NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A PHASE III STUDY OF STANDARD FRACTIONATION RADIOTHERAPY WITH CONCURRENT HIGH-DOSE CISPLATIN VERSUS ACCELERATED FRACTIONATION RADIOTHERAPY WITH PANITUMUMAB IN PATIENTS WITH LOCALLY ADVANCED STAGE III AND IV SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

NCIC CTG Protocol Number: **HN.6**

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TABLE OF CONTENTS

STUDY ACKNOWLEDGMENT/DISCLOSURE ........................................................................................................... 1

TREATMENT SCHEMA........................................................................................................................................... 2

1.0 OBJECTIVES .................................................................................................................................................. 3
  1.1 Primary Objective ......................................................................................................................................... 3
  1.2 Secondary Objectives ................................................................................................................................. 3

2.0 BACKGROUND INFORMATION AND RATIONALE ..................................................................................... 4
  2.1 Background .................................................................................................................................................. 4
  2.2 Quality of Life .............................................................................................................................................. 6
  2.3 Functional Swallowing Outcome ................................................................................................................ 7
  2.4 Correlative Studies ....................................................................................................................................... 9
  2.5 Health Economics ..................................................................................................................................... 12

3.0 BACKGROUND THERAPEUTIC INFORMATION ...................................................................................... 13
  3.1 Cisplatin ..................................................................................................................................................... 13
  3.2 Panitumumab ............................................................................................................................................. 13
  3.3 Chemical Structure .................................................................................................................................... 13
  3.4 Mechanism of Action ............................................................................................................................... 13
  3.5 Experimental Antitumour Activity ............................................................................................................ 14
  3.6 Animal Toxicology ................................................................................................................................... 14
  3.7 Phase I Trials ............................................................................................................................................. 14
  3.8 Phase II and III Trials ............................................................................................................................. 17
  3.9 Pharmacokinetic Studies .......................................................................................................................... 18
  3.10 Pharmaceutical Data .............................................................................................................................. 19

4.0 TRIAL DESIGN............................................................................................................................................. 21
  4.1 Stratification ............................................................................................................................................... 21
  4.2 Randomization ........................................................................................................................................... 21

5.0 STUDY POPULATION ............................................................................................................................... 22
  5.1 Eligibility Criteria ..................................................................................................................................... 22
  5.2 Ineligibility Criteria ................................................................................................................................. 23

6.0 PRE-TREATMENT EVALUATION ................................................................................................................ 25

7.0 ENTRY/RANDOMIZATION PROCEDURES ................................................................................................. 26
  7.1 Entry Procedures ....................................................................................................................................... 26
  7.2 BSA Calculation ...................................................................................................................................... 26
  7.3 Stratification ............................................................................................................................................... 26
  7.4 Randomization ......................................................................................................................................... 27

8.0 TREATMENT PLAN ................................................................................................................................... 28
  8.1 Chemotherapy Treatment Plan ................................................................................................................ 28
  8.2 Radiation Therapy .................................................................................................................................... 34
  8.3 Surgical Treatment Plan Of The Neck For Patients With Nodal Positive Disease At Baseline .............. 46
  8.4 Concomitant Therapy ............................................................................................................................ 47
16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES .......................................................... 64
16.1 Institution Eligibility for Participation ................................................................................... 64
16.2 Investigator Qualifications ..................................................................................................... 64
16.3 REB (Research Ethics Board) Approval for Protocols .......................................................... 64
16.4 Informed Consent ................................................................................................................... 66
16.5 Retention of Patient Records and Study Files ................................................................. 66
16.6 Centre Performance Monitoring ......................................................................................... 66
16.7 On-Site Monitoring/Auditing ............................................................................................... 67
16.8 Case Report Forms (CRFs) .................................................................................................. 67

17.0 REFERENCES ....................................................................................................................... 68

APPENDIX I - PATIENT EVALUATION FLOW SHEET ................................................................. 73
APPENDIX II - PERFORMANCE STATUS SCALES/SCORES ....................................................... 76
APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL ............................................. 77
APPENDIX IV - DOCUMENTATION FOR STUDY ....................................................................... 78
APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
 VERSION 3.0 (CTCAE) ............................................................................................................... 80
APPENDIX VI - QUALITY OF LIFE ASSESSMENT ...................................................................... 81
APPENDIX VII - LOST PRODUCTIVITY QUESTIONNAIRE .......................................................... 98
APPENDIX VIII - 6TH EDITION OF THE TNM CLASSIFICATION OF MALIGNANT TUMOURS ... 108
APPENDIX IX - NOMENCLATURE ............................................................................................... 109
APPENDIX X - STEPS IN THE CENTRAL RADIOTHERAPY QUALITY ASSURANCE PROGRAM ................................................................. 111
APPENDIX XI - RADIOTHERAPY QUALITY ASSURANCE DOCUMENTATION .............................. 112
APPENDIX XII - DIGITAL DATA SUBMISSION PROCEDURES TO QARC ................................. 115
APPENDIX XIII - SWALLOWING IMPAIRMENT SUB-STUDY PROCEDURES .............................. 118
APPENDIX XIV - CENTRAL RADILOGY ARCHIVING ................................................................. 119
APPENDIX XV - CORRELATIVE SCIENCES QUESTIONNAIRE .................................................. 119

LIST OF CONTACTS .................................................................................................................... Final Page
STUDY ACKNOWLEDGMENT/DISCLOSURE

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

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, 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 will provide copies of the protocol and access to all information furnished by NCIC CTG and Amgen 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 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 Amgen and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Amgen and NCIC CTG of any such disclosure.

I understand that I may terminate or suspend enrolment 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 NCIC CTG. The study may be terminated at any time by NCIC CTG with or without cause. Amgen has the right to withdraw their support for this study at any time, with or without cause.

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

We will only use the Study Drug for the purposes of carrying out the Study and shall not permit any third party to use the Study Drug except as set out in the Protocol.

We agree that any inventions or discoveries made during the course of this Study that relate to the Study Drug shall be disclosed to Company and shall be the property of Company and/or its affiliates.

We agree that use of the Study Drug provided by Company to conduct the Study for any purpose outside of the Study is prohibited. If we use the Study Drug provided by Company for any purpose outside of the Study, all data, results, conclusions, observations, discoveries, inventions, ideas, know-how, procedures, advancements and the like, whether patentable or not, shall be disclosed to Company and shall be the sole property of Company.

______________________________________________ _________________ ________
Investigator Date
(printed name and signature)

______________________________________________ _________________ ________
Institutional Authority and Signatory Date
(please print name)

Protocol Number: NCIC CTG HN.6

Centre: _____________________________

CONFIDENTIAL
TREATMENT SCHEMA

Patients with histologically confirmed squamous cell carcinoma of the head and neck of the oral cavity, oropharynx, larynx or hypopharynx which is locally advanced as defined by $T_{\text{any}}N^+M0$ or $T3-4 N0M0$.

**Stratification:**

1. $T$ category: $T1-3$ versus $T4$
2. Nodal status: $N0$, $N1$ versus $N2$, versus $N3$
3. Radiotherapy delivery modality: Intensity modulated radiotherapy (IMRT) versus 3D conformal radiotherapy (3D CRT)
4. Anatomic location: hypopharynx versus oral cavity versus oropharynx versus larynx
5. Participation in Swallowing Impairment Sub-study

| RANDOMIZE | ARM 1 | Standard radiation: 70 Gy in 35 fractions over 7 weeks  
|          |      | Cisplatin 100 mg/m² IV days 1, 22, 43 of radiotherapy  |
|          | ARM 2 | Accelerated radiation: 70 Gy in 35 fractions over 6 weeks  
|          |      | Panitumumab 9 mg/kg IV every 3 weeks starting 1 week prior to and days 15 and 36 of radiotherapy |

Planned sample size = 320

**Primary Endpoint:**
- Progression Free Survival

**Secondary Endpoints:**
- Overall survival
- Local progression free survival
- Regional progression free survival
- Distant metastasis
- Adverse events, including late radiotherapy related adverse events
- Quality of life
- Swallowing related quality of life
- Functional swallowing outcome (selected centres)
- Significance of tissue and blood biomarkers
- Economic evaluation, including healthcare utilization, health utilities and indirect costs.
1.0 OBJECTIVES

1.1 Primary Objective

The primary objective is to compare the progression free survival of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) treated with standard fractionation radiotherapy and high dose cisplatin or accelerated fractionation radiotherapy and panitumumab.

1.2 Secondary Objectives

The secondary objectives are to compare the two arms with respect to:
- Overall survival
- Local progression free survival
- Regional progression free survival
- Distant metastasis
- Adverse events, including late radiotherapy related adverse events
- Quality of life
- Swallowing related quality of life
- Functional swallowing outcome (selected centres)
- Significance of tissue and blood biomarkers
- Economic evaluation: cost effectiveness analysis and cost utility, including both healthcare utilization and indirect costs
2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Background

There are approximately 48,000 [American Cancer Society 2008] and 5,000 cases [Canadian Cancer Society/National Cancer Institute of Canada 2008] of SCCHN diagnosed annually in the US and Canada respectively. Approximately two-thirds of these patients present with advanced stage III or IV disease. At present, the standard of care for patients with stage III or IV, non-metastatic SCCHN is concurrent chemoradiotherapy except for cases where surgical resection is the preferred primary therapeutic modality. The 5-year survival for patients with stage III disease varies from about 30-55%, and stage IV disease from about 20-40% based on the site of the primary in head and neck.

The Bonner study [Bonner 2006] is a landmark study which compared radiotherapy (once daily 70 Gy/35; twice daily 72-76.8 Gy/60-64; concomitant boost 72 Gy/42) alone with radiotherapy and the anti-EGFR monoclonal antibody cetuximab. The primary endpoint of the study was the duration of locoregional control, defined as the absence of progression of locoregional disease at the scheduled follow-up visits. The median duration of locoregional control was 24.4 months in the combined therapy arm, and 14.9 months in the radiotherapy alone arm (hazard ratio for locoregional progression or death = 0.68, 95% C.I. 0.52-0.89, p=0.005). The 2-year PFS rates were 46% versus 37%, and 3-year OS rates were 55% versus 45%, favoring the combined therapy arm. The median PFS were 17.1 months versus 12.4 months (p=0.006), and median OS were 49 months versus 29.3 months (p=0.03), favoring the combined therapy arm. With the exception of acneiform rash and infusion reactions, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups. Grade 3 or 4 late toxicities were similar between the two groups.

