT scan. The scanning limits should at least encompass the orbits superiorly to 1 cm below the suprasternal notch inferiorly. CT scan thickness must be ≤ 3 mm. The use of intravenous CT contrast agents is permitted when clinically indicated. All specified target volumes and organs-at-risk (OAR) will be contoured on the planning CT scan. For purposes of contouring, MRI and positron emission tomography (PET) images, if available and clinically indicated, may be co-registered with the planning CT data set. Use of MRI (for staging and/or simulation) is recommended for base-of-tongue primary tumours.

7.2.8 *Volume Definitions*

Nomenclature:
All contoured objects will be assigned names according to the descriptions below and/or Tables 2-5.

Table 2: Contoured target volumes:

Dose Level	Contour Name	Description	Notes
High	GTVp	Primary gross tumour volume	
High	CTVp_7000	5 mm expansion on GTVp	May be trimmed according to anatomical barriers to spread
High	PTVp_7000	3-5 mm expansion on CTVp_7000	
High	Eval_PTVp_7000	PTVp_7000 trimmed from critical OARs and skin	
High	GTVn_2_R	Nodal gross tumour volume within right level II	GTVn_[X]_[R/L] nomenclature: X denotes the nodal level *[Grégoire 2014]* and R/L denotes the laterality
High	GTVn_23_L	Nodal gross tumour volume that spans left levels II and III	
High	CTVn_2_R_7000	5 mm expansion on GTVn_2_R	May be trimmed according to anatomical barriers to spread
High	PTVn_2_R_7000	3-5 mm expansion on CTVn_2_R_7000	
High	Eval_PTVn_2_R_7000	PTVp_7000 trimmed from critical OARs and skin	
High	Eval_PTV_7000	Merged volume	Union of 70 Gy Eval volumes
Low	CTVp_5600	10 mm expansion on GTVp	May be trimmed according to anatomical barriers to spread
Low	PTVp_5600	3-5 mm expansion on CTVp_5600	
Low	Eval_PTVp_5600	PTVp_5600 trimmed from critical OARs and skin	
Low	CTVn_R_5600	Right neck ENI CTV	CTVn_[R/L] nomenclature: R/L denotes the laterality
Low	PTVn_R_5600	3-5 mm expansion on CTVn_R_5600	
Low	Eval_PTVn_R_5600	PTVn_R_5600 trimmed from critical OARs and skin	
Low	Eval_PTV_5600	Merged volume	Union of 56 Gy Eval volumes
Intermediate*	CTVp_6300	Optional expansion on GTVp	Permitted in cases of uncertainty as to the extent of the GTVp; may replace CTVp_5600
Intermediate	PTVp_6300	3-5 mm expansion on CTVp_6300	
Intermediate	Eval_PTV_6300	PTVp_6300 trimmed from critical OARs and skin	
* Intermediate dose level is optional for the primary site and is not allowed for nodal sites.			

Gross Tumour Volume (GTV):
The GTV represents grossly involved regions of primary tumour (GTVp) or involved nodes (GTVn). These regions will be defined based on clinical examination, examination under anesthetic, and CT scan. When indicated and available, MRI and/or PET scans may also be used to define the extent of the GTV.

Cervical lymph nodes in the drainage area of the tumour will be contoured individually as GTVn targets (i.e. separate GTVn targets for each gross node, except in cases of nodal conglomerates) when meeting one or more of the following criteria:

- exceeding one or both size criteria as defined below:
  - maximal axial longitudinal diameter (long axis) > 15 mm for jugulodigastric and submandibular nodes, > 10 mm for all other nodes except retropharyngeal nodes, and > 8 mm for retropharyngeal nodes;
  - minimum axial diameter (short axis) of > 11 mm for jugulodigastric nodes and > 10 mm for all other nodes;
- evidence of necrosis;
- extracapsular extension (ECE) based on irregular borders or invasion of adjacent structures radiographically;
- significant PET avidity as defined below:
  - uptake above liver avidity for nodes with maximal axial longitudinal diameter ≥ 10 mm;
  - uptake above blood pool for nodes with maximal axial longitudinal diameter < 10 mm (especially if morphologically suspicious);
- biopsy demonstrating the presence of cancer.

Additional morphologic features may also be considered when contouring GTVn targets, including:

- length-to-width ratio in the axial plane of < 2 (i.e. round node vs. lima bean–shaped node), especially if PET avidity is above blood pool;
- a group of three or more nodes in the drainage area of the tumour that are round or borderline by size criteria (e.g. maximal axial longitudinal diameter 9-15 mm and/or minimum axial diameter 8-10 mm), especially if PET avidity is above blood pool.

Clinical Target Volumes (CTV):
CTVs are contoured in relation to the gross targets and regions of potential subclinical spread they are intended to encompass, and according to the dose they are intended to receive. Although defined as a 3D expansion of these targets, CTVs should be limited by potential barriers to tumour spread such as air cavities, external contour and boney or fascial planes through which tumour spread is not possible or apparent. Dose to be delivered to CTVs are provided in subsequent sections.

CTVs for the Primary Site and Involved Nodes:
The primary site GTVp will be encompassed by a high dose CTVp_7000 with a margin of 5 mm. Exceptions to the 5 mm minimum are regions limited by potential barriers to tumour spread as described above. CTVp_5600 is a further expansion of 5 mm on the CTVp_7000 (total of 10 mm margin around GTVp). In cases of uncertainty as to the extent of the GTVp, another CTV delivering an intermediate dose level (CTVp_6300) may be used to replace the subclinical dose CTVp_5600 expansion around this GTV.

Each grossly involved nodal volume (GTVn_[X]_[R/L]) will be encompassed by a separate high dose CTVn_[X]_[R/L]_7000 volume with a margin of 5 mm. Exceptions to the 5 mm minimum are regions limited by potential barriers to tumour spread as described above. No CTVn_6300 volumes are permitted in necks.

CTVs for Neck Regions of Subclinical Disease (Elective Nodal Irradiation):
Elective nodal irradiation (ENI) regions will be included in the CTVn_L_5600 (left neck ENI regions) and the CTVn_R_5600 (right neck ENI regions). The included ENI levels will depend on the location and extent of the existing grossly involved nodes and primary site, with the intent of treating levels that harbor nodes at > 5% risk of subclinical spread of tumour. Neck CTVs will be defined according to the tables below, with additional details provided in Appendix II and the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines *[Grégoire 2014]*.

Table 3: ENI levels to be included based on primary location, T category, and N category:

Base-of-Tongue Primary AJCC 8th Ed. Stage		**ENI levels to be included in the CTVn_[R/L]_5600** *[Grégoire 2014]*	
T category	N category	Ipsilateral neck	Contralateral neck
T1-2	N0	• II	• II
T1-2	N1	• II, III, and VIIb; • IV and V to be included 2 cm below the caudal edge of any 7000 cGy CTVn volume • Ib to be included only if involved by gross nodal disease	• II
T3	N0	• II and III • VIIa and VIIb to be included for posterior pharyngeal wall involvement or > 1 cm soft palate involvement	• II and III
T3	N1	• II, III, and VIIb; • IV and V to be included 2 cm below the caudal edge of any 7000 cGy CTVn volume • VIIa to be included for posterior pharyngeal wall involvement or > 1 cm soft palate involvement • Ib to be included only if involved by gross nodal disease	• II and III

Palatine Tonsil Primary AJCC 8th Ed. Stage		**ENI levels to be included in the CTVn_[R/L]_5600** *[Grégoire 2014]*	
T category	N category	Ipsilateral neck	Contralateral neck
T1-2	N0	• II • VIIa and VIIb to be included for posterior pharyngeal wall involvement or > 1 cm soft palate involvement	• II to be included for base-of-tongue involvement extending to within 1 cm of midline • II, VIIa and VIIb to be included for posterior pharyngeal wall involvement or soft palate involvement extending to within 1 cm of midline
T1-2	N1	• II, III, and VIIb; • IV and V to be included 2 cm below the caudal edge of any 7000 cGy CTVn volume • VIIa to be included for posterior pharyngeal wall involvement or > 1 cm soft palate involvement • Ib to be included only if involved by gross nodal disease	• II to be included for base-of-tongue involvement extending to within 1 cm of midline • II, VIIa and VIIb to be included for posterior pharyngeal wall involvement or soft palate involvement extending to within 1 cm of midline
T3	N0	• II and III • VIIa and VIIb to be included for posterior pharyngeal wall involvement or > 1 cm soft palate involvement	• II to be included for base-of-tongue involvement extending to within 1 cm of midline • II, VIIa and VIIb to be included for posterior pharyngeal wall involvement or soft palate involvement extending to within 1 cm of midline
T3	N1	• II, III, and VIIb; • IV and V to be included 2 cm below the caudal edge of any 7000 cGy CTVn volume • VIIa to be included for posterior pharyngeal wall involvement or > 1 cm soft palate involvement • Ib to be included only if involved by gross nodal disease	• II to be included for base-of-tongue involvement extending to within 1 cm of midline • II, VIIa and VIIb to be included for posterior pharyngeal wall involvement or soft palate involvement extending to within 1 cm of midline

Soft Palate Primary AJCC 8th Ed. Stage		**ENI levels to be included in the CTVn_[R/L]_5600** *[Grégoire 2014]*	
T category	N category	Ipsilateral neck	Contralateral neck
T1-3	N0	• II, VIIa, and VIIb	• II, VIIa, and VIIb
T1-3	N1	• II, III, VIIa, and VIIb; • IV and V to be included 2 cm below the caudal edge of any 7000 cGy CTVn volume • Ib to be included only if involved by gross nodal disease	• II, VIIa, and VIIb

Unilateral Neck Treatment:
Unilateral neck treatment should be performed for patients with palatine tonsil primary unless gross disease extends to within 1 cm of midline (along base-of-tongue, posterior pharyngeal wall, and/or soft palate), in which case bilateral neck treatment should be performed covering the ENI levels as specified above. Bilateral neck treatment should be performed for patients with base-of-tongue or soft palate primary.

Planning Target Volume (PTV):
The PTVs are geometric expansions of the CTVs to account for internal motion and residual set-up error. The PTVs represent the volumes to which dose will be prescribed, delivered and evaluated. All CTVs will have a corresponding PTV which will represent at least a 3-5 mm expansion of the CTV in all planes. For centres utilizing daily volumetric image-guided radiation therapy (IGRT), smaller PTV margins of 3-4 mm will be permitted to continue as long as they have their own immobilization data to support this.

Modification of PTVs to create Eval_PTVs:
In instances where the PTV overlaps a critical OAR (Table 4) or it's associated PRV, the PTV will be modified to exclude the PRV.

When expansion of a CTV results in PTVs that extend beyond the patient's surface, or within 5 mm of the patient surface, the PTV should be constrained to 5 mm within the external contour. A 3 mm constraint may be used if disease is near the skin surface. For situations where disease is at or just below the surface, the use of tissue equivalent material (bolus) is required.

These modified PTV volumes are the evaluation volumes that will be used to assess dose coverage. Eval_PTV_#### (without any identification of primary or nodal PTV) will be a merged volume for evaluation (the union of all PTVs for a specific dose level). Eval_PTV doses are defined in Table 6.

Organs-at-Risk (OAR):
Critical OARs must be contoured on every CT slice in which they appear. Critical OARs are spinal cord, brainstem and brain. Optic nerves, optic chiasm, and globes should be contoured and dose evaluated for cases in which the treated volumes (PTVs) are within 1 cm of any of these structures, otherwise they can be omitted. When at risk, and hence contoured, the optic structures would be regarded as critical OARs. Other OARs to be contoured include parotid glands, mandible, submandibular glands, glottic larynx, and midline mucosa. Brachial plexus should be contoured ipsilateral to any gross nodes below the level of C5 otherwise can be omitted. Critical OAR dose limits are defined in Table 4 and dose limits for other OARs in Table 5.

Planning Organ-at-Risk Volume (PRV):
Critical OARs requiring PRVs include spinal cord and brainstem. PRVs will represent 3-5 mm expansions of the critical OARs to account for interfraction patient and organ motion and for purposes of dose assessment and limitation during the planning and review process. For spinal cord, 5 mm PRV expansion is required, regardless of local IGRT practice. For centres utilizing daily volumetric IGRT, 3-4 mm PRV expansion will be permitted for brainstem.

7.2.9 *Dose Limits to Normal Tissues*

The dose delivered to normal structures (OARs and PRVs) will be determined by review of both DVHs and axial dose distributions for the OARs and PRVs as defined above. Strict dose limitations are assigned to the critical OARs listed in Table 4 and may not be exceeded under any circumstances. The dose limits of other OARs (Table 5) should be achieved as long as these structures are not directly involved by tumour and/or dose to the adjacent PTVs is not compromised to do so. The volumes listed in Tables 4 and 5 will be contoured for all cases.

Table 4: Critical OAR dose limits:

Region of Interest (ROI)	Standard Names	Criterion	Dose Limit
Brainstem	Brainstem	Max dose to 0.1 cc	50 Gy
PRV Brainstem	Brainstem_PRV03	Max dose to 0.1 cc	60 Gy
Spinal Cord	SpinalCord	Max dose to 0.1 cc	45 Gy
PRV Spinal Cord	SpinalCord_PRV05	Max dose to 0.1 cc	52 Gy
Brain	Brain	Max dose to 0.1 cc	70 Gy
Optic Nerves	OpticNrv_R or L	Max dose to 0.1 cc	42 Gy
Chiasm	Chiasm	Max dose to 0.1 cc	42 Gy

Non-targeted Neck CTVs:
The dose delivered to neck nodal regions that are not part of any PTV will be evaluated as specified in Table 5. Neck nodal levels Ib, II, III, IV, V, VIIa, and VIIb are to be contoured. Separate structures are to be created for the right and left necks, but separate sub-structures for each nodal level are not required. The volume that does not overlap with any of the PTVs will be designated ref_Neck_R or ref_Neck_L. Both sides must be contoured even in cases where unilateral neck treatment is performed. Contouring of nodal levels is to be performed according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines *[Grégoire 2014]*.

As mentioned above, dose to PTVs should not be compromised to achieve the dose limits stipulated in Table 5.

Table 5: Other (non-critical) OAR dose limits:

Region of Interest (ROI)	Standard Names	Scenario or Criterion	Dose Limit
Submandibular Glands	Submand_R or L	When the adjacent level II is included in CTVs	Mean: < 39 Gy
		When the adjacent level II is *not* included in CTVs	Mean: < 26 Gy
Larynx	Larynx	When *bilateral* level III is included in CTVs	Mean: < 45 Gy
		When *unilateral* level III is included in CTVs	Mean: < 35 Gy
		When *neither* level III is included in CTVs	Mean: < 15 Gy
Parotid Glands	Parotid_R or L	Mean	< 26 Gy
		D50%	< 30 Gy
Oral Cavity	OralCavity	Mean	< 30 Gy
Lips	Lips	Mean	< 25 Gy
Pharyngeal constrictors	Musc_Constrict	Mean	< 45 Gy
Cervical Esophagus	Esophagus	Mean	< 35 Gy
Mandible	Mandible	Max dose to 0.1 cc	< 73.5 Gy within Eval_PTV_7000 and < 70 Gy outside of Eval_PTV_7000
Contoured* neck nodal levels Ib, II, III, IV, V, VIIa, and VIIb outside the PTVs	ref_NECK_R or L	The treated neck (i.e. each neck in bilateral cases or the treated neck in unilateral neck cases)	V25: < 50 cc
		The untreated neck (i.e. the untreated neck in unilateral neck cases)	V25: < 10 cc
Unspecified normal tissues outside defined PTVs	External-PTV	Max dose to 1 cc	< 73.5 Gy

* Comprehensive neck volumes (both sides: ref_NECK_R and ref_NECK_L) must be contoured for all cases in order to assess dose to non-targeted neck levels. Efforts should be made to minimize the volume of each ref_Neck ROI that receives > 25 Gy. Dose limits apply to each ref_NECK ROI individually.

7.2.10 *Planning Procedures*

Planning Priorities:
For purposes of plan optimization, the priorities are: 1) critical OAR and PRV, 2) PTV coverage, 3) non-critical OAR, 4) undefined normal tissue.

Beam Arrangement:
The beam arrangements will be those necessary to treat the defined target volumes (see Section 7.2.8) and spare OARs. Beam arrangements are discretionary and defined to achieve study dosimetric goal specifications.

Beam Segmentation and Optimization:
Beam segmentation and optimization is at the discretion of the planner, subject to institutional practice.

7.2.11 *Dose Reporting*

Dose is to be prescribed to an isodose line that encompasses the respective PTV and satisfies the dose heterogeneity criteria in Section 7.2.12.

7.2.12 *Dose Heterogeneity*

Dose heterogeneity limits to PTVs are illustrated in Table 5. Plan normalization should provide coverage of 95% of the PTV_7000 with the prescription dose (70 Gy). No more than 1% of any PTV will receive less than 93% of the prescribed dose. Maximum doses to Eval_PTV_7000, Eval_PTV_5600 and Eval_PTV_6300 (optional) are 115%, 125% and 120% of their prescribed doses respectively. However, it is recognized that small volumes of lower dose PTVs surrounding or adjacent to higher dose PTVs may exceed this (see Table 6).

Table 6: Planning target volume dose limits:

	Eval_PTV_7000	Eval_PTV_5600	Eval_PTV_6300 (optional)
Percent Volume	(% of 70Gy)	(% of 56Gy)	(% of 63Gy)
< 5%	< 100%	< 100%	< 100%
< 1%	< 93%	< 93%	< 93%
0%	> 115%	> 125%*	> 120%*
< 20%	> 110%	> 110%*	> 110%*
Mean dose	≤ 105%		

* These limits are applicable to portions of Eval_PTV_5600 and Eval_PTV_6300 which (i) do not overlap higher-dose PTVs and (ii) are not adjacent to higher-dose PTVs

7.2.13 *Dose Fractionation Schemes*

Radiotherapy will be delivered to a prescribed dose of 70 Gy in 35 fractions of 2 Gy. Permitted fractionation schemes include:

- Conventional fractionation, 5 fractions per week over 7 weeks, when delivered with concurrent cisplatin; or
- Accelerated fractionation, 6 fractions per week over 6 weeks, when delivered alone. The sixth fraction can be delivered on a weekend or as a second treatment on a weekday, provided that the treatment interval is at least 6 hours.

Treatment breaks should be minimized, and twice-daily radiation treatments are encouraged to make up for unexpected treatment breaks or hospital closures. When twice-daily radiation treatments are delivered as part of planned accelerated fractionation or to make up missed treatments, the minimum treatment interval is 6 hours.

IMRT Dose Specifications:
A single-phase IMRT plan will be given delivering 35 fractions,

- PTV_7000 will receive 2 Gy per fraction.
- PTV_5600 will receive 1.6 Gy per fraction.
- PTV_6300 (optional) will receive 1.8 Gy per fraction.

7.2.14 *Treatment Delivery*

Patient Set Up and Verification Imaging:
Patients will be positioned for treatment on the treatment bed within their immobilization mask and aligned according to marks placed on this mask to indicate the isocenter. Image guided radiation therapy (IGRT) is to be completed to verify patient positioning. Daily IGRT is strongly recommended, however, the minimum requirement is weekly imaging, starting on the first day of treatment.

On-board volumetric imaging (e.g. kilovoltage (kV) or megavoltage (MV) conebeam CT (CBCT)) is recommended to be used and compared to the planning CT to verify daily positioning. Alternatively, this can be done with portal images of orthogonal fields localizing the isocentre placement for IMRT plans. Image matching will be based on alignment of regional boney landmarks with offsets of greater than 3 mm requiring patient repositioning. Imaging post-recommendation is recommended but not required.

7.2.15 *Corrections For Radiotherapy Treatment Interruptions*

Treatment interruptions of a single day will be compensated for with the addition of a second daily treatment on one day of the week preceding or following the interruption. These treatments should have a strict minimum interfraction interval of 6 hours. For patients receiving accelerated fractionation the compensatory second fraction should have a minimum two-day separation from the regularly scheduled two fraction day. A maximum of three such compensatory treatments will be permitted during the treatment course. Interruptions not compensated for will be recorded and accounted for in the determination of protocol compliance according to Section 7.2.16.

7.2.16 *Compliance Criteria*

Radiation treatment related deviations outside protocol recommendations and likely to influence clinical outcome will be considered as major. Such deviations could include failure to identify and treat appropriate targets and excessive treatment of non-target tissues. These determinations will be made during the plan review process. Deviations outside protocol recommendations and unlikely to influence clinical outcome will be considered as minor.

Treatment Interruptions:
Treatment breaks must be clearly indicated in the treatment record along with the reasons for the treatment breaks. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons

Single day interruptions will be compensated for according to guidelines in Section 7.2.15 for a maximum of 3 treatment day interruptions.

Any uncompensated treatment break(s) for any non-medical reason exceeding two sequential treatment days or 5 total days during the course of treatment will be considered as a protocol deviation.

Treatment interruptions of 3-5 sequential treatment days at a time for any reason will be considered a minor deviation and more than 5 sequential treatment days at a time will be considered as a major deviation.

Over the full course of treatment total treatment breaks of 6-10 days for any non-medical reason will be considered a minor deviation and if more than total 10 treatment days will be considered as a major deviation.