In subgroup analyses, it would appear that patients who received radiotherapy with the concomitant boost regimen derived the most benefit in combination with cetuximab. The hazard ratios were as follows: for the 26% of patients who received once-daily fractionation HR = 1.01; for the 18% of patients who received twice-daily fractionation HR = 0.74; for the 56% of patients who received concomitant boost radiotherapy HR = 0.64. Furthermore, when analyzed by disease site, patients with primary tumours in the oropharynx derived the most benefit from the combination of radiotherapy and cetuximab (HR = 0.62), compared to those with primary tumours in the larynx (HR = 0.87) and in the hypopharynx (HR = 0.94). There are several possible explanations for the results of this latter subgroup analysis. First, it is possible that the addition of an anti-EGFR antibody preferentially benefits locally advanced SCCHN based on its primary anatomical location, favoring oropharyngeal tumours. Second, and perhaps a more plausible explanation, is that this finding is related to the fact that the human papillomavirus (HPV) is associated primarily with oropharyngeal SCCHN [Gillison 2000]. As such, it is possible that HPV-related SCCHN derives a greater benefit from the addition of an anti-EGFR antibody compared to non HPV-related SCCHN. Alternatively, if there was an imbalance of HPV-related oropharyngeal cancers between the study arms in the Bonner study, the better outcome may be due to a better prognosis seen with HPV-related tumours [Fakhry 2008], regardless of the addition of cetuximab. This subgroup analysis finding underscores the importance of stratifying patients based on the anatomical sites of their primary tumours in HN.6.

There are concerns in applying the results of this important study to current practice. First, the current treatment standard for patients with locally advanced head and neck cancer is concurrent chemoradiotherapy, and not radiotherapy alone. Second, the efficacy outcome of the control arm with radiotherapy alone in the Bonner trial compares poorly with other published series, or with the experiences of large institutional series. Hence, the underperformance of the control arm has raised concerns about the generalizability of the results of this trial.
While many groups have decided to build upon the results of this trial and devise further trials using the triple combination of anti-EGFR antibody, chemotherapy and radiotherapy (e.g. RTOG 0522), there are realistic concerns as to whether this type of regimen can result in profound toxicity [Pfister 2006] thus reversing the therapeutic index. The comparison of standard fractionation radiotherapy with concurrent high-dose cisplatin versus accelerated fractionation radiotherapy with an anti-EGFR antibody (such as panitumumab) would be extremely appealing as a chemotherapy-sparing strategy in the management of locally advanced SCCHN.

Chemotherapy-sparing using targeted agents in the therapy of locally advanced SCCHN is an unanswered but important question. Most ongoing large, intergroup trials are comparing strategies of increasing aggressiveness (e.g. sequential therapy with triplet cytotoxic agents, concurrent chemotherapy plus targeted agents etc.) against standard chemoradiotherapy alone. The question of whether radiotherapy plus an anti-EGFR antibody can produce – similar or superior results than standard chemoradiotherapy is not answered by the Bonner trial.

Accelerated fractionation radiotherapy was shown to be more efficacious than standard fractionation radiotherapy in RTOG 9003 [Fu 2000], with improved loco-regional control at 2-years (54.5% vs 46%, p=0.05) and a trend towards improved 2-year disease-free survival (39.3% vs 31.7%, p=0.054). There was no difference in overall survival. Accelerated fractionation radiotherapy has never been directly compared against standard fractionation radiotherapy plus concurrent chemotherapy, but most head and neck oncologists feel that their incremental benefits over standard fractionation radiotherapy alone are similar. In a meta-analysis of hyperfractionated or accelerated radiotherapy in SCCHN, which included 15 trials with 6515 patients, reported a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years (HR = 0.92, 95% CI 0.86-0.97; p=0.003). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1.7% with total dose reduction at 5 years, p=0.02) [Bourhis 2006].

Accelerated fractionation radiotherapy plus concurrent chemotherapy has been compared against standard fractionation radiotherapy plus concurrent chemotherapy, in RTOG 0129, but results are not yet mature. While RTOG 0522 selected accelerated fractionation radiotherapy plus concurrent chemotherapy as its control arm, to compare against accelerated fractionation radiotherapy plus concurrent chemotherapy plus cetuximab, this decision was not based on published data. In addition, the acute and long term toxicities of such a regimen are unknown and will impact the uptake of the results of the trial into clinical practice.

Our group feels that the question being addressed in our proposal: standard fractionation radiotherapy with concurrent high-dose cisplatin versus accelerated fractionation radiotherapy with panitumumab in patients with locally advanced stage III and IV SCCHN is highly relevant and needs to be answered with a well designed and conducted randomized phase III clinical trial.

Data from the Bonner study [Bonner 2006] indicates that combination treatment with the EGRF antibody cetuximab and radical radiotherapy is feasible and does not exacerbate acute and long term in field radiation toxicities such as mucositis, pharyngitis, radiation dermatitis, xerostomia and dysphagia. In addition, radiotherapy compliance does not appear to be compromised with combination therapy.
To ensure the tolerability and feasibility of administration of panitumumab and accelerated radiotherapy as proposed in this study, a comprehensive review of the adverse event experience and compliance with radiotherapy will be performed using data from the first 30 randomized patients who receive at least one dose of protocol therapy (Section 14, Safety Review). In addition, relevant recommendations arising from the safety analyses of ongoing Amgen sponsored studies 20062079 and 20062080 (Section 3.8 Phase II and III Trials) will be taken into consideration.

2014 Update

Subsequent to the activation of HN.6, results have become available that inform the continued conduct of this study. RTOG 0129 compared accelerated versus standard fractionation radiotherapy in combination with concurrent cisplatin chemotherapy. No difference in efficacy between the treatment arms was seen, indicating the continued relevance of the control arm of HN.6 [Nguyen-Tan 2014]. The results of more recently conducted study RTOG 0522 were reported [Ang 2014]. This phase III clinical trial involved randomization of nine hundred and forty patients between 2005 - 2009 and compared concurrent accelerated radiotherapy plus cisplatin with or without the anti EGFR antibody, cetuximab. No statistically significant difference in PFS was seen between the arms. A high proportion of tumours were located in the oropharynx (approximately 70% compared to 81% in HN.6). The PFS and OS and cumulative incidence curves for all patients and those with oropharyngeal tumours showed a relative plateau in events by the 3 year post randomization time point. Furthermore, the PFS extrapolated from the K-M curves for all patients at the 2 year post randomization time point is approximately 65% which differs from our original assumption of 2 year PFS of 45% for the control arm in our study. For those patients with oropharyngeal tumours and sufficient tissue for analysis, 73% were positive for HPV by p16 testing indicating a contemporaneous population to HN.6.

The median follow-up on HN.6 is 38 months as of October 31, 2014 and 100 events have been observed on study. A minimum of 123 events are required to trigger the protocol specified interim analysis. We estimate an additional minimum of 48 months will be required before the interim analysis is performed. This is likely an underestimate based on the trend in event rate seen to date on study; 2011 annual 41 events, 2012 annual 20 events, 2013 annual 9 events, 2014 to date 3 events. There is a real possibility that this number of events may never be reached if these patients are cured of their cancers due to the favorable prognosis of HPV positive SCCHN which is estimated to be a significant proportion of the HN.6 population.

Based on these considerations, a request was made to Data Safety Monitoring Committee (DSMC) of NCIC CTG to perform a time based, primary efficacy analysis using a clinical cutoff date of October 31, 2014 with retention of the same primary and secondary endpoints. The request was approved by the Data Safety Monitoring Committee after its closed meeting on November 19, 2014.

2.2 Quality of Life

Improvements in survival rate for locally advanced head and neck cancer by the addition of chemotherapy or accelerated fractionation are at the expense of increased acute and late toxicity, impacting on long-term well being and quality of life (QOL) [Dische 1997]. Although studied with increasing frequency [Rogers 2007], QOL outcomes have been reported in few prospective head and neck cancer randomized trials. The QOL effect of combining panitumumab with accelerated fractionation radiotherapy is unknown, and may be highly relevant to treatment decision-making if the progression free survival benefit is small, or if opposing results are found for survival and toxicity/QOL.
QOL will be measured using the Functional Assessment of Cancer Therapy Head and Neck (FACT-H&N) questionnaire version 4. The 39-item FACT-H&N consists of a 12-item head and neck cancer specific subscale (HN) appended to the oncology-specific QOL instrument, FACT-G. FACT-G includes 27 questions in four domains - Physical (7), Social (7), Emotional (6), and Functional (7). Each response is rated by the patient from 0-4 on a Likert scale, with 0 described as “not at all” and 4 as “very much”. Scores are calculated separately for each domain, and an unweighted summary score is calculated for the FACT-G and the total FACT-H&N. The maximum score of 144 reflects the best possible quality of life. FACT-H&N has demonstrated reliability and validity, and was chosen because it is commonly used in studies of head and neck cancer, short, and provides a summary score for ease of analysis. A clinically significant change in score on this instrument is represented by an increase of about 6 units or a decrease of about 12 units [Ringash 2004].

In this study, we hypothesize a statistically and clinically significant QOL benefit in the experimental (chemosparing) arm of the study. Specifically, we anticipate that the median change in overall QOL score on the FACT-H&N from baseline to 1 year will be 6 units higher in the experimental arm as compared with the control arm. A previous study of accelerated fractionation showed a median improvement of 8 units over 1 year, however due to the additional toxicity of systemic treatment, it is anticipated that overall QOL may decrease in one or both arms as compared to baseline [Ringash 2008]. As a secondary analysis, we will also determine the proportion of patients in each arm who achieved a clinically significant (6 unit) increase in FACT-H&N score at 1 year.