Dose Delivery
Major and minor dose delivery deviations for PTVs are described relative to dose objectives in the RTQA & Radiomics Manual on the HN.10 trial specific website. To be categorized as a major protocol deviation a plan will be determined to have i) failed to meet dose criteria and ii) such failure will have to be deemed as likely to have an adverse impact on patient outcome at the time of central review of the volumes and distributions.

The reviewers recognize achieving 100% of the dose to 95% of the Eval_PTVs will be challenging for cases in which the Eval_PTV is in close proximity to a critical OAR (Table 4) and/or skin surface, however these objectives would be expected to be achieved otherwise. Summary of minor and major deviations relating to target coverage is summarized in Table 7.

Non-compliance with the dose limitations assigned to critical OARs (Table 4) will always be considered a major deviation. Non-compliance with the dose limits of "other OARs" (Table 5) will be analyzed case per case by the reviewers to define if they should be considered deviations or not. Cases for which the doses to these OARs exceed the protocol limits due to proximity to PTVs will not be considered deviations. For example, exceeding dose limits to parotid glands is acceptable when needed to achieve acceptable dose to an adjacent or overlapping PTV.

Table 7: Major and Minor Dose Delivery Deviations for Planning target volumes.

	Eval_PTV_ 7000	Eval_PTV_5600	Eval_PTV_6300 (optional)	Dose Criteria for Deviations	
Percent Volume	(% of 70Gy)	(% of 56Gy)	(% of 63Gy)	Minor Deviation (% Volume)	Major Deviation (% Volume)
< 5%	< 100%	< 100%	< 100%		>5%
< 1%	< 93%	< 93%	< 93%	1-3%	>3%
0%	> 115%	> 125%*	> 120%*		
< 20%	> 110%	> 110%*	> 110%*		
Mean dose to Eval_PTV_7000	≤ 105%			105-107% of 70 Gy	>107% of 70 Gy

* These limits are applicable to portions of Eval_PTV_5600 and Eval_PTV_6300 which (i) do not overlap higher-dose PTVs and (ii) are not adjacent to higher-dose PTVs.

7.2.17 *Central Radiotherapy Quality Assurance Review*

Central quality assurance review of radiation delivery will consist of two components:

i) real time rapid review of contoured targets (GTVs, CTVs, PTVs), OARs, and diagnostic imaging prior to commencement of treatment;

ii) post treatment final review of radiotherapy plans.

Radiotherapy quality assurance reviews will be conducted centrally through QARC for all patients. Procedures, information and forms about the external review process can be found at http://www.qarc.org. Data required for plan documentation and quality assurance will be submitted according to QARC guidelines.

The real time rapid review and final review will be performed for every case.

Real Time Rapid Review:
The simulation scan, contours (targets and OARs as defined in Tables 2-5), diagnostic head and neck cross-sectional imaging (CT, MRI, PET), and supporting documentation is to be submitted and approved by QARC prior to commencement of treatment. This should be done as soon as possible to enable modifications to the contours to conform with the protocol. Feedback from the Rapid Review will be returned to the treating centre within 2 working days. The treating centre will implement corrective action if applicable and respond to QARC recommendations prior to commencement of treatment.

Final Review:
The required documentation is to be submitted to QARC within 2 weeks of treatment completion. A written report of the Final Review will be created by QARC. Additional details can be found in the RTQA & Radiomics Manual.

7.2.18 *Central Review of Regional Failures*

With reduction of the elective nodal irradiation volumes, there may be increased risk of out-of-field regional recurrence. Rigorous analysis of patterns of failure in the neck will be important for informing the results of this study and any future studies that utilize a similar treatment approach.

Any subject with regional recurrence in the lymph nodes of the neck (either as first or subsequent recurrence) will require central review of the radiological images (CT, MRI, and/or PET-CT) obtained at the time of recurrence in order to categorize the regional recurrence as in-field or out-of-field. The radiological images showing regional recurrence will be submitted within 4 weeks of confirming the recurrence.

The recurrent tumour volume will be identified on the earliest available diagnostic scan that shows the recurrent node. If the identified recurrent lymph node corresponds to a lymph node that was present on the planning scan, the node from the planning scan will be contoured and named "RECUR_NODE." Otherwise, the identified recurrent lymph node volume will be contoured on the radiological images obtained at the time of recurrence and named "RECUR_NODE"; following registration to the planning scan, the RECUR_NODE volume will be transferred to the planning CT structure set.

The radiation dose received by the RECUR_NODE volume will be determined.

An "in-field regional recurrence" will be defined in cases in which ≥ 95% of RECUR_NODE was within the 95% isodose of PTV_5600.

An "out-of-field regional recurrence" will be defined in cases in which < 95% of RECUR_NODE was within the 95% isodose of PTV_5600.

7.3 Surgical Treatment Plan of the Neck

Patients will have an evaluation of their primary tumour and neck (CT, MRI, and/or PET-CT) 12 weeks following the completion of radiotherapy (Section 5.0).

Institutional policies will be followed regarding surgical treatment of the neck for suspected residual, recurrent, or progressive nodal disease. Guidance is provided below regarding surgical treatment of the neck in specific settings. Regardless of the policy adopted for the management of the neck, any surgical intervention requires that new or persistent nodal disease be deemed operable by the treating surgeon.

7.3.1 *Surgical Treatment Plan for Node-Positive Patients With Residual Abnormal Treated Lymph Nodes at 12 Weeks*

The decision to undertake a neck dissection as a result of residual abnormal lymph nodes in the treatment field will be based on the clinical and radiographic examinations at 12 weeks post radiotherapy and institutional policies regarding planned neck dissections. Because of high rates of eventual CR in the neck for HPV positive patients presenting with involved lymph nodes coupled with low rates of pathologic positivity in residual nodes, it is suggested that centres follow the algorithm presented below:

Elective neck dissection should be completed ≤ 20 weeks following completion of radiotherapy.

Nodal disease* at week 12	Recommendation
No new or persistent disease	Follow as per protocol (Section 5.0)
Persistent treated nodes ≤ 2 cm	Repeat imaging in < 2 months
Persistent treated nodes > 2 cm with evidence of regression	Repeat imaging in < 2 months
Persistent treated nodes > 2 cm with no regression or progression compared to baseline	Neck dissection
Persistent treated nodes of any size with significant PET avidity (if performed as per institutional standards)	Consider neck dissection as per institutional policy
* on clinical and/or radiographic examinations	

7.3.2 *Surgical Treatment Plan for Patients With New Abnormal Lymph Nodes*

New lymph nodes that are abnormal based on the clinical and radiographic examinations at 12 weeks post radiotherapy or on any subsequent examinations should be biopsied without delay to confirm regional recurrence.

For a negative biopsy, at the discretion of the treating team, the subject may undergo re-attempt at biopsy, repeat imaging within 1-2 months, or proceed directly to prompt neck dissection.

For a positive biopsy, full re-staging examinations must be performed (Section 5.0). For isolated biopsy-proven regional recurrence, prompt neck dissection is recommended, provided that the disease is deemed to be operable by the treating surgeon. For inoperable isolated regional recurrence, salvage re-irradiation with or without concurrent chemotherapy may be employed at the discretion of the treating team. If there is overlap of the re-irradiation treatment field with the original treatment field, twice daily hyperfractionated radiotherapy should be performed in order to minimize potential late toxicity.

7.4 Concomitant Therapy

7.4.1 *Permitted*

Patients will receive ongoing supportive and symptom control (e.g. nutritional support including G tubes insertion, analgesics for pain) as indicated throughout the study. Other ancillary treatments such as intravenous hydration will be given as medically indicated. All treatment must be recorded in the case report forms.

7.4.2 *Not Permitted*

Administration of any other anti-cancer therapy is not permitted while the patient is receiving protocol therapy. Thereafter, patients may be treated at the investigator's discretion.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events*

All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.2 *Evaluable for Quality of Life Assessment*

All patients who have completed the quality of life questionnaire are evaluable for quality of life.

8.1.3 *Evaluable for Health Economics Assessment*

All enrolled patients are evaluable for health economics. Those who have completed the resource utilization and lost productivity questionnaires will be evaluable for cost-utility analyses.

8.1.4 *Evaluable for Event-free Survival*

Event-free survival (EFS) is defined as the time from the date of registration to the date of first record of any of the following events:

- Investigator determined:
  - Local-regional progression or recurrence.
  - Distant metastasis.
- Surgery:
  - Surgery at any time for clinical or radiological (RECIST 1.1) disease persistence/progression/recurrence at the primary tumour site with tumour present/unknown on final pathology.
  - Neck dissection or surgery performed for clinical or radiological (RECIST 1.1) disease persistence/recurrence/progression within the target volumes > 20 weeks from the end of radiation therapy with tumour present/unknown on final pathology.
  - Neck dissection or surgery performed for clinical or radiological disease recurrence/progression outside the target volumes or without documentation of the site of failure at any time after registration with tumour present/unknown on final pathology.
- Non-protocol RT, chemotherapy, or biologic therapy (for the current cancer diagnosis) without documentation of the site of failure.
- Death due to any cause.

8.1.5 *Local-regional Control (LRC)*

Local-regional control is defined as the time from the date of registration to the date of any of the following, whichever comes first:

- Surgery of primary tumour at any time performed for clinical or radiological (RECIST 1.1) disease persistence/progression/recurrence with tumour present/unknown on final pathology

- Neck dissection > 20 weeks from the end of radiation therapy performed for clinical or radiological (RECIST 1.1) disease persistence/progression/recurrence within target volumes with tumour present/unknown on final pathology
- Neck dissection at any time after registration performed for clinical or radiological (RECIST 1.1) disease recurrence/progression outside the target volumes or without documentation of the site of failure with tumour present/unknown on final pathology.
- the first record of appearance (radiological or clinical) of local or regional disease progression/recurrence.

Distant recurrence/progression diagnosed before local-regional failure and death in absence of local-regional failure are not considered events of interest, but as competing risks events in the analysis of this endpoint. Subjects without any of the listed events (i.e. events of interest or competing risks events) are censored at the date of the most recent follow-up examination.

8.1.6 *Out-of-field Regional Control*

Time to out-of-field regional failure is defined as the time from the date of registration to the date of the first record of appearance of regional progression/recurrence outside the treatment field, or to the date of neck dissection at any time after registration with tumour present/unknown performed for clinical or radiological disease progression outside the target volumes, whichever comes first.

Local or distant recurrence/progression diagnosed before out-of-field regional failure and death in absence of out-of-field regional failure are not considered events of interest, but as competing risks events in the analysis of this endpoint. Subjects without any of the listed events (i.e. events of interest or competing risks events) are censored at the date of the most recent follow-up examination.