2.3 Functional Swallowing Outcome

Swallowing problems (dysphagia) are common following treatment for head and neck cancer. Normal swallowing physiology is often disrupted by structural changes that result from the cancer as well as its treatment. In addition, the presence of dysphagia itself may have adverse implications for pulmonary health, nutrition and quality of life. Two recently published systematic reviews have looked at swallowing function after radiotherapy and/or chemotherapy [Frowen 2006, Reiger 2006]. These organ preserving treatments often resulted in impaired movements of the oropharyngeal and laryngeal structures. Of the published articles, no level I and one level II evidence was identified. Most available articles were descriptive or level IV. The most common swallowing outcomes related to impairment. A select few articles reported swallowing-related function, but even fewer reported swallowing related QOL. Albeit sparse, the available evidence is further weakened by poor methodological rigor (no reliability check and missing data); small sample size (over 50% of the studies had less than 20 patients and no study had more than 255 patients); heterogeneity with respect to staging and primary tumour site; and, absence of baseline or longitudinal data. Therefore to date, the evidence about swallowing and its consequences related to treatment for head and neck cancer, and in particular combination therapy with chemotherapy or a targeted therapy plus radical radiotherapy, is limited. Considering the high prevalence of dysphagia among patients with head and neck cancer, knowledge about swallowing and swallowing related QOL is critical. Clinicians need this knowledge to anticipate swallowing complications and required interventions and to better inform patients of the expected effects from their treatments.

Given the current state of the literature, a descriptive study of swallowing impairments related to combined modality therapy in an adequate sample of patients with locally advanced disease is a necessary first step. HN6 will assess the feasibility of swallowing outcome assessment in a large randomized trial, document physical evidence of swallowing impairment and swallowing related QOL, assess some promising instruments for measuring swallowing outcome, and explore the relationship between disease-specific QOL, swallowing outcomes, and survival. This study will be the first to compare differences in these swallowing related outcomes in patients treated with standard fractionation radiotherapy and high dose cisplatin versus accelerated fractionation radiotherapy and panitumumab.
The specific instruments to be used to measure swallowing outcome in this study include the SWAL-QOL, MDADI and the FOIS. In addition, the MBSImP will be used in a group of patients who consent to undergo videofluoroscopic assessment of swallowing function.

The SWAL-QOL [McHorney 2002] is a 44 item self-administered questionnaire assessing swallowing related QOL. The questionnaire taps 10 quality of life domains; namely, food selection, eating duration, fatigue, social function, general burden, mental health, symptom frequency, sleep, communication, fear of eating and eating desire. Patients score each question along a 5-point ordinal scale according to how true the statement is for them. Responses for items within each domain are summated into an overall domain score.

The MDADI [Chen 2001] is a 20 item self-administered questionnaire assessing swallowing related quality of life specific to patients with head and neck cancer. It has 3 subscales: emotional, functional and physical health. Responses for each item are ordinal along a 5-point scale. Scores from all items are summed to obtain a total score.
The FOIS [Crary 2005] is a 7 item ordinal scale that measures functional oral intake of patients with dysphagia, ranging from level 1 (nothing by mouth) to level 7 (total oral diet with no restrictions). The scale is completed by a clinician or research assistant from information extracted from a variety of sources, including medical charts, dietary journals, and/or verified patient reports.

In this study we will explore the correlation of two commonly used swallowing specific quality of life tools, the SWAL-QOL and the MDADI, to each other and to the generic cancer quality of life scale FACT-H&N. These results will be the first to identify differences in accuracy between the two swallowing specific quality of life tools and thereby will help establish the standard for both clinical practice and future research. The FOIS will provide a reliable and valid measure of functional status for comparison to impairment status (MBSImP- see below) and quality of life status (SWAL-QOL and the MDADI).

The role of videofluoroscopy in assessment of swallowing function is the accepted gold standard. The MBSImP [Martin-Harris 2007,2008] is a newly validated tool that rates the videofluoroscopic exam findings to derive the degree and type of swallowing impairment. It contains 13 items all of which are completed by a clinician or suitably qualified individual with expertise in swallowing and who has been trained on its administration and scoring. The MBSImP score can be derived from either live or digitized recordings of videofluoroscopic swallow assessments. In this study, videofluoroscopic measurements of swallowing impairment will be performed in a subgroup of patients (n=50) who consent to the Swallowing Impairment Sub-study (Appendix XIII). We will conduct test-retest blinded administrations of the MBSImP and therefore be the first to provide further psychometric evidence and generalization for this new tool. The objectives of this sub-study are to assess the feasibility of measuring swallowing impairment in head and neck cancer patients using the MBSImP, to assess the reliability between trained speech-language pathology raters of the MBSImP and to describe the swallowing impairment findings in both treatment groups as a means of identifying future research questions.

Of the participating centers, only those with the necessary speech-language pathology expertise and fluoroscopic equipment to conduct videofluoroscopy assessments will be eligible. From our preliminary survey of Canadian sites, we anticipate the inclusion of 3-4 centres. At each of these centres and only after consent to the larger study, we will seek separate consent from patients for this sub-study. In this way, this sub-study will not influence successful consent to the larger study.

NCIC CTG HN.6 will be the first study to include swallowing related measures of impairment, function and quality of life specific to head and neck cancer patients in the context of a phase III study.

2.4 Correlative Studies

Correlative studies are an important part of this study and every attempt will be made to collect biological specimens to further the understanding of tumour biology and response to therapy. The biomarkers of interest for further study are outlined below.

2.4.1 Archival Tumour Biomarkers

Archival tumour will be collected on study. The following sections describe planned biomarkers studies that will be conducted following the primary analysis of this study. Prior to the initiation of any biomarker study, the current knowledge of the biomarker will be reviewed to ensure continued relevance for this patient population and therapeutic interventions. Any unused tumour will be banked at Queen’s University as part of the NCIC CTG tumour biorepository.
**EGFR by immunohistochemistry:**
There is no definitive evidence from the literature that EGFR status as determined by immunohistochemistry predicts for clinical outcome in HNSCC. In the phase III trial of cetuximab plus cisplatin versus placebo plus cisplatin in patients with recurrent or metastatic HNSCC [Burtness 2005], patients with low-to-moderate EGFR expression (i.e. intensity score 0-2+, or staining in < 80% of cells) had a higher objective response rate than those with high EGFR expression. PFS and OS were not shown to differ by EGFR expression. In the pharmacodynamic evaluation of archival specimens on PHL-002/IND.157 (a phase II trial of erlotinib plus cisplatin in patients with recurrent or metastatic HNSCC) [Agulnik 2007], high EGFR expression (i.e. strong staining, or staining in ≥ 67% of cells) was associated with a higher response rate. PFS and OS were not shown to differ by EGFR expression. Thus, conflicting results have been reported in the literature, and further evaluation of this marker and its impact on clinically relevant endpoints is appropriate.

**IGF-1R by immunohistochemistry:**
Insulin-like growth factor type 1 receptor (IGF-1R) has been shown to be overexpressed in HNSCC cell lines and tumours [Barnes 2007]. Inhibition of IGF-1R signaling using a human anti-IGF-1R monoclonal antibody IMC-A12, significantly influences the proliferation, motility and tumourigenicity of HNSCC cell lines. Furthermore, EGFR and IGF-1R heterodimerize upon stimulation with EGF or IGF, but only IGF causes activating phosphorylation of both receptors. It would be of interest to evaluate the association between pre-treatment IGF-1R expression status and clinical outcome in this trial, especially for patients who receive the anti-EGFR antibody panitumumab.

**EGFR gene amplification status by FISH:**
In the group of HNSCC patients who have not been treated with an EGFR inhibitor, EGFR high polysomy and/or gene amplification (i.e. fluorescent in situ hybridization (FISH) positive) have a worse PFS and OS than those who are FISH negative, and appears to be a prognostic factor [Chung 2006]. For patients with recurrent or metastatic HNSCC who have had treatment with an EGFR inhibitor, FISH positive patients had a higher response rate (50% versus 15%, or 2/4 patients versus 4/27 patients) to erlotinib in PHL-002/IND.157 trial [Agulnik 2007]. The differences in TTP (3.5 months versus 2.8 months) and OS (7.1 months versus 5.6 months) for FISH positive versus FISH negative patients were not statistically significant.

**P53 by immunohistochemistry and mutational analysis and p16 by immunohistochemistry:**
P53 mutations occur frequently in HNSCC [Strano 2006], and may play a role in chemoresistance and prognosis. The progression of cells from G1 to S phase is blocked by a potent tumour suppressor protein, p16, which acts to disrupt the cyclin D1/CDK-4/6 complex. Low expression of p16 occurs in 55% to 89% of head and neck cancers, and studies that assessed patient outcome have correlated abnormal levels of the p16 protein with poor survival, increased tumour recurrence, tumour progression, and nodal metastasis [Bova 1999; Danahey 1999].

**E-cadherin, vimentin and snail by immunohistochemistry:**
Epithelial-mesenchymal transition (EMT) refers to critical events occasionally observed during tumour progression, including invasion and metastasis, by which cancer cells acquire a fibroblast-like phenotype [Onoue 2006]. In this context, the downregulation of epithelial markers, cytokeratin, E-cadherin and beta-catenin, and the upregulation of mesenchymal marker, vimentin and snail can be detected.

**HPV status by in situ hybridization and/or PCR:**
Human papillomavirus (HPV) is now recognized to play a role in the pathogenesis of a subset of HNSCC, particularly those that arise from the lingual and palatine tonsils within the oropharynx. There is sufficient evidence to conclude that a diagnosis of HPV-positive HNSCC has significant prognostic implications; these patients have at least half the risk of death from HNSCC when compared with the HPV-negative patient population. In situ hybridization for HPV16 can be done with paraffin-embedded tissues [Begum 2007].
DNA repair proteins:
In non small cell lung cancer, immunohistochemical analysis of the expression of the excision repair cross-complementation group 1 (ERCC1) protein in operative specimens has been performed among patients with completely resected tumours [Olaussen 2006]. Among non small cell lung cancer patients who did not receive adjuvant chemotherapy, those with ERCC1-positive tumours survived longer than those with ERCC1-negative tumours (hazard ratio for death 0.66, 95% C.I. 0.49-0.90). For patients who received cisplatin-based adjuvant chemotherapy, as compared with observation, patients with ERCC1-negative tumours derived a significantly prolonged survival (hazard ratio for death 0.65, 95% C.I. 0.5-0.86). This benefit was not seen among patients with ERCC1-positive patients who received adjuvant chemotherapy versus observation.