8.1.7 *Distant Metastasis Free Survival (DMFS)*

Distant metastasis free survival is defined as the time from the date of registration to the date of first record of appearance of distant metastasis or death for any cause. Local-regional failure or second cancers diagnosed before the distant metastases are not considered events of interest for this endpoint. Subjects alive and free of distant metastasis are censored at the date of the most recent follow-up examination.

8.1.8 *Overall Survival (OS)*

Overall survival is defined as the time from the date of registration to the date of death for any cause. The follow-up of subjects still alive will be censored at the date of last visit/contact.

8.2 Evaluation of Efficacy

The efficacy endpoints will be measured clinically and radiologically using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee.

8.2.1 *Measurable Disease*

Categorization of measurable disease will be based on the RECIST 1.1 criteria with clinical examination as appropriate.

Measurable tumour lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.3 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

8.3 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.3.1 *Clinical Lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.3.2 *Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.3.3 *CT, MRI*

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.3.4 *Ultrasound*

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.3.5 *Endoscopy, Laparoscopy*

The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.3.6 *Cytology, Histology*

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

8.3.7 *Date of Objective Failure (see Section 8.4.6)*

This is defined as the date of the first of the following events, whichever comes first:

- The first record of appearance (radiological or clinical) of local or regional disease progression/recurrence.
- The first record of appearance (radiological or clinical) of distant metastasis.
- Non-protocol RT, chemotherapy, or biologic therapy (for the current OSCC) without documentation of the site of failure.
- Surgery of primary tumour site at any time performed for clinical or radiological (RECIST 1.1) disease persistence/progression/recurrence with tumour present/unknown on final pathology.
- Neck dissection or surgery performed for clinical or radiological (RECIST 1.1) disease persistence/recurrence/progression within the target volumes > 20 weeks from the end of radiation therapy with tumour present/unknown on final pathology.
- Neck dissection or surgery performed for clinical or radiological disease recurrence/progression outside the target volumes or without documentation of the site of failure at any time after registration with tumour present/unknown on final pathology.
- Death due to any cause.

8.3.8 *Date of Progression*

The date of progressive disease is defined as the first day when RECIST (version 1.1) criteria for PD are met. The criteria for PD are met when there is at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

8.4 Evaluation of Endpoints

As event-free survival is the primary endpoint in this study, it is vital that it be adequately and precisely documented. Due to the difficulties in objectively assessing response following radiation, response will not be a study endpoint but measurements will be recorded to assist with determination of progressive disease and local-regional failure status. Measurements will be taken from CT or MRI and the same method should be used to follow subjects. All subjects will have a clinical and radiological (CT or MRI +/- PET per institutional standards) assessment at 3 months post-completion of RT as defined in Section 5.0.

8.4.1 *Local Recurrence or Progression*

Local failure will be primarily determined by evidence of progression or recurrence clinically or radiologically. For clinical and radiographic assessments, RECIST 1.1 criteria for progressive or recurrent disease shall be used whenever applicable. In the case of nonmeasurable disease or in circumstances where laryngeal edema complicates the interpretation of radiological measurements, unequivocal clinical description of disease progression or recurrence is required. Biopsy proof (fine needle aspirate is not sufficient) of progressive/recurrent disease is desirable but is not essential if progression/recurrence is documented clinically. Any form of surgery at the primary site will be considered local progression/recurrence unless the pathology shows no evidence of disease.

8.4.2 *Regional Lymph Node Recurrence or Progression*

Neck dissection performed for clinical or radiological (RECIST 1.1) disease persistence/progression/recurrence within target volumes after 20 weeks from the end of radiation therapy with evidence of tumour present or unknown will be considered a treatment failure.

Neck dissection performed at any time after registration for clinical or radiological (RECIST 1.1) disease recurrence/progression outside the target volumes or without documentation of the site of failure with tumour present/unknown will be considered a treatment failure.

Development of any new clinically or biopsy proven malignant regional nodes not present at baseline or clinically or biopsy proven recurring or progressing nodes will be considered evidence of regional recurrence/progression.

8.4.3 *Out-of-field Regional Failure*

An out-of-field regional failure is defined as regional recurrence or progression outside the treatment field. Subjects with clinical or radiological evidence concerning for nodal failure outside the treatment field should have pathologic confirmation and restaging for local and distant disease. A positive biopsy and/or a neck dissection at any time after registration performed for suspected nodal failure outside the treatment field that is positive/unknown for tumour on pathology will be considered out-of-field regional failure. Subjects who do not have a neck dissection because their neck disease is judged to be unresectable will only be deemed to have failure in the neck after biopsy or cytological confirmation is obtained or disease progression is documented.

If failure is not confirmed, subjects may be observed with CT repeated at 3 monthly intervals or following local institutional guidelines to confirm stability or regression of the lymph nodes.

Categorizing regional failure as in-field or out-of-field will be done by the local investigator based on review of the original treatment volumes and the site of tumour recurrence in the neck. Post-hoc central review of the patterns of regional failure will also be performed on all subjects that have regional failure (either as first or subsequent recurrence).

8.4.4 *Local-regional Failure*

This is defined as local failure, regional failure or both. For the purposes of determining site of first failure the category of both will be applicable if local and regional failure occurs within one month of each other.

8.4.5 *Distant Metastasis*

This is defined as the presence of positive pathological or radiological evidence of recurrent disease at any site of the body with the exception of those defined as 'local' or 'regional'.

When distant metastases are the first indication of relapse, then the patient must be examined for local-regional disease.

8.4.6 *Event-Free Survival Endpoint*

First Event	Event-free Survival
None	Censored
Local-regional progression or recurrence	Failure
Distant metastasis	Failure
Non-protocol RT, chemotherapy, or biologic therapy (for the current OPSCC) without documentation of the site of failure	Failure
Surgery of primary site (at any time after RT) with tumour present/unknown	Failure
Neck dissection with tumour present/unknown, > 20 weeks from end of RT	Failure
Neck dissection (at any time after registration) with tumour present/unknown outside the treatment field	Failure
Death due to study cancer or from unknown causes	Failure
Death due to any other reason	Failure

Note: The following are not considered events:

- Second primary neoplasm which is defined as a primary head and neck tumour which does not fulfill the criteria for local progression/recurrence or a neoplasm arising from a non-head and neck site;
- Surgery of primary with no tumour on pathology specimen;
- Planned neck dissection for disease inside the treatment field ≤ 20 weeks from end of RT;
- Neck dissection with no tumour on pathology specimen.

9.0 SERIOUS ADVERSE EVENT REPORTING

This protocol does not contain investigational agent(s), and adverse events occurring as a result of this commercially available treatment should be reported to CCTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix IV). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the product monograph or package insert.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the HN.10 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

Within 10 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website

FAX paper SAE Report to:

HN.10 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the HN.10 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.10. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants and female partners of male participants. Pregnancies occurring up to 6 months for female participants and up to 24 months for female partners of male participants after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage, under the "Toolbox" link.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

9.3.3 *Exposure Reporting (Non-study Participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure, using the CCTG Exposure Reporting Form available from the trial webpage, under the "Toolbox" link.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual for a period of 30 days. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613 -533-2812/ safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.5 Reporting Serious Adverse Events to Investigators

CCTG will notify Investigators of all serious adverse events from this trial that are reportable to regulatory authorities in Canada as reported to CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial HN.10 web-based safety monitoring utility. Investigators must review and document in the trial files proof of review of these events as per ICH GCP.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes and any other event required by their REB. The date of REB Submission for these SAEs will need to be entered into the CCTG trial HN.10 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Disease progression, recurrence, or treatment failure as defined in Section 8.4.6.
- Request by the patient.
- Completion of therapy as outlined in Section 7.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

10.3 Follow-up Off Protocol Treatment

Please see Section 5.0.

For phase Ib and phase II studies, continued follow up after progression (on treatment or during follow up), using an abbreviated form (including subsequent therapies) every 6 months is required until CCTG advises centres that the final analysis has been performed and follow up can be discontinued. If patient is unable to return to participating centre for follow up, please contact CCTG to discuss possible options prior to considering 'withdrawal of consent' processes. Remote oversight allowing data submission may be feasible.

Final report (Form 6) will be required only on patients who die during protocol therapy, within 30 days after last dose, or within the protocol defined follow-up period for patients as above. Due within 2 weeks of knowledge of death (see Appendix III - Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

CCTG receives core support from the Canadian Cancer Society. To ensure efficient use of limited funding, the CCTG has, over the past 40 years, optimized their risk based trial oversight and monitoring program. A critical component is central data review of submitted deidentified source documents, allowing source data verification and confirmation of key aspects including eligibility, endpoints and safety outcomes. Depending on the trial's design, these source documents may include such source documents as surgical and histopathology reports to confirm disease stage and type, imaging reports to confirm extent of disease and assess efficacy, or include submission of tumour samples (to confirm diagnosis and eligibility or DICOM images (to verify response or radiation therapy planning). These source documents are reviewed by experienced data managers and physicians and are critical to ensuring the accuracy of the data and consistency of conclusions drawn.

The collection of this critical data involves uploading documents through the password protected and secure CCTG electronic Supporting Document Upload Tool (SDUT) data capture linked system. See Appendix III (Documentation for Study) for details of supporting document requirements for this trial and for requirements for the redaction of personal identifiers. Although it remains the centres responsibility to ensure adequate redaction of any information provided to CCTG, submitted source documents are reviewed prior to acceptance at CCTG; in the case of incomplete redaction, documents are removed and the site assigned a violation and required to resubmit.

All patients will provide written informed consent for submission of source documents, and the rationale and documents to be collected will be detailed in the informed consent document.

11.2 Central Radiology Review

For any patient with local-regional failure, central radiology review will be performed to confirm site of failure. Please refer to Section 7.2.18.

11.3 Central Pathology Review

There will be no central pathology review for this study.

11.4 Central Radiotherapy Review

All patients will undergo central review of radiotherapy contours and plans. Please refer to Section 7.2.17.

12.0 CORRELATIVE STUDIES

When considering the implementation of de-escalated treatment approaches such as the reduction of radiotherapy treatment volumes, it is important to be able to accurately categorize a patient's prognosis. Currently, risk stratification for HPV-related OPSCC relies primarily on clinical stage. We will evaluate 4 putative prognostic biomarkers to assess their prognostic significance in this cohort of low-risk patients receiving de-escalated treatment. These putative prognostic biomarkers are: 1) a 4-feature radiomic signature; 2) HPV genotype in tumour tissue; 3) *TP53* mutation with chromosome 3p deletion; and 4) HPV DNA levels in baseline plasma cell-free DNA. The association of each putative prognostic biomarker with EFS will be determined using the Cox proportional hazards method. Discriminative performance of the putative prognostic biomarkers will be compared with each other and with clinical features using the concordance index.

A detailed Correlative Studies Manual will be provided on the HN.10 trial specific website, which will include details regarding sample preparation, handling and shipping.

Specimens collected may be used by researchers now or in the future to better understand the nature of HPV-related OPSCC and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of registration to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out.

All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

12.1 Protocol-Mandated Correlative Studies

Radiologic Image and RT Structure Collection:
The submission of a RT planning CT scans with associated contours is mandatory for participation in this trial.

The association of a published radiomic signature with EFS will be determined in this population of HPV-related OPSCC patients treated with reduced ENI volumes. Specifically, the 4-feature radiomic signature of Aerts et al.*[Aerts 2014]* will be derived from each gross tumour volume contour using PyRadiomics or comparable software.

Tumour Tissue Collection:
The submission of a representative block of the diagnostic tumour tissue at the request of the CCTG Central Tumour Bank is mandatory for participation in this trial**.** One tumour block is requested from a biopsy of the primary oropharyngeal tumour. If no primary cancer blocks are available, one block of metastatic lymph node tissue can be sent instead. Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to registration of the first patient to allow cores (two 2 mm cores of tumour from the block) and a predetermined number of slides of representative tumour tissue to be substituted in response to the Central Tumour Bank request.

Somatic mutations and HPV genotype will be detected within tumour DNA in order to determine their prognostic significance in patients treated with reduced ENI volumes. Genomic DNA will be extracted from tumour blocks and peripheral blood leukocytes (germ line) and will be subjected to high throughput sequencing using published methods *[Newman 2014]*. Briefly, DNA libraries will be constructed from tumour genomic DNA and germline genomic DNA. Targeted sequencing will be performed in order to detect frequent OPSCC-associated HPV genotypes as well as mutations within TP53 and genetic deletions within FHIT (chromosome 3p14 marker).

Blood and Plasma Collection:
The submission of whole blood and plasma is also mandatory for participation in this trial.

Whole blood will be used as a source of germ line DNA (from peripheral blood leukocytes) for targeted sequencing of the TP53 and FHIT genes and comparison with tumour DNA as described above.

Plasma will be used for detection of circulating tumour-derived HPV DNA (ctDNA) levels in pre-treatment and post-treatment plasma. The levels of ctDNA will be measured and correlated with EFS in order to determine prognostic significance. Cell-free DNA will be extracted from plasma and subjected to droplet digital PCR or high throughput sequencing in order to detect HPV sequences. The number of HPV copies per milliliter plasma will be determined for comparison with EFS and with the other putative prognostic biomarkers.

12.2 Optional Banking of Samples

Banking of Radiologic Images and RT Structures:
Mandatory submission of RT planning CT scans with associated contours has been described above. The subsequent banking of collected data is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Data will be banked by QARC (www.qarc.org).

Proposals to use the banked data for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the data will take place and any proposals approved will have undergone ethics approval.

Banking of Tumour Tissue:
Mandatory submission of tumour tissue has been described above. The subsequent banking of collected diagnostic tissue is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Blocks and blood will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

After patient consent, collection of paraffin tumour blocks will preferred, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If tumour blocks are unavailable, then two x 2 mm cores of tumour from the block and 30 specimen slides are preferred. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval.

Banking of Blood and Plasma:
Mandatory submission of whole blood and plasma has been described above. The subsequent banking of collected samples is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Samples will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is a phase II single arm trial.

The primary objective is to evaluate the efficacy of primary definitive RT or CRT utilizing volume-reduced ENI as measured by 2-year EFS in patients with low-risk HPV-related OPSCC.

The secondary objectives are to evaluate overall survival, local control, regional control, local-regional control, out-of-field regional control, distant metastasis free survival, early and late toxicities of treatment, subjective swallowing functions, QOL, resource utilization and lost productivity, and prognostic biomarkers.

The tertiary objectives are to assemble an imaging and biospecimen bank for future research that could improve risk stratification and patient selection for volume-reduced ENI.

13.2 Primary Endpoints and Analysis

The primary endpoint is 2-year EFS.

13.3 Sample Size and Duration of Study

We estimate 2-year EFS to be 91% (Ha) for low-risk HPV-related OPSCC. Assuming that the experimental treatment will be considered as ineffective if the 2-year EFS is $\leq 85\%$ (H_0), with one-sided alpha of 0.1, a sample size of 100 patients will have 80% power to detect a 6% difference of 2-year EFS. With 3 years of accrual and 2 years of follow-up, the total duration of this study will be 5 years. A total of 304.7 person-years of follow-up is needed for the final analysis. The null hypothesis (H_0) will be rejected when the observed survival rate is 88.85% or higher (i.e. if there are 18 or fewer EFS events observed).

13.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.

13.5 Interim Analysis

A built in interim futility analysis is planned when 162.9 person-years of follow-up are observed. The alternative hypothesis (Ha) will be rejected at significant level 0.05 when 12 or more EFS events are observed. The interim analysis is expected to occur 38 months after trial activation.

13.6 Quality of Life Analysis

Descriptive summary statistics will be reported from QOL instruments.

13.7 Economic Analyses

Data regarding resource utilization data and productivity loss will be analysed using descriptive summary statistics. This data will allow us to establish direct comparison with data from other CCTG studies.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the correlative sciences (quality of life outcomes, health economics and biologics) the first author will generally be the corresponding Coordinator on the trial committee.

14.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results
CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

14.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

15.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/*exposure*. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an "Exposure Follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

15.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 Retention of Patient Records and Study Files

All essential documents must be maintained in accordance with ICH-GCP.

In accordance with GCP 4.9.5, essential documents must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In most cases, this will be for 10 years following the completion of the trial (10 years post final analysis, last data collected, or closure notification to REB, whichever is later) at the centre, or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