2.4.2 Serum, Plasma and Cellular Component Biomarkers

Serum, plasma and cellular component will be collected on study. The following sections describe planned biomarkers studies that will be conducted following the primary analysis of this study. Prior to the initiation of any biomarker study, the current knowledge of the biomarker will be reviewed to ensure continued relevance for this patient population and therapeutic interventions. Any unused plasma, cellular component and serum will also be banked at Queen’s University as part of the NCIC CTG tumour biorepository.

Serum/plasma ligands of EGFR (TGF-\(\alpha\), amphiregulin) and serum soluble EGFR extra-cellular domain:
These biomarkers will be analyzed in serum samples obtained pre-treatment serum samples and at week 4 after protocol treatment completion to determine if they are prognostic or predictive of clinical outcomes, and if treatment results in modification of their levels. Antibodies will be obtained from commercially available validated kits. These kits include the TGF-\(\alpha\) antibody ELISA kit (Biosource, Sunnyvale, CA), amphiregulin ELISA kit (R&D Systems, Minneapolis, MN) and EGFr antibody ELISA kit (Oncogene Science, Cambridge, MA, distributed by DAKO, Carpintera, CA). Remaining serum/plasma will be banked for mass spectrometric proteomics studies.

Serum polymorphic variants of EGFR gene:
These will be measured using standard sequencing approaches, and will be correlated with clinical outcome and toxicity [Liu 2007]. EGFR intron 1 and -216G/T polymorphisms have recently been shown to influence clinical outcomes in non-small-cell lung cancer patients treated with the small molecule tyrosine kinase inhibitor, gefitinib [Liu 2007]. A total of 30 polymorphisms will be evaluated in the EGFR pathway.

DNA repair gene polymorphisms:
In a study of 103 patients with stage IV HNSCC, a polymerase chain reaction-restriction fragment length polymorphism (RFLP) approach was used to determine the frequency of polymorphic variants in DNA-repair genes [Quintela-Fandino 2006]. Using a multivariate model, the presence of polymorphic variants in DNA-repair genes predicted for better overall survival and response to cisplatin. We will utilize a pathway approach to evaluate sets of polymorphic variants in DNA repair gene pathways [Gurubhagavatula 2004], in addition to polymorphisms of multi-drug resistance genes (e.g. ABC family) [Casatis 2006] and genes of enzymes involved with the metabolism of platinums such as the glutathione s-transferase superfamily. A total of 75 polymorphisms will be evaluated in DNA repair, xenobiotic metabolism, and multi-drug resistance pathways.
2.4.3 **Correlative Sciences Questionnaire**

Over the past few years, there has been mounting evidence that clinicoepidemiologic factors may influence tumour and blood genetic characteristics and ultimately, response to anti-cancer therapy. Examples include smoking status and EGFR-TKI therapy in lung cancer, post-menopausal status and hormonal therapy in breast cancer. In anticipation of the conduct of future pharmacogenetic studies in this study, data relevant to interpretation of such data in the head and neck population will be collected in a trial specific questionnaire. This will include information such as race and ethnicity, family history, smoking and alcohol exposure, vitamin and medication use as well as demographic data. This questionnaire will be completed by all patients who participate in the specimen banking portion of the study and will be completed after patient consent obtained (Appendix XV).

2.5 **Health Economics**

There is an immense cost burden related to the diagnosis and treatment of head and neck cancer [Agthoven 2001; Lang 2004; Lee 2004; Watters 1994]. Accelerated fractionation radiotherapy in head and neck cancer may improve locoregional control, but at a high cost as well as potential toxicity and ensuing costs [Fountzilas 2006; Hind 2008]. The addition of molecularly targeted therapy will also increase direct treatment costs but further improve patient outcomes.

The importance of costing new therapies relative to efficacy has been established [Coyle 1997; Menzin 2007; Wineland 2008]. Prospective collection of costs and health care resource utilization in the context of a clinical trial is advantageous in yielding high quality cost and efficacy data, especially in providing inputs into a robust cost-effectiveness calculation taking into account resource use and costs associated with toxicities [Glick 2007; Drummond 2005; Hollenbeack 2007].

All subjects will participate in the economic evaluation. Furthermore, it may be propitious to identify groups based on molecular or clinical characteristics who might benefit preferentially from a particular treatment.

In this study, currently utilized radiotherapy techniques will be costed, providing data not previously published in the literature. The economic evaluation will be completed using existing case report forms and source documentation for each patient. Health care resource utilization related to the study treatment, but not protocol driven, such as supportive medications, laboratory and imaging investigations, hospitalization, transfusions and outpatient care, including physician and emergency room visits, will be documented. To capture these data, additional resource utilization case report forms will be used.
3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Cisplatin

Cisplatin is a commercially available anticancer agent used routinely in the treatment of several types of cancer. Therefore, a short outline only of background data will be described.

This drug is one of a group of coordination compounds of platinum, whose effect on DNA resembles that of bi-functional alkylating agents. The drug strongly inhibits DNA synthesis, with little effect on RNA and protein synthesis. The major toxic effects are gastrointestinal, hematopoietic, otologic, neurologic and renal. The gastrointestinal toxicity consists mainly of nausea and vomiting, lasting from 4-6 hours in most patients, though it may be prolonged. Prophylactic 5HT3 antagonists (e.g. ondansetron or granisetron) are helpful in reducing acute nausea and vomiting. Hematologic toxicity may be seen with the dose of cisplatin used in this protocol. Blood counts (Hg, WBC and Plts) will be closely monitored on this trial. Nephrotoxicity can occur with cisplatin although severe nephrotoxicity is rare. Renal function will be closely monitored and all patients will receive adequate hydration during the study.

Administration: Cisplatin will be given as outlined in section 8.0.

Commercial supply of cisplatin will be used for this study.

3.2 Panitumumab

Name and Chemical Information:

Panitumumab is a high affinity (Kd = 5 x 10^{-11} M) fully human IgG2 monoclonal antibody directed against human EGFR.

3.3 Chemical Structure:

Panitumumab has a molecular weight of approximately 147 kDa and is composed of 445 amino acids in each heavy chain and 214 amino acids in each light chain. The expected heavy chain C-terminal lysine residue is almost entirely processed (approximately 95%).

3.4 Mechanism of Action:

The anti-tumour effects of panitumumab are primarily mediated by direct targeting of the EGFR. Panitumumab binds to the EGFR ligand-binding domain 2 (L2 domain) and blocks the tyrosine phosphorylation of EGFR by known ligands (EGF, TGF-α, amphiregulin, betacellulin, HB-EGF, and epiregulin). Panitumumab (0.2 to 133 nM) also blocked EGF-induced tyrosine phosphorylation of EGFR in A431 epidermoid carcinoma cells in a concentration-dependent manner with an IC_{50} of 3.1 nM. In addition, panitumumab blocked ligand-induced phosphorylation in non-small-cell lung cancer cell lines that express kinase domain mutant EGFR with an IC_{50} comparable to wild type expressing non-small-cell lung cancer cells or A431 cells. Furthermore, panitumumab induces internalization of the receptor in EGFR-expressing cells. However, the internalization of EGFR induced by panitumumab was significantly less pronounced and displayed slower kinetics compared to the internalization induced by EGF, indicating a different mechanism of internalization.
3.5 Experimental Antitumour Activity

In vitro studies have demonstrated that treatment with panitumumab inhibits EGFR-dependent cellular responses, including extracellular acidification, cell proliferation, and production of angiogenic factors by tumour cells. The anti-proliferative activity of panitumumab has been correlated with a concomitant inhibition of autophosphorylated EGFR. In vitro proliferation studies also have identified cell lines that are nonresponsive to panitumumab treatment, even though data demonstrate that they express EGFR and that panitumumab inhibits ligand-induced EGFR autophosphorylation. These results support the fact that the response to panitumumab in EGFR expressing cells is dependent upon the functional dependency of tumour cells on the EGFR pathway. Treatment with panitumumab as monotherapy or in combination with a chemotherapeutic agent or a targeted agent results in growth inhibition as well as eradication, in some cases, of tumour xenografts [Yang 1999]. Anti-tumour effects have been observed after treatment with both hybridoma- and Chinese hamster ovary-derived panitumumab in a wide range of human carcinoma xenografts with variable EGFR expression levels using colorectal, renal, breast, pancreatic, lung, head and neck, ovarian, prostate, and glioblastoma tumour cell lines, but not in human tumour xenografts not expressing EGFR. These data indicate that EGFR must be present to demonstrate an anti-tumour response.

3.6 Animal Toxicology

Results of panitumumab toxicology studies (1- and 3-month duration) have identified diarrhea and skin rash as the principal toxicities, which were considered related to the pharmacological action of panitumumab. Pharmacokinetics were shown to be nonlinear, and the production of monkey anti-human antibodies (MAHA) against panitumumab in animals caused a significant decrease in exposure over the course of the 3-month study.

In a 6-month toxicology study where panitumumab was administered intravenously at weekly doses of 7.5, 15, and 30 mg/kg to cynomolgus monkeys, skin rash and diarrhea were observed in several animals in all dose groups; both of these toxicities were considered to be related to the pharmacological action of panitumumab. Additionally, several animals showed decreased food consumption and body weight loss (Panitumumab Toxicology Study 103419).

3.7 Phase I Trials

Since the commencement of clinical studies 1,700 subjects with cancer have been enrolled in panitumumab phase 1, 2 and 3 clinical studies, receiving panitumumab doses ranging from 0.01 mg/kg to 5 mg/kg given once every week, 6 mg/kg given once every 2 weeks, and 9 mg/kg given once every 3 weeks.
Phase I study of different schedules of panitumumab:
In the phase I study of 96 patients that evaluated the safety, pharmacokinetics, and activity of panitumumab monotherapy at various doses and schedules, safety profiles and drug exposures were found to be comparable for panitumumab given at 2.5 mg/kg weekly, 6 mg/kg every 2 weeks, and 9.0 mg/kg every 3 weeks. Panitumumab given at 9 mg/kg every 3 weeks was safe and did not reach the maximum tolerated dose on this trial. In terms of safety, the incidences of treatment-related grade 3 and 4 adverse events for these three dose schedules (i.e. 2.5 mg/kg weekly, 6 mg/kg every 2 weeks, and 9.0 mg/kg every 3 weeks) were: 1/8 patients (13%), 1/17 patients (6%) and 5/23 patients (21%), respectively. No treatment related deaths were encountered. The frequencies of skin rash encountered on these three dose schedules were 8/8 patients (100%), 14/17 patients (82%) and 18/23 patients (78%), respectively. The most common adverse events occurring in at least 10% of subjects (all grades), treated at 9.0 mg/kg every 3 weeks were: rash (78%), dry skin (48%), dyspnea (22%), headache (22%), diarrhea (17%), vomiting (13%) and stomatitis (13%). No human anti-panitumumab antibodies were detected. Partial responses were seen in colorectal patients treated across all dosing schedules.