15.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

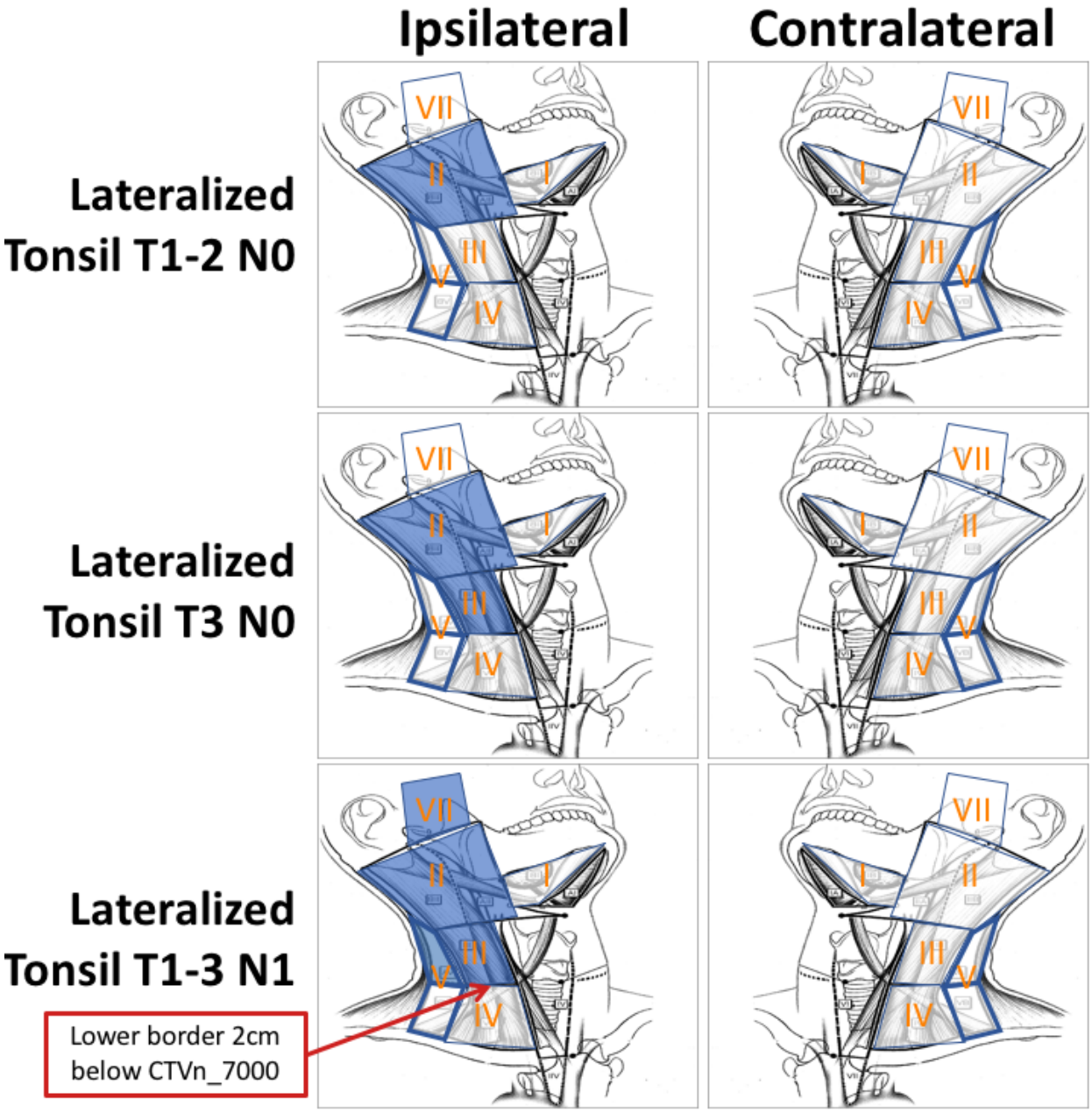
PERFORMANCE STATUS CRITERIA

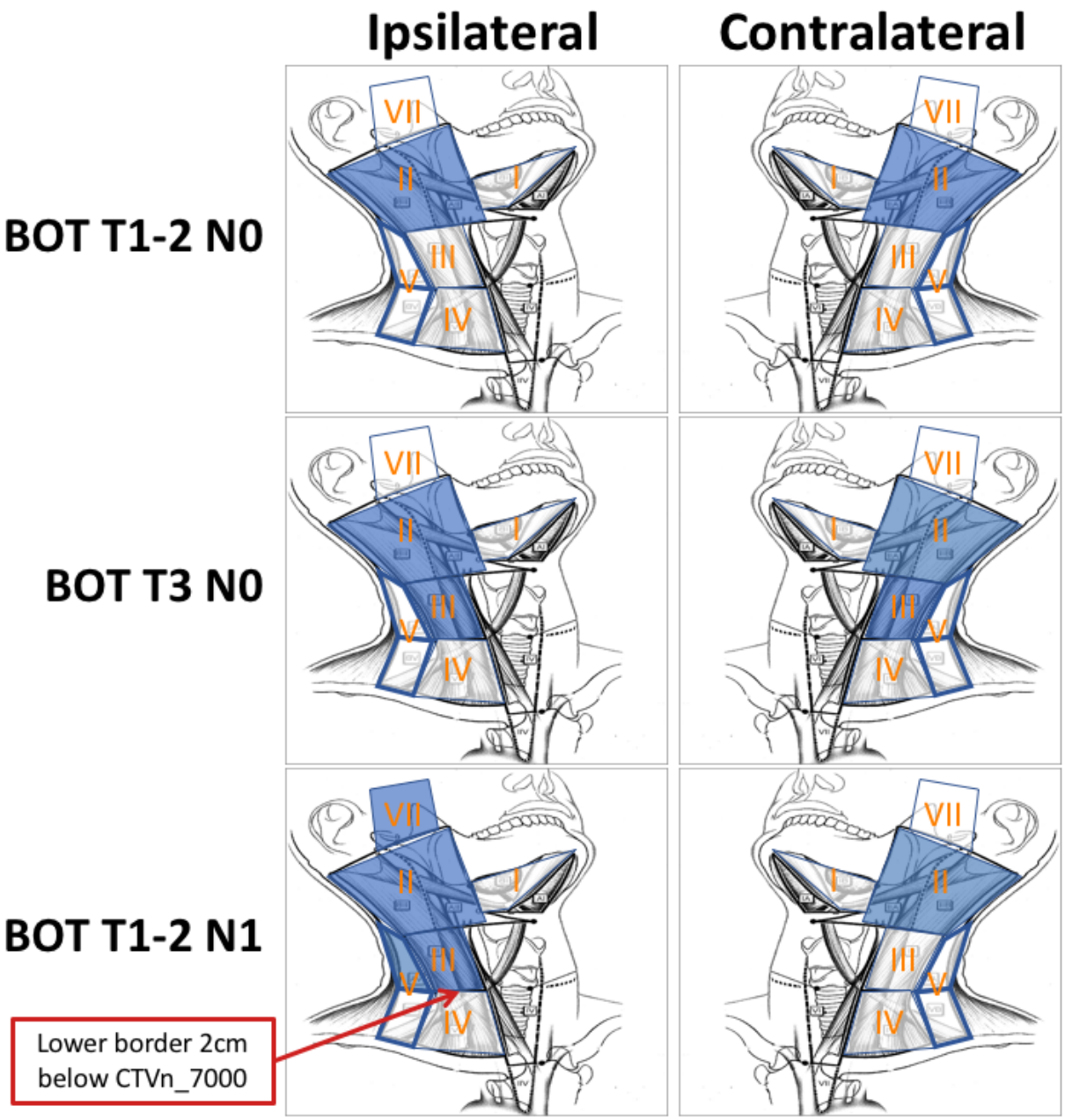
Karnofsky and Lansky performance scores are intended to be multiples of 10.

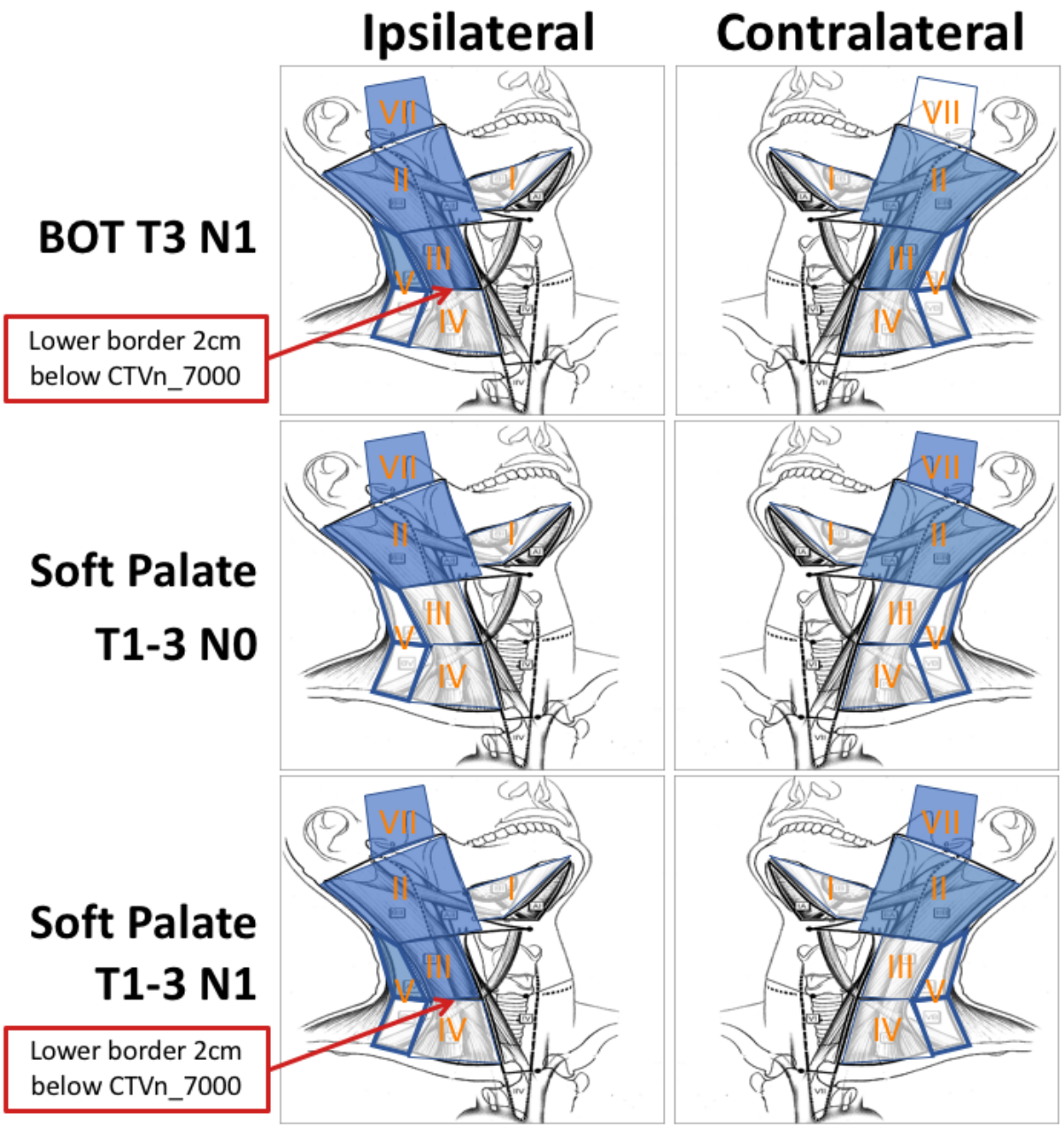
ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - EXAMPLES OF VOLUME-REDUCED ENI TREATED LEVELS ON HN.10




Ipsilateral
Contralateral
BOT T1-2 N0
BOT T3 N0
BOT T1-2 N1
Lower border 2cm below CTVn_7000
VII
II
I
III
V
IV


Ipsilateral
Contralateral
BOT T3 N1
Lower border 2cm below CTVn_7000
Soft Palate T1-3 N0
Soft Palate T1-3 N1
Lower border 2cm below CTVn_7000

APPENDIX III - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the HN.10 area of the CCTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Timing	To be completed electronically	Supporting Documentation[1]	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Eligibility Checklist		At the time of registration	Signature pages of main and optional consent forms[2] diagnostic pathology report(s) HPV (p16, PCR, or ISH) result radiology reports (including CT/MRI head and neck, CT chest x-ray relevant physical exam notes tumour measurement worksheet	ECG, LVEF, QOL additional clinical, laboratory or imaging reports that may impact on decision regarding eligibility
Baseline Report		Within 2 weeks of registration		
Correlative Studies Report (Tumour, Blood, and Imaging)	Continuous running-log folder	Information pertaining **to tumour tissue submission** must be completed as soon as possible after registration, and tissue submitted within 4 weeks of registration.		
		Information pertaining to **baseline/pretreatment blood collection for correlative studies** (i.e. whole blood and plasma) must be completed within 2 weeks of registration.		
		Information pertaining to **post registration collection samples** (i.e. whole blood and plasma) for correlative studies and banking should be completed within 2 weeks after collection of blood specimens.		
Radiotherapy Report	Required at completion of radiotherapy	Within 4 weeks of completion of treatment.	*If available/applicable:* CT/MRI head and neck, CT chest other radiology reports tumour measurement worksheet physical exam notes (as applicable)	ECG, LVEF, QOL, additional clinical, laboratory or imaging reports that may inform evaluation of safety
Systemic Treatment Report	Every 4 weeks while the patient is on treatment.	Within 2 weeks of the end of each 4 week reporting period.		

table continues on next page ...

Electronic Folder	Timing	To be completed electronically	Supporting Documentation[1]	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Follow Up Report	1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36 months post RT then q6 months until 60 months post RT.	Within 2 weeks of follow-up visit	*If available/applicable:* tumour measurement worksheet CT/MRI head and neck CT chest report other radiology reports physical exam notes (as applicable)	Additional clinical, laboratory or imaging reports that may inform evaluation of safety
Relapse/Progression Report	Upon the patient's objective disease progression / relapse	Within 4 weeks of confirmation	radiology, operative, physical exam and pathology reports	
Telephone Follow-up Report	Annually after 60 months post-RT	Within 4 weeks of the phone call	*If available/applicable:* tumour measurement worksheet CT/MRI head and neck CT chest report other radiology reports physical exam notes (as applicable)	
Short Follow-up Report	Every 6 months after objective disease progression	Within 2 weeks of follow-up visit		
Death Report	When patient dies	Within 4 weeks of patient's death	autopsy report if performed	Additional clinical, laboratory or imaging reports that may inform evaluation of cause of death
SAE Report[3]	At time of event and reported to CCTG	Within 1 working day[3]		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including, admission and discharge summaries/notes

1 Scan and upload in the EDC Supporting Document Upload Tool (SDUT) - please refer to the slide set on the HN.10 website for guidance. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All patient identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:

- **fully opaque** sticker/tab placed over the identifiers prior to scanning
- **fully opaque** black marker; prior to upload please ensure that the information is no longer visible on the scanned document
- electronic black box placed over identifiers in PDF document that is subsequently printed and then scanned. (*NOTE:* do not send the unprotected PDF file with black boxes included as those can be moved / removed easily after opening)
- electronic stripping of identifiers prior to upload (typically only possible for DICOM images)

Note that supporting documents must include the participant's trial code, CCTG patient serial number, and participant initials (or a two/three masking letter code assigned by your centre)

2 For Canadian centres: it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. Centres are expected to redact the participant's name and signature on the submitted copy, leaving only a portion visible (e.g. initials or loops) to confirm that a person has signed but that cannot identify that individual.