Safety data of panitumumab monotherapy:
An integrated analysis of the safety of panitumumab has been conducted for 1052 subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set). Subjects primarily received panitumumab doses of 2.5 mg/kg once weekly (15%) or 6.0 mg/kg every 2 weeks (82%).

Almost all subjects [1051/1052 (100%)] in the mCRC Monotherapy Set experienced at least 1 adverse event during the study period. Thirty-six percent of subjects had 1 or more adverse events reported at a worst grade of 3 (i.e. severe); 5% had events with a worst grade of 4 (i.e. life-threatening), and 16% had a fatal event. These events were primarily attributable to the underlying disease. The majority of mCRC subjects (94%) experienced at least 1 adverse event considered by the investigator to be related to panitumumab therapy; 20% were graded as severe or life-threatening, and 2 fatal treatment-related adverse events were reported. Adverse events leading to discontinuation of panitumumab were reported for 12% of subjects; however, of these, only 3% of subjects had events that were considered related to panitumumab, and most of these were associated with skin toxicity.

Serious adverse events were reported for 401 subjects (38%). However, only 48 subjects (5%) had serious adverse events considered by the investigator to be related to panitumumab. The most frequently reported serious, treatment-related adverse event was hypomagnesemia (8 subjects, 1%). All other treatment-related serious adverse events were reported in < 1% of subjects. Importantly, no notable differences were observed in the overall safety profile when assessed by sex, age, race, primary tumour type, panitumumab dosing regimen, or manufacturing process. Overall, 167 subjects (16%) had fatal adverse events; 147 subjects (14%) died either during panitumumab treatment or within 30 days of study drug discontinuation. Of these subjects, disease progression was attributed as the primary reason for death in 129 subjects (12% of all subjects, or 88% of deaths). Most non-disease progression causes of death appeared to be related to the underlying primary malignancy (such as hepatic failure, intestinal perforation, pleural effusion, or small intestinal obstruction). Of the deaths in the mCRC Monotherapy Set that were not reported as directly due to disease progression, 2 were considered to be possibly related to panitumumab by the investigator (pulmonary edema and myocardial infarction/cerebrovascular accident). Consistent with the published data on subjects treated with EGFR inhibitors (i.e. class/target effect), the most commonly reported treatment-related adverse events in subjects treated with panitumumab were associated with the skin, including pruritus (52%), acneiform dermatitis (51%), erythema (50%), and rash (38%). Most subjects (833 of 1052 subjects, 79%) with any dermatologic toxicity had events that were considered to be mild or moderate. Only 3% of subjects permanently discontinued panitumumab administration for dermatologic toxicities. Dermatologic toxicities typically were observed after initiation of panitumumab, with a median time to first integument toxicity (of any severity) of 10 days (95% CI: 8, 11).
Other common treatment-related adverse events (i.e. subject incidence ≥ 10%) included fatigue (15%) and diarrhea (13%).

Infusion reactions to panitumumab were infrequent even though premedication was not mandated in the panitumumab clinical program. Overall, 1% of subjects had an infusion reaction reported by the investigator as an adverse event. Using a definition consistent with the Vectibix USPI (2007), 3% of panitumumab-treated subjects had a potential infusion reaction; < 1% of subjects had a potential infusion reaction by this definition ≥ grade 3.

Phase I study of panitumumab, chemotherapy and radiotherapy in SCCHN:
In an ongoing single-centre phase I trial, conducted by the Dana Farber group, panitumumab is combined with chemotherapy and intensity modulated radiotherapy (IMRT) in patients with stage III and IV squamous cell cancer of the head and neck [Wirth 2008]. Part A of the study adds panitumumab to concurrent paclitaxel/carboplatin and IMRT. In groups of 3, patients receive escalating doses of weekly paclitaxel (dose level 1 = 15 mg/m²; dose level 2 = 30 mg/m²) with fixed dose weekly panitumumab (2.5 mg/kg) and carboplatin (AUC = 1.5) during IMRT. All patients receive daily radiotherapy to a total of 70 Gy in 2 Gy daily fractions to Gross Tumour Volumes. High Risk Clinical Target Volumes are treated to 64 Gy in 1.82 Gy fractions and Low Risk Clinical Target Volumes are treated to 60 Gy in 1.71 Gy fractions. Part B of this study will explore the addition of panitumumab to docetaxel/5-fluorouracil/cisplatin induction chemotherapy followed by panitumumab and chemoradiotherapy at the maximum tolerated dose established in Part A.

Dose-limiting toxicities were defined as follows: ≥ grade 3 non-hematologic toxicity except untreated nausea, vomiting, diarrhea, dysphagia, mucositis, radiation-induced dermatitis, or panitumumab skin rash; ≥ grade 4 mucositis or dermatitis resulting in radiation break more than 7 days in aggregate; ≥ grade 3 febrile neutropenia; ≥ grade 4 neutropenia lasting ≥ 7 days; and ≥ grade 3 thrombocytopenia. As of reporting at the 2008 American Society of Clinical Oncology meeting, 19 patients have been enrolled into Part A, all patients had T1-2 and N1-2b disease. No dose-limiting toxicity were encountered in dose level 1 (n=3). One dose-limiting toxicity (febrile neutropenia) occurred in dose level 2 (n=16), and thus this dose level has been declared as recommended dose appropriate for further study. Treatment compliance evaluation at dose level 2, the recommended dose, demonstrated that 5 patients had their systemic treatments modified: 4 patients missed 1 weekly chemotherapy and panitumumab due to nausea and vomiting (n=1), grade 3 rash (n=1) and grade 4 mucositis (n=2); 1 patient missed 1 weekly chemotherapy, but not panitumumab, due to paclitaxel reaction (n=1).

Other acute toxicities of intensity grade 3 or higher, at dose level 2 (n=16), include dysphagia (94% of patients), mucositis/stomatitis (81% of patients), radiation dermatitis (38%), acneiform rash (13%), and febrile neutropenia (6%). One patient experienced grade 4 sepsis and thromboembolic disease (pulmonary embolus and stroke) 3 weeks after completion of therapy. One patient experienced grade 4 aspiration pneumonia associated with pleural effusion requiring thoracoscopic decortication and drainage 11 weeks after therapy. One patient was diagnosed with prostate cancer 11 months after therapy. As for long-term toxicity, no grade 3 or higher salivary gland, mucous membrane or cutaneous toxicities occurred. Percutaneous endoscopic gastrostomy tubes have been removed in all 19 patients, with a median time of removal of 11 weeks after completion of therapy. Weight loss occurred in 84% of patients, but no ≥ grade 3 weight loss was encountered. Primary tumour was evaluable by RECIST in 13 patients with 9 complete and 4 partial responses. Cervical lymphadenopathy was evaluable in all 19 patients and all achieved partial responses by RECIST. All 19 patients remain alive and disease-free at median follow-up of 60 weeks (range 27-105 weeks).
An open-label, dose-finding study (Study 20040235) of AMG706 or panitumumab when administered with induction chemotherapy (IC) and/or chemo-radiotherapy (CRT) in the treatment of subjects with loco-regionally advanced squamous cell carcinoma of the head and neck is ongoing. Five dose cohorts are currently planned for this study. As of the data cut-off date (18 May 2007), 5 subjects were enrolled in cohort A [TPF (T – docetaxel 75 mg/m²; P - cisplatin 75 mg/m²; F – 5-fluorouracil 750 mg/m² days 1 to 5) induction chemotherapy followed by chemoradiotherapy + panitumumab 1.5 mg/kg QW (n = 7) and 2.5 mg/kg (n = 3), and 4 subjects were enrolled in cohort B (TPF induction chemotherapy followed by chemoradiotherapy + AMG706). Of the 9 subjects enrolled in cohorts A and B, 8 had completed study and 1 had treatment ongoing (data on file at Amgen Inc). Safety data was available for all 9 subjects.

At least 1 treatment-emergent adverse event was reported for all 9 subjects (100%) in cohorts A and B. Two subjects in cohort A1 experienced a DLT (one each grade 3 and 4 mucositis). Subsequently, the protocol was amended to modify the DLT definition for mucositis to limit it to grade ≥ 3 toxicity that occurred in the first 5 weeks of radiotherapy or led to a 5-day radiotherapy delay. There were no further DLTs. The most common grade ≥ 3 AE during the panitumumab + chemoradiotherapy phase was mucositis (n = 6). There was 1 event each of grade 3 esophagitis, dysphagia, and odynophagia, all reported as unrelated to panitumumab. One subject also experienced grade 3 radiation dermatitis that was considered related but did not meet the criteria of a DLT. The most common grade ≥ 3 adverse events during induction chemotherapy were febrile neutropenia (n = 5) and mucositis (N = 4). No subjects in cohort A have died within 30 days of last dose of investigational product [data on file at Amgen Inc].

As of 31 May 2010, 1 serious case of keratitis and 3 serious cases of ulcerative keratitis have been reported in the postmarketing setting for panitumumab. Three of the cases were reported in patients who were administered panitumumab in the monotherapy setting and 1 case was reported in a patient who received Vectibix in combination with chemotherapy. In addition, there have been 7 non-serious cases of keratitis reported from the panitumumab clinical trials with a study subject incidence rate between 0.2% and 0.7% [data on file at Amgen Inc].

Please refer to the current Panitumumab Investigator’s Brochure for further details.

### 3.8 Phase II and III Trials

Several phase II trials of panitumumab given as a monotherapy have been conducted. In a multi-center, open-label, 2-part, phase II clinical trial evaluating the safety and efficacy of panitumumab in subjects with renal cell carcinoma, the first part of the study involved open-label, sequential enrolment of 88 subjects to 1 of 4 escalating weekly dose levels of panitumumab (1.0, 1.5, 2.0, and 2.5 mg/kg). Of the 88 subjects enrolled in part 1, 2 subjects (2%) had a partial response, while 44 subjects (50%) had stable disease.

In a multi-centre, single-arm study of 33 subjects with hormone-resistant prostate cancer who received panitumumab at a dose of 2.5 mg/kg once weekly, no tumour responses were observed after the initial 8-week course. Responses across the entire treatment period showed a similar result. Three single-arm, phase II studies were conducted to provide supportive efficacy and safety data for the use of panitumumab in metastatic colorectal cancer. These studies provide evidence of the anti-tumour activity of panitumumab in subjects who had disease progression after 1 or more fluoropyrimidine-based regimens (with or without leucovorin) plus either irinotecan, oxaliplatin or both (given concurrently or sequentially).
In a multi-centre, open-label, controlled phase III study conducted in Europe, Australia and Canada, 463 patients with metastatic colorectal cancer who had failed standard chemotherapy, including oxaliplatin and irinotecan were enrolled. Patients were randomized to receive panitumumab plus best supportive care (n=231) or best supportive care alone (n=232). Panitumumab was administered at a dose of 6 mg/kg once every two weeks. Best supportive care was defined as the best palliative care available, as judged appropriate by the investigator, and could not include palliative chemotherapy. Patients who received panitumumab every two weeks showed a 46 percent decrease in progression or death (primary endpoint) versus those who received best supportive care alone (p < 0.0001). Median progression-free survival was 8 weeks (95% CI, 7.9 to 8.4) for panitumumab and 7.3 weeks (95% CI, 7.1 to 7.7) for best supportive care alone arm. Mean (standard error) progression-free survival was 13.8 (0.8) weeks for panitumumab and 8.5 (0.5) weeks for best supportive care alone arm. Objective response rates also favored panitumumab over best supportive care alone arm; after a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for best supportive care alone arm (p < 0.0001). No difference was observed in overall survival (HR, 1.00; 95% CI, 0.82 to 1.22), which was confounded by similar activity of panitumumab after 76% of best supportive care alone arm patients entered the cross-over study. Panitumumab was well tolerated. Skin toxicities, hypomagnesaemia, and diarrhea were the most common toxicities observed. No patients had grade 3 or 4 infusion reactions [Van Cutsem 2007]. This study has led to the approval of panitumumab by the US Food and Drug Administration, the European Committee for Medicinal Products for Human Use (CHMP) in the European Union, and health authorities in Canada and Australia for the treatment of patients with metastatic colorectal cancer following standard chemotherapy. Approvals of panitumumab in metastatic colorectal cancer in Europe and in Canada are restricted to patients who have wild-type K-RAS tumours.

At the time of generation of this protocol, there are no completed phase II or III studies with panitumumab, alone as monotherapy or in combination with radiotherapy in squamous cell cancer of the head and neck. Two ongoing Amgen sponsored randomized phase II studies in patients with locally advanced squamous cell carcinoma of the head and neck evaluate radiotherapy plus panitumumab and chemoradiotherapy plus panitumumab (Studies 20062079 and 20062080 respectively). Both studies utilize the same dose of panitumumb as NCIC CTG HN.6 (9 mg/kg IV q 3 weekly) and comparable radiotherapy techniques (accelerated radiotherapy using 3DCRT or IMRT). The first interim safety analysis is planned for both studies in Fall 2008 (personal communication Amgen).In addition, a phase III randomized trial of chemotherapy with or without panitumumab in patients with metastatic and/or recurrent squamous cell carcinoma of the head and neck is ongoing.

3.9 Pharmacokinetic Studies

Panitumumab administered as a single agent or in combination with concomitant chemotherapy exhibits non-linear pharmacokinetics. The time-averaged clearance value decreases with increasing dose and approaches the clearance value of endogenous IgG2 (1 to 4 mL/day/kg). The concentration-time profile of panitumumab is best described by a 2-compartment pharmacokinetic model with dual linear and non-linear clearance pathways, presumably mediated by the reticuloendothelial system and EGFR, respectively. Since panitumumab that is bound to cell-surface EGFR can be internalized and degraded, the non-linear clearance is probably related to saturable protein binding of panitumumab to EGFR.
Panitumumab administered at 2.5 mg/kg once weekly, 6 mg/kg every 2 weeks, or 9 mg/kg every 3 weeks achieve similar and consistent trough concentrations over time. Pharmacokinetic steady-state is obtained after 6 doses at 2.5 mg/kg once weekly, 3 doses at 6 mg/kg every 2 weeks, and 2 doses at 9 mg/kg every 3 weeks. At steady-state, the mean half-life value during the dosing interval was 8.5 days for 2.5 mg/kg once weekly, 7.5 days for 6 mg/kg every 2 weeks, and 8.4 days for 9 mg/kg every 3 weeks. The minimal serum panitumumab concentrations (C\text{trough}) were similar among the 2.5 mg/kg weekly, 6 mg/kg every 2 weeks, and 9 mg/kg every 3 weeks doses, with steady-state reached after about 6 weeks for all schedules [Weiner 2008].

Age, sex, tumour type, race, hepatic function, renal function, chemotherapy (paclitaxel or irinotecan), and EGFR membrane expression in tumour cells had no meaningful impact on the pharmacokinetics of panitumumab. Panitumumab exposure was higher for heavier subjects than for lighter subjects when dosed by subject’s actual body weight. Data from simulations suggest that a weight-adjusted dosing regimen would result in less variability in exposure to panitumumab across body weights than fixed dosing, and therefore, support the current weight-adjusted dosing regimen (mg/kg).

The pharmacokinetics of panitumumab derived from the hybridoma and Chinese hamster ovary cell expression systems were similar in subjects with solid tumours. Similar panitumumab pharmacokinetic profiles also were observed between the 2-kL and 12-kL Chinese hamster ovary production scales in subjects with solid tumours.

No apparent trends were observed between the pharmacokinetics of panitumumab and the presence of anti-panitumumab antibodies (neutralizing or non-neutralizing), and no clinical sequelae were associated with the presence or development of neutralizing antibodies to panitumumab.

3.10 Pharmaceutical Data

**Supplied:**
Panitumumab will be manufactured and packaged by Amgen and distributed using Amgen’s clinical trial drug distribution procedures. Each vial of panitumumab will contain 10 mL of a sterile protein solution containing a 20 mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Boxes of panitumumab will contain 12 or 25 vials of panitumumab. Each vial of panitumumab will be labeled in accordance with current ICH GCP, Food and Drug Administration and specific national requirements.

**Stability:**
The diluted solution should be used ≤ 6 hours after dilution, if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2° to 8°C (36° to 46° F).

**Storage:**
Panitumumab must be stored at 2-8°C (36° to 46° F) in a secured area upon receipt. Vials are to be stored in the original carton under refrigeration at 2-8°C (36° to 46°F) until time of use. The product should be protected from direct sunlight and should not be frozen or shaken excessively. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions.

As panitumumab contains no preservative, vials are designed for single use only. Any unused portion of panitumumab remaining in the vial must not be used. The diluted solution should be used ≤ 6 hours after dilution, if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2° to 8°C (36° to 46° F).
Solution Preparation:
Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the intravenous bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems, that could potentially lead to excessive shaking or vibration that would lead to particulate formation in the protein product.

The pharmacist, using aseptic techniques, will prepare panitumumab infusion. The dose of panitumumab will be 9 mg/kg every 3 weeks and will be based upon the subject’s baseline weight. The dose will not be recalculated unless the weight changes at least +/- 10% from the baseline weight. The calculated amount of panitumumab (may be rounded to the nearest ten milligrams [e.g. 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) will be removed from the vials and added to a total volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP. Doses higher than 1000 mg should be diluted to 150 mL. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL.

Route of Administration:
Panitumumab will be diluted in a total volume of 100 mL pyrogen-free 0.9% sodium chloride solution, USP (saline solution) and must be administered intravenously by an infusion pump through a peripheral line or indwelling catheter using a 0.22-micron in-line filter infusion set-up over 1 hour ± 15 minutes by a trained healthcare professional. If the first infusion is well tolerated (i.e. without any serious infusion related reactions) all subsequent infusions may be administered over 30 ± 10 minutes.

In the event a subject’s actual body weight requires greater than a 150 mL volume infusion, panitumumab will be administered over 60 to 90 ± 15 minutes, as tolerated. The diluted solution should be used ≤ 6 hours after dilution, if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2 ° to 8°C (36 ° to 46 ° F). Panitumumab will be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion.
4.0 TRIAL DESIGN

This is a multicentre, randomized phase III study conducted by the NCIC Clinical Trials Group with support by Amgen.

4.1 Stratification

Patients will be stratified by:
- T category: T1-3 versus T4
- Nodal status: N0, N1 versus N2, versus N3
- Radiotherapy delivery modality: Intensity modulated radiotherapy (IMRT) versus 3D conformal radiotherapy (3D CRT)
- Anatomic location: hypopharynx versus oral cavity versus oropharynx versus larynx
- Participation in Swallowing Impairment Sub-study

4.2 Randomization

<table>
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Planned sample size: 320
5.0 STUDY POPULATION

Patients with histologically confirmed squamous cell carcinoma of the head and neck of the oral cavity, oropharynx, larynx or hypopharynx which is locally advanced as defined by $T_{\text{any}}N+M0$ or $T3-4N0M0$.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to calling for randomization.

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. For the safety of the patients, as well as 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.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histologically and/or cytologically confirmed (primary lesion or regional lymph nodes) squamous cell carcinoma of the oral cavity, oropharynx, larynx or hypopharynx which is locally advanced as defined by the following:
- $T_{\text{any}}N+, M0$
- $T3-4N0, M0$

5.1.2 ECOG PS: 0, 1

5.1.3 Age $\geq 18$ years

5.1.4 The following radiological investigations must be done within 8 weeks of randomization:
- MRI or CT of the head and neck
- CT chest

5.1.5 Hematology and biochemistry within 2 weeks prior to randomization with confirmation of the following:
- Absolute granulocyte count (AGC) $\geq 1.5 \times 10^9/L$
- Platelets $\geq 100 \times 10^9/L$
- Bilirubin $\leq 1.5 \times \text{ULN}$
- AST or ALT $\leq 3 \times \text{ULN}$
- Calculated creatinine clearance $> 50 \text{ ml/min}$ (see section 8.1.6 Cockcroft formula)
- Magnesium $> 0.5 \text{ mmol/L}$

5.1.6 Negative pregnancy test within 72 hours prior to randomization for women of childbearing potential.

5.1.7 Adequate contraception for patients of reproductive potential for men and women during and for at least 6 months following study treatment.