3 See Section 9.0 Serious Adverse Event Reporting for details.

The collection of the following information will ***NOT*** be done through the EDC system. Instead submit as follows:

Data	Timing	Collection /Submission	Comments
FACT H&N	• Prior to registration • Last week of radiotherapy • After RT (prior to PD): 3, 6, 12, 24 and 36 months	On paper; site CRA to enter relevant data (as required) in the EDC system within corresponding folders	Retain questionnaires at the site
EQ-5D-5L Questionnaire			
MDADI			
PRO-CTCAE			
Lost Productivity Questionnaire	• During the last week of RT • After RT (prior to PD): 6 and 12 months		
* See Appendices V, VI, VII and VIII. If the questionnaire is completed on paper then it should be scanned and uploaded to the EDC Supporting Document Upload Tool.			

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX V - QUALITY OF LIFE ASSESSMENT

This study will use five patient-reported questionnaires:

Quality of Life:

1. **FACT-H&N** is a quality of life questionnaire specific for head and neck cancer
2. **MDADI** assesses swallowing related quality of life and is specific for head and neck cancer

Adverse Events:

3. **PRO-CTCAE** is a relatively new instrument in the process of validation for patient self-report of toxicity.

Health Economics:

4. **EQ-5D-5L** is a health utility instrument.
5. **Lost Productivity Questionnaire** is a questionnaire for economic evaluation.

The five questionnaires are formatted as separate documents. Accordingly, if paper versions of the questionnaires are being used (see instructions for Administration of a Quality of Life Questionnaire below), the CRA will need to give attention to the order of the documents and their scheduled assessment.

The patient should first complete the FACT-H&N followed by the other questionnaires in any order.

The Lost Productivity Questionnaire should be completed after the FACT-H&N, MDADI, EQ-5D-5L and PRO-CTCAE have been completed, on the last week of radiotherapy. See Appendix VII.

Please make every effort to have the patient complete the correct questionnaires in order at the scheduled assessment.

Scheduled Assessment	Questionnaire
Within 2 weeks prior to registration	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE
Last week of radiotherapy	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE, Lost Productivity
3 months post radiotherapy	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE
6 months post radiotherapy	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE, Lost Productivity
12 months post radiotherapy	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE, Lost Productivity
24 months post radiotherapy	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE
36 months post radiotherapy	FACT-H&N, MDADI, EQ-5D-5L, PRO-CTCAE

Instructions for Administration of a Quality of Life Questionnaire

The instructions below are intended as a guide for the administration of the Quality of Life questionnaires.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient. If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, side effects, etcetera.

The CRA should collect the questionnaire as soon as it has been completed. For paper questionnaires, the CRA should check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he does not understand either English or French. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English and/or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

FACT Head & Neck

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **HN.10**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to registration ☐ Last week of radiotherapy

Post Radiotherapy Treatment, Prior to Progression

☐ month 3 ☐ month 6 ☐ month 12 ☐ month 24 ☐ month 36

The FACT-H&N questionnaire should be completed before the MDADI, EQ-5D-5L, PRO-CTCAE and Lost Productivity Questionnaire (when applicable).

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

FACT-H&N (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

FACT-H&N (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N 1	I am able to eat the foods that I like	0	1	2	3	4
H&N 2	My mouth is dry	0	1	2	3	4
H&N 3	I have trouble breathing	0	1	2	3	4
H&N 4	My voice has its usual quality and strength	0	1	2	3	4
H&N 5	I am able to eat as much food as I want	0	1	2	3	4
H&N 6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N 7	I can swallow naturally and easily	0	1	2	3	4
H&N 8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N 9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

MDADI

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **HN.10**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to registration ☐ Last week of radiotherapy

Post Radiotherapy Treatment, Prior to Progression

☐ month 3 ☐ month 6 ☐ month 12 ☐ month 24 ☐ month 36

The FACT-H&N questionnaire should be completed before the MDADI, EQ-5D-5L, PRO-CTCAE and Lost Productivity Questionnaire (when applicable).

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

The M. D. Anderson Swallowing Inventory (MDADI)

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of these statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day to day activities	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
E2. I am embarrassed by my eating habits	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
F1. People have difficulty cooking for me	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P2. Swallowing is more difficult at the end of the day	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
E7. I do not feel self-conscious when I eat.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
E4. I am upset by my swallowing problem.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P6. Swallowing takes great effort.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
E5. I do not go out because of my swallowing problem.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
F5. My swallowing difficulty has caused me to lose income.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P7. It takes me longer to eat because of my swallowing problem	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

P3.	People ask me, "Why can't you eat that?"	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
E3.	Other people are irritated by my eating problem.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P8.	I cough when I try to drink liquids.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
F3.	My swallowing problems limit my social and personal life.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
F2.	I feel free to go out to eat with my friends, neighbors, and relatives.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P5.	I limit my food intake because of my swallowing difficulty.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P1.	I cannot maintain my weight because of my swallowing problem.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
E6.	I have low self-esteem because of my swallowing problem.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P4.	I feel that I am swallowing a huge amount of food.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
F4.	I feel excluded because of my eating habits.	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

Thank you for completing this questionnaire!

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VI - PRO-CTCAE QUESTIONNAIRE

PRO-CTCAE

It is recognized that clinician-reported adverse events (AEs) may substantially under-report the incidence and severity of symptoms occurring as a consequence of treatment *[Basch 2014]*. In response to this awareness, the NCI has developed a set of patient-reported items (called PRO-CTCAE) that complement the CTCAE and capture the patient's perspective on the subjective aspects of adverse events *[Basch 2014]*. The potential for under-reporting of adverse events is particularly likely with symptoms such as fatigue, pain, and depression, which can only be gauged accurately by the person experiencing the symptom, and with long-term head and neck symptoms, such as mouth dryness, voice hoarseness, and difficulty swallowing, which are often subtle and may be difficult for clinicians to grade using standard CTCAE grading methods. Several CTCAE scales (e.g. taste changes, hair loss) only include 2-3 severity ratings, whereas the PRO-CTCAE offers a 5-point response scale.

PRO-CTCAE H&N information will complement the clinician CTCAE reporting, as well as the other PRO measures.

A collection of 18 H&N specific PRO-CTCAE H&N items is proposed for comparison with the prior CCTG HN.9 and RTOG/NRG 1016 protocols, which have overlapping inclusion criteria relative to HN.10. Inclusion of these items in HN.10 will facilitate an exploratory analysis comparing clinician-rated adverse events with patient scores on analogous issues, build experience within CCTG in the use of these instruments, and contribute to the ongoing validation of the PRO-CTCAE system.

NCI PRO-CTCAE - at Registration

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **HN.10**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to registration

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days ...

The first time you complete this questionnaire, you will also be asked a question on the highest level of school you have and how easy the questions are for you to understand. You will not have to reply about your understanding of the questions the next time you complete the questionnaire.

What is the highest level of school that you have completed? ***Mark only one.***

- ☐ Grade school or some high school
- ☐ High school graduate or equivalent
- ☐ Some college/technical school
- ☐ College graduate (4-year degree)
- ☐ Advanced degree (such as MS, JD, Ph.D.)

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

2.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

3.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

4.	In the last 7 days, what was the SEVERITY of your HOARSE VOICE at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

5.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

6.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

7.	In the last 7 days, how OFTEN did you have NAUSEA?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

8.	In the last 7 days, how OFTEN did you have VOMITING?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

9.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

10.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

11.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe	☐ Not applicable

12.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST??				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

13.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

14.	In the last 7 days, what was the SEVERITY of RINGING IN YOUR EARS at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

15.	In the last 7 days, how OFTEN did you have PAIN?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

16.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Do you have any other symptoms that you wish to report?					
☐ Yes ☐ No Please list any other symptoms:					
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

Thank you for completing this questionnaire!

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

NCI PRO-CTCAE - Post Registration

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **HN.10**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Last week of radiotherapy

Post Radiotherapy Treatment, Prior to Progression

☐ month 3 ☐ month 6 ☐ month 12 ☐ month 24 ☐ month 36

The FACT-H&N questionnaire should be completed before the MDADI, EQ-5D-5L, PRO-CTCAE and Lost Productivity Questionnaire (when applicable).

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days ...

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

2.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

3.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

4.	In the last 7 days, what was the SEVERITY of your HOARSE VOICE at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

5.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

6.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

7.	In the last 7 days, how OFTEN did you have NAUSEA?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

8.	In the last 7 days, how OFTEN did you have VOMITING?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

9.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

10.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

11.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe	☐ Not applicable

12.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

13.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

14.	In the last 7 days, what was the SEVERITY of RINGING IN YOUR EARS at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

15.	In the last 7 days, how OFTEN did you have PAIN?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

16.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Do you have any other symptoms that you wish to report?					
☐ Yes ☐ No Please list any other symptoms:					
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

Thank you for completing this questionnaire!

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VII - LOST PRODUCTIVITY QUESTIONNAIRE

Introduction

Economic evaluations assess the benefits and costs of an intervention for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about costs is becoming common in clinical trial protocols. Direct costs include the costs of treatment, such as drug therapy and hospital admission. However, there are also indirect costs, such as costs to the patient and society, for example through lost productivity or loss of work. The collection of information about indirect costs is also becoming common in clinical protocols. In clinical trials, lost productivity and patient costs are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Data on costs, both direct and indirect, can be used in various ways, including (a) to support approval of new drug applications or patient management strategies, (b) to provide the best value for health care dollars within and across diseases and health, and (c) to compare costs and benefits of various financial and organizational aspects of health care services.

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using economic analysis techniques.

Instructions for Administration of the Lost Productivity Questionnaire

Please see the instructions for Administration of a Quality of Life Questionnaire in Appendix V.

The instructions below are intended as a guide for the administration of the Lost Productivity Questionnaire

1. Preamble

   Lost productivity data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self-reported questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The scheduled time to obtain the questionnaires is at the:

   - last week of radiotherapy and at 6 and 12 months post radiotherapy

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-Treatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, for example productivity, change in work status, caregiver assistance, and so on.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed. For paper questionnaires, the CRA should check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The Lost Productivity Questionnaire should be given to the patient on the final day of treatment, as required by the schedule in the protocol.

4. Assessments During Follow-up

The questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because he/she may feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

However, there may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if productivity data can still be collected.

5. What If…

5A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one.

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form

5B. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

5C. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after registration all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

6. Waiving the Lost Productivity Component

The only time that we will not require a patient to complete the Lost Productivity questionnaires is if s/he is not literate in either English or French. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Lost Productivity Questionnaire

If a patient speaks and reads English or French, but does not wish to complete this questionnaire then s/he is still eligible and could be put on study.