5.1.8 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of treatment, adverse events and follow-up.
5.1.9 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life and swallowing quality of life questionnaires in either English or French. The baseline quality of life and swallowing quality of life assessment must already have been completed within 2 weeks prior to randomization. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) 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.

5.1.10 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is given in Appendix XVI. A copy of the initial full board REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to randomization or registration. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTG and monitoring agencies to review patient records (see Section 16.4 for further details).

5.1.11 Patients must be assessed by a radiation oncologist and medical oncologist and deemed suitable for study participation.

5.1.12 In accordance with NCIC CTG policy, protocol treatment is to begin within 3 weeks of patient randomization.

5.1.13 *For patients participating in Swallowing Impairment Sub-study:* Ability to speak English or French and signed Swallowing Impairment Sub-study consent for patients already enrolled in the primary study at participating centres.

5.2 Ineligibility Criteria

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

5.2.1 Prior history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.

5.2.2 Current history of unknown primary squamous cell carcinoma of the head and neck, primary nasopharyngeal, paranasal or salivary gland tumours of the head and neck.

5.2.3 Prior radiation to the head and neck region that would result in overlap of fields for the current study.

5.2.4 Prior surgical treatment of the current cancer except for a diagnostic biopsy.

5.2.5 Prior cisplatin or carboplatin chemotherapy.

5.2.6 Prior induction chemotherapy for current squamous cell carcinoma of the head and neck.

5.2.7 Prior targeted, anti EGFR therapy of any kind.

5.2.8 History of allergic or hypersensitivity reactions to any study drug or their excipients.
5.2.9 Investigational agent of any kind within 30 days prior to randomization.

5.2.10 History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline CT scan.

5.2.11 Peripheral neuropathy $\geq$ grade 2 (CTCAE v3.0).

5.2.12 Hearing loss/tinnitus $\geq$ grade 3 (CTCAE v3.0).

5.2.13 Pregnant or lactating women.

5.2.14 History of a thromboembolic event in the last 12 months despite being treated with anticoagulation. However, patients are eligible if they have experienced a thromboembolic event greater than 12 months previously and have initiated and are stable on anticoagulation or if they have previously initiated and are stable on anticoagulation for prevention of thromboembolic events.

5.2.15 History of myocardial infarction within 12 months prior to entry, uncontrolled severe congestive heart failure, unstable angina, active cardiomyopathy, unstable ventricular arrhythmia, uncontrolled hypertension, uncontrolled psychiatric disorders, active serious infections, active peptic ulcer disease or any other medical conditions which might interfere with protocol therapy delivery.

5.2.16 Ongoing ocular inflammation or infection.

5.2.17 Patients with significant ophthalmologic abnormalities such as:
- Severe dry eye syndrome
- Keratoconjunctivitis sicca
- Sjogren's syndrome
- Severe exposure keratopathy
- Disorders that might increase the risk for epithelium related complications (e.g. bullous keratopathy, aniridia, severe chemical burns, neutrophilic keratitis)
6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and Physical Exam including:</strong></td>
<td></td>
</tr>
<tr>
<td>• Height</td>
<td>Within 4 weeks prior to randomization</td>
</tr>
<tr>
<td>• Weight</td>
<td></td>
</tr>
<tr>
<td>• ECOG PS</td>
<td></td>
</tr>
<tr>
<td>• BSA</td>
<td></td>
</tr>
<tr>
<td>• Mucosal clinical assessment</td>
<td></td>
</tr>
<tr>
<td>• Direct or indirect visualization of tumour and</td>
<td>Within 8 weeks prior to randomization</td>
</tr>
<tr>
<td>surrounding area</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td>Within 2 weeks prior to randomization</td>
</tr>
<tr>
<td>• CBC</td>
<td></td>
</tr>
<tr>
<td>• Differential</td>
<td></td>
</tr>
<tr>
<td>• Platelets</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td>Within 2 weeks prior to randomization</td>
</tr>
<tr>
<td>• AST or ALT</td>
<td></td>
</tr>
<tr>
<td>• Bilirubin</td>
<td></td>
</tr>
<tr>
<td>• Mg, Ca, Na, K, Cl, albumin</td>
<td></td>
</tr>
<tr>
<td>• Serum creatinine and calculated creatinine</td>
<td></td>
</tr>
<tr>
<td>clearance</td>
<td></td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>Within 8 weeks prior to randomization</td>
</tr>
<tr>
<td>• CT or MRI of head and neck</td>
<td></td>
</tr>
<tr>
<td>• CT scan of chest</td>
<td></td>
</tr>
<tr>
<td>• Other radiology tests as clinically indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>• Pregnancy test**</td>
<td>Within 72 hours prior to randomization</td>
</tr>
<tr>
<td>• Audiogram</td>
<td>Within 8 weeks prior to randomization</td>
</tr>
<tr>
<td>• Archival tumour collection**</td>
<td>After patient consent obtained</td>
</tr>
<tr>
<td>• Tumour HPV status</td>
<td>Tumour HPV status for all patients</td>
</tr>
<tr>
<td>• Plasma, cellular component and serum samples***</td>
<td>After patient consent obtained</td>
</tr>
<tr>
<td>• Correlative Sciences Questionnaire***</td>
<td>After patient consent obtained</td>
</tr>
<tr>
<td><strong>Adverse Event</strong></td>
<td>Within 2 weeks prior to randomization</td>
</tr>
<tr>
<td>• Baseline adverse event evaluation (to document</td>
<td></td>
</tr>
<tr>
<td>baseline symptoms)</td>
<td></td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>Within 2 weeks prior to randomization</td>
</tr>
<tr>
<td>• FACT-H&amp;N**</td>
<td></td>
</tr>
<tr>
<td><strong>Swallowing Related Quality of Life</strong></td>
<td>Within 2 weeks prior to randomization</td>
</tr>
<tr>
<td>• MDADI</td>
<td></td>
</tr>
<tr>
<td>• SWAL-QOL</td>
<td></td>
</tr>
<tr>
<td><strong>Swallowing Function</strong></td>
<td>Within 2 weeks prior to randomization</td>
</tr>
<tr>
<td>• FOIS</td>
<td></td>
</tr>
<tr>
<td>• MBSImP***</td>
<td>After the Swallowing Impairment Sub-study consent</td>
</tr>
<tr>
<td>is signed for the Swallowing Sub-study and</td>
<td>is signed for the Swallowing Sub-study and</td>
</tr>
<tr>
<td>prior to commencement of protocol therapy</td>
<td>prior to commencement of protocol therapy</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>• AST or ALT</td>
<td></td>
</tr>
<tr>
<td>• Bilirubin</td>
<td></td>
</tr>
<tr>
<td>• Mg, Ca, Na, K, Cl, albumin</td>
<td></td>
</tr>
<tr>
<td>• Serum creatinine and calculated creatinine</td>
<td></td>
</tr>
<tr>
<td>clearance</td>
<td></td>
</tr>
</tbody>
</table>

* Tests must be within one week of the start of treatment. Repeat tests if the pre-randomization tests are done more than one week prior to treatment day 1. Eligibility criteria (as per 5.1.5) must be fulfilled.
** For women of childbearing potential
*** Optional for consenting patients only
♦ Adverse events will be recorded and graded according to the CTCAE v 3.0 (Appendix V).
** The FACT-H&N questionnaire should be completed before the MDADI and the SWAL-QOL.
*** For consenting patients participating in Swallowing Impairment Sub-study only (Appendix XIII).
♦♦ Participants who refused tumour banking and for whom the tumour HPV status is unknown must be re-consented with the participant information letter to obtain consent to test tumour HPV status and to collect the results.
7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done by the NCIC CTG by means of a web-based, password-operated electronic system. Complete details regarding obtaining a password, accessing the system and carrying out randomizations will be provided at the time of study activation and are also be included in the "Data Management Guidebook", posted on the HN6 area of the NCIC CTG web-site. If sites experience difficulties accessing the system and/or performing randomizations the HN6 Study Coordinator should be contacted (see last page of this protocol for contact details).

The following information will be required:
- trial code (NCIC CTG HN.6)
- treatment centre and investigator
- version of the informed consent that the patient signed
- version of the Tissue Collection and Banking consent that the patient signed (if applicable)
- patient's initials, hospital number (if permitted by the local REB) and NCIC CTG serial number
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- stratification parameters
- height and weight

7.2 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 m² 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.

7.3 Stratification

- T category: T1-3 versus T4
- Nodal status: N0, N1 versus N2, versus N3
- Radiotherapy delivery modality: Intensity modulated radiotherapy (IMRT) versus 3D conformal radiotherapy (3D CRT)
- Anatomic location: hypopharynx versus oral cavity versus oropharynx versus larynx
- Participation in Swallowing Impairment Sub-study
7.4 Randomization

Randomization will be given by the NCIC CTG website.

**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, except on disclosure of initial ineligibility.

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 randomization.

All randomized patients are to be followed until death. The follow-up requirement for ineligible patients is minimal follow-up using a “Follow-up of Ineligible Patients” report form.
8.0 TREATMENT PLAN

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

In accordance with NCIC CTG policy, protocol treatment is to begin within 3 weeks of patient randomization.

8.1 Systemic Therapy Treatment Plan

8.1.1 Drug Administration

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>IV</td>
<td>Day 1, 22, 43 of radiotherapy</td>
</tr>
<tr>
<td>2</td>
<td>Panitumumab</td>
<td>9 mg/kg</td>
<td>IV every 3 weeks</td>
<td>7 weeks: starting one week prior to and days 15 and 36 of radiotherapy</td>
</tr>
</tbody>
</table>

Weight will be collected and evaluated prior to panitumumab therapy and BSA will be collected and evaluated prior to the cisplatin therapy.

ARM 1: Cisplatin

8.1.2 Premedication (Arm 1)

Premedication to prevent nausea and vomiting according to local institutional guidelines for highly emetogenic regimens should be given. All patients should receive a 5HT3 antagonist. Hydration and use of mannitol will be according to local institutional standards.