8. Inability to Complete Lost Productivity Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the Lost Productivity Questionnaire in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Lost Productivity Questionnaire – ENGLISH

CCTG Trial: HN.10

This page only to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain this Lost Productivity Questionnaire: please check (✓)

☐ Last week of radiotherapy (RT)

☐ 6 months post RT

☐ 12 months post RT

The Lost Productivity Questionnaire should be completed after the FACT-H&N, MDADI, EQ-5D-5L and PRO-CTCAE have been completed.

Date Questionnaire Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

HN.10 - Lost Productivity Questionnaire

To the patient:

We would like to ask you several questions about the work that you do for pay. The answers to these questions will allow us to study the financial impact of head and neck cancer and its treatment. The information collected will be used for research purposes only.

We would appreciate it if you answered all of the questions; however, you do not need to answer any question you do not wish to answer. The answers provided will not affect your medical care.

Section A: General Questions

1) What type of medical insurance do you currently have?

(Check ✓all that apply.)

☐ Provincial health insurance

☐ Individual / group health

☐ Other (specify): _____

2) If you are working for pay or have done paid work in the past, what would best describe your field of employment? *(Check ✓one only. Choose your most recent employment; if more than one paid job at once, choose the employment involving the most time commitment.)*

☐ Management

☐ Business/ finance/ administrative

☐ Natural and applied sciences

☐ Health services

☐ Education

☐ Government services

☐ Social science

☐ Religion

☐ Art/culture

☐ Recreation and/or sport

☐ Sales and/or service

☐ Trades/ transport/ construction

☐ Primary industry

☐ Processing/manufacturing/utilities

☐ Other (specify): _____

☐ Not applicable; no paid work

COMMENTS: _____

_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

3) Which of the following best describes your work status at this time?

(Check ✓ one only.)

☐ Working full-time for pay (> 30 hours per week) -- (includes self-employed)

☐ Working part-time for pay (< 30 hours per week) -- (includes self-employed)

☐ On sick leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)

☐ On disability leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)

☐ Unemployed

☐ Retired

☐ Homemaker/ Stay at home parent or caregiver

☐ Other, specify _____

4) *Since the start of treatment*, has there been any change in your work status compared to before that?

(Check ✓ one only.)

☐ No, no change

☐ Yes, started working full time hours (> 30 hours per week)

☐ Yes, started working part time hours (≤ 30 hours per week)

☐ Yes, started sick or disability leave: (Date leave started: _____)
(Year – Month – Day)

☐ Yes, quit work/ became unemployed or retired: (Date leave started: _____)
(Year – Month – Day)

☐ Yes, other: specify _____

5) *Since the start of treatment*, how much time have you been unproductive (unable to work or do usual household activities) due to not feeling well, receiving treatment and / or being in hospital for your head and neck cancer?

(Check ✓ one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)

☐ < 1 day (specify # of hours: _____)

☐ 1 to 3 days (specify # of days: _____)

☐ More than 3 days (specify # of days _____)

☐ Don't know – can't remember

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

6a) *Since the start of treatment*, how much **paid** work time have you missed due to illness, treatment and/ or being in hospital for your head and neck cancer?

(Check ✓one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)
☐ < 1 day (specify # of hours: _____)
☐ 1 to 3 days (specify # of days: _____)
☐ More than 3 days (specify # of days _____)
☐ Not applicable – not currently working
☐ Don't know – can't remember

6b) *Since the start of treatment*, how much **unpaid** work time have you missed due to illness, treatment and/ or being in hospital for your head and neck cancer?

(Check ✓one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)
☐ < 1 day (specify # of hours: _____)
☐ 1 to 3 days (specify # of days: _____)
☐ More than 3 days (specify # of days _____)
☐ Not applicable – not currently working
☐ Don't know – can't remember

7) Please rate your activity level on average *since the start of treatment* (circle applicable number):

0	1	2	3	4	5	6	7	8	9	10
Exhausted in bed all day										Normal activity level

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Paid Assistance and Professional Care for Your Head and Neck Cancer

8) *Since the start of treatment*, how much paid health and / or home worker time have you needed?
(Examples include a home visiting nurse or someone to do blood work, VON, home care worker.)

(Check ✓one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)

☐ < 1 day (specify # of hours: _____ and also the # of visits involved: _____)

☐ 1 to 3 days (specify # of days: _____ and also the # of visits involved: _____)

☐ More than 3 days (specify # of days: _____ and also the # of visits involved: _____)

☐ Don't know – can't remember

9) *Since the start of treatment*, how much other paid assistance have you needed?
(Examples include a translator to attend doctor visits, a driver to take you to appointments).

(Check ✓one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)

☐ < 1 day (specify # of hours: _____) Specify type of assistance: _____

☐ 1 to 3 days (specify # of days: _____) Specify type of assistance: _____

☐ More than 3 days (specify # of days: _____) Specify type of assistance: _____

☐ Don't know – can't remember

Unpaid Caregiver(s)

10) *Since the start of treatment*, who has primarily helped to look after your needs without formal pay?

(Check ✓all that apply.)

☐ No one (no unpaid caregiver)

☐ Spouse

☐ Child/Parent

☐ Other relative

☐ Friend

☐ Neighbor

☐ Other (specify) _____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

11) *Since the start of treatment*, how much time has your unpaid caregiver(s) helped you?

(Check ✓one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)

☐ < 1 day (specify # of hours: _____)

☐ 1 to 3 days (specify # of days: _____)

☐ More than 3 days (specify # of days: _____)

☐ Don't know – can't remember

☐ Not applicable – I have no unpaid caregiver(s)

12) *Since the start of treatment*, how many paid work days at his or her paying job(s) has your unpaid caregiver(s) missed in order to help you?

(Check ✓one only.) Estimate to the nearest ½ day; assume 1 day is 8 hours.

☐ none (0 days)

☐ < 1 day (specify # of hours: _____)

☐ 1 to 3 days (specify # of days: _____)

☐ More than 3 days (specify # of day: _____)

☐ Don't know

☐ Not applicable – no unpaid caregiver(s) or unpaid caregiver(s) not currently working for pay

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Section B. Financial Implications

Your Personal Financial Implications Concerning This Medical Visit

1. Did you miss work to attend this medical appointment?

   ☐ Yes ☐ No If No, go to question 4

2. How many hours of work did you miss today to attend your appointment? _____ hours

3. Did the number work hours you missed affect your pay or was the time granted by your employer?

   ☐ It affected my pay ☐ It was time granted by my employer

4. Estimate the total time you had to devote to this appointment, including transportation, waiting time, meeting with the doctor.

   _____ hours and _____ minutes

5. What means of transportation did you use to come to this appointment?

   ☐ Private: (car) Estimate the round trip distance in kilometers: _____km

   ☐ Public transportation (bus, metro, train, taxi)

6. Quantify your expenses from this appointment.
   (Please, enter "0" if you had no expenses):

☐ Parking:		$ _____
☐ Public transportation:	Taxi:	$ _____
	Bus/Metro/Train:	$ _____
☐ Babysitter:		$ _____
☐ Other: (e.g. meals) _____		$ _____

7. What is your usual yearly gross (before taxes) household income? (all income data will be anonymized and kept entirely confidential. It will be used only by the research team)

   ☐ < $10,000
   ☐ $10,000 to $19,999
   ☐ $20,000 to $29,999
   ☐ $30,000 to $39,999
   ☐ $40,000 to $49,999
   ☐ $50,000 to $59,999
   ☐ $60,000 to $69,999
   ☐ $70,000 to $79,999
   ☐ $80,000 to $89,999
   ☐ $90,000 to $99,999
   ☐ $100,000 to $124,999
   ☐ $125,000 to $149,999
   ☐ ≥ $150,000

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Thank you

APPENDIX VIII - HEALTH UTILITIES ASSESSMENT

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, disease free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations;
- to evaluate the extent of change in health benefits of an individual, group, or population across time;
- to evaluate new treatments, technologies, and patient management strategies;
- to support approval of new drug applications or patient management strategies;
- to try to provide the best value for health care dollars within and across diseases and health;
- to compare costs and benefits of various financial and organizational aspects of health care services.

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

Please see the instructions for Administration of a Quality of Life Questionnaire in Appendix V.

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

   Health utilities data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, symptoms, side-effects, *et cetera*.

   The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

However, there may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if health utilities data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

D. The patient is no longer attending clinic during the scheduled follow-up period. Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after registration all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic.

6. Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D-5L assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

EQ-5D-5L

Health Utilities Questionnaire – ENGLISH

CCTG Trial: **HN.10**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to health utilities assessment: please check (✓)

☐ Prior to registration ☐ Last week of radiotherapy

Post Radiotherapy Treatment, Prior to Progression

☐ month 3 ☐ month 6 ☐ month 12 ☐ month 24 ☐ month 36

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __ (yyyy mmm dd)

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

EQ-5D-5L Questionnaire

CCTG : HN10

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

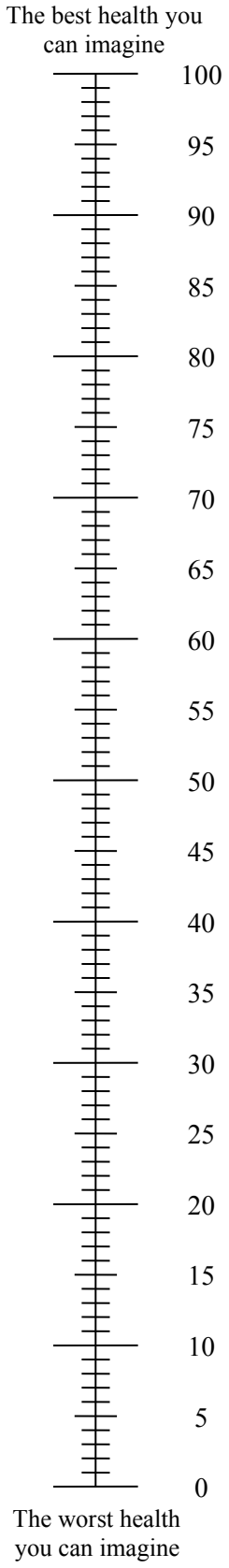
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____
Today's date (Year, Month, Day): _____

Thank you.

APPENDIX IX - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

APPENDIX X - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB, and review the trial website for additional guidance specific to the trial.

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. *Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.*
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.

  **Must be approved by CCTG or acceptable per further instruction from CCTG.*
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to allocation.	Susan Casey Clinical Trials Assistant, CCTG Email: scasey@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Sarah Hunter Study Coordinator, CCTG Email: shunter@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator, CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Scott Bratman Study Chair Email: Scott.Bratman@rmp.uhn.ca	416-946-2132	416-946-6561
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Wendy Parulekar Senior Investigator, CCTG Email: wparulekar@ctg.queensu.ca or: Sarah Hunter Study Coordinator, CCTG Email: shunter@ctg.queensu.ca	613-533-6430	613-533-2941