8.1.3 Patient Monitoring (Arm 1)

Patients should be monitored as directed in the Product Monograph and/or institutional guidelines.

8.1.4 Dose Adjustments (Arm 1)

Doses will be adjusted for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V).

The major toxic effects are gastrointestinal, hematopoietic, otologic, neurologic and renal. Nausea and vomiting are common. Hematologic toxicity is usually minimal although anemia requiring transfusional support may be seen. Nephrotoxicity is unusual providing there is ample hydration. Hypomagnesemia may be seen. Ototoxicities include tinnitus and/or hearing loss. The incidence of peripheral neuropathies increases with prolonged therapy.
The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

8.1.5 *Hematologic Adverse Events (Arm 1): Dose Adjustments*

<table>
<thead>
<tr>
<th>Previous Dose Adverse Event</th>
<th>Cisplatin Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia or AGC &lt; 0.5</td>
<td>Permanent dose reduction by 25%</td>
</tr>
<tr>
<td>Thrombocytopenic bleeding or platelets &lt; 50</td>
<td>Permanent dose reduction by 25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Day Counts</th>
<th>Absolute Granulocyte Count (AGC) (x10⁹/L)</th>
<th>Platelets (x10⁹/L)</th>
<th>Cisplatin Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.2 and ≥ 75</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>&lt; 1.2 and/or &lt; 75</td>
<td></td>
<td></td>
<td>Hold and repeat blood test and administer 100% of dose if recovered*</td>
</tr>
</tbody>
</table>

* Cisplatin dose may be held a maximum of seven days and must be given while radiotherapy is ongoing.

8.1.6 *Non-hematologic Adverse Events (Arm 1)*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix V).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cisplatin Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated creatinine clearance*</td>
<td>40-50 ml/min</td>
</tr>
<tr>
<td></td>
<td>&lt; 40 ml/min (after appropriate hydration)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>≥ Grade 3</td>
</tr>
<tr>
<td>Major organ adverse event** (except infield radiation toxicities such as mucositis and dermatitis)</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>Grade 4</td>
</tr>
</tbody>
</table>

* Clearance to be calculated using Cockcroft formula:

- Males: \[1.23 \times (140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine (\mu mol/l)})\]
- Females: \[1.05 \times (140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine (\mu mol/l)})\]

** Dose adjustment for nausea and vomiting only if persistent despite maximal supportive therapy.
8.1.7 **Duration of therapy (Arm 1):**

If radiotherapy never started, cisplatin should not be given on its own. If radiotherapy discontinued early, then cisplatin should also be discontinued. If radiotherapy is held and then resumed, cisplatin should be held when radiotherapy is being held. When radiotherapy resumed cisplatin should fall onto the planned days for cisplatin delivery (i.e. days 1, 22 and 43). Missed doses will not be made up.

8.1.8 **Compliance (Arm 1):**

All administered doses of cisplatin will be recorded on the case report form.

**ARM 2: Panitumumab**

Please refer to section 3.10 for detailed information regarding route of administration of panitumumab.

8.1.9 **Premedication (Arm 2):**

If, during or after any infusion, a reaction occurs, pre-medication may be used for subsequent panitumumab infusions (e.g. acetaminophen/paracetamol and/or an H1 blocker, e.g. diphenhydramine).

Pre-emptive therapy for panitumumab skin toxicity may be used at the investigator discretion. The following pre-emptive regimen is recommended:
- Skin moisturizer: apply to face, hands, feet, neck, back and chest daily in the morning upon rising.
- Sunscreen (PABA free, SPF >15, UVA/UVB protection): apply to exposed skin areas before going outdoors.
- Topical steroid (1% hydrocortisone cream): apply to face, hands, feet, back and chest at bedtime.
- Doxycycline 100mg BID PO or minocycline 100mg BID PO.

8.1.10 **Patient Monitoring (Arm 2):**

Patients should be monitored for hypersensitivity reactions during panitumumab infusion as per the Product Monograph or institutional standards. Subjects who experience any serious infusion reaction during panitumumab administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the investigator. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

8.1.11 **Dose Adjustments (Arm 2):**

Doses will be adjusted for adverse events as detailed below. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V).
The major toxic effects of panitumumab which could limit dose are: frequent skin reactions including acne form rash, occasional asthenia, mucositis/stomatitis (especially infield radiation toxicity), nausea/vomiting, diarrhea, and infrequent hypersensitivity reactions. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>First Dose Reduction Level</th>
<th>Second Dose Reduction Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3 week dose of</td>
<td>Every 3 week dose of</td>
<td>Every 3 week dose of</td>
</tr>
<tr>
<td>9 mg/kg</td>
<td>7.2 mg/kg</td>
<td>5.4 mg/kg</td>
</tr>
</tbody>
</table>

There will be no dose level reductions below the every 3 week dose of 5.4 mg/kg. Panitumumab dose reductions are permanent. There will not be any re-escalation of dose.

### Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Hypersensitivity Reaction</th>
<th>Action</th>
</tr>
</thead>
</table>
| Grade 1                   | • Treat with antipyretics and antihistamines  
|                           | • Re-treat with panitumumab next dose                                                                                                 |
| Grade 2                   | • Slow or stop the panitumumab infusion.  
|                           | • Provide supportive care with oxygen, beta agonists, antihistamines or corticosteroids.  
|                           | • Patient may be retreated with panitumumab.  
|                           | • Premedication with corticosteroids, antihistamines and antipyretics may be used before subsequent panitumumab infusions.          |
| Grade 3                   | • Stop the panitumumab infusion.  
|                           | • Provide supportive care with oxygen, beta agonists, antihistamines or corticosteroids.  
|                           | • Subsequent doses consider discontinuing panitumumab therapy or pretreatment with corticosteroids, antihistamines and antipyretics before subsequent panitumumab infusions.  
|                           | • For subsequent infusions the infusion time must be maintained at 1 hour ± 15 minutes                                                                 |
| Grade 4                   | • Stop the infusion  
|                           | • Subsequent infusions: discontinue panitumumab infusion                                                                 |

### Skin Adverse Events

Pre-emptive therapy for panitumumab skin toxicity maybe used at the investigator discretion (see section 8.1.9)

A papulopustular rash is the most commonly observed skin adverse event for panitumumab. Such rash frequently improves with an unchanged, uninterrupted dose of panitumumab therapy. Severe skin AEs (CTC Grade 3 or more) associated with panitumumab are infrequent (up to 12%). In general, patients with poorly tolerated skin toxicities may be successfully managed by providing a brief (up to 21 days) therapy interruption and resuming panitumumab at the same dose. In some cases, the rash may improve without the need for interrupting therapy with panitumumab.
Subjects should be encouraged to avoid exposure to sunlight. Broad spectrum sunscreens (containing titanium dioxide or zinc oxide) with an SPF of at least 15 should be applied.

A variety of agents can be used to manage skin reactions. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, as well as moisturizers.

There is no standard treatment, known or established, that is proven effective for drug-related skin rashes or changes due to panitumumab. The need for oral or topical antibiotics and topical steroids is a clinical decision of the investigator and, if indicated, a dermatology consultation. Oral steroids may be used for a short treatment course (maximum of 21 days) which may help patients to remain on study therapy.

The decision to administer, delay or discontinue panitumumab due to skin adverse events is as follows:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Guideline for Management</th>
<th>Panitumumab dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Nail Adverse Events***</td>
<td>1</td>
<td>Any of the following as appropriate: oral or topical antibiotics, topical steroids, oral steroids (short course) skin moisturizers, sunscreen.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>None *</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>Hold until recovery to ≤ grade 2** If this is the first occurrence, resume at the same dose; if this constitutes recurrence, reduce 1 dose level A maximum of 2 dose reductions are allowed.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>As clinically appropriate</td>
<td>Discontinue panitumumab</td>
</tr>
</tbody>
</table>

* if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1** and then resume at the same dose; if dose has been previously held for grade 2 skin toxicity and grade 2 symptoms recur, hold dose until recovery to ≤ grade 1 and then reduce 1 dose level. A maximum of 2 dose reductions are allowed.

** maximum hold for 21 days; if no recovery to ≤ grade 2 after 21 days, discontinue panitumumab

*** Rash occurring outside the radiation field should be graded using the following CTCAE v3.0 terms: rash/desquamation or rash: acne/acneiform.

**Interstitial Pneumonitis**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Guideline for management</th>
<th>Panitumumab dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated</td>
<td>Hold pending diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue if interstitial pneumonitis diagnosis is confirmed</td>
</tr>
</tbody>
</table>

**Infield Radiation Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Panitumumab dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>Grade 1-3</td>
<td>Treat symptomatically, no change in dose</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Hold dose of panitumumab until ≤ Grade 3. Reduce by one dose level for subsequent treatment. If grade 4 mucositis recurs, discontinue panitumumab permanently.</td>
</tr>
<tr>
<td>Dermatitis*</td>
<td>Grade 1-3</td>
<td>Treat symptomatically, no change in dose</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue panitumumab permanently.</td>
</tr>
</tbody>
</table>

* Rash occurring inside the radiation field should be graded using the following CTCAE v3.0 term: Rash: dermatitis associated with radiation
### Hypomagnesemia

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Serum Magnesium mg/dL</th>
<th>mmol/L</th>
<th>Guidelines for management</th>
<th>Panitumumab dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; LLN – 1.2</td>
<td>≤ LLN – 0.5</td>
<td>Consider replacement with IV magnesium sulphate 2-5 g in normal saline or D5W. Infusion schedule based on institutional guidelines.</td>
<td>Maintain dose and schedule</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 1.2 – 0.9</td>
<td>&lt; 0.5 – 0.4</td>
<td>As above for grade 1 and consider prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) if grade 2 of higher hypomagnesemia persists.</td>
<td>Maintain dose and schedule</td>
</tr>
<tr>
<td>3</td>
<td>&lt; 0.9 – 0.7</td>
<td>&lt; 0.4 – 0.3</td>
<td>As above for grades 1 and 2</td>
<td>Hold panitumumab until recovery to ≤ grade 2. If recurs, hold panitumumab until recovery to ≤ grade 2, and then reduce by 1 dose level. A maximum of 2 dose reductions are allowed.</td>
</tr>
<tr>
<td>4</td>
<td>&lt; 0.7</td>
<td>&lt; 0.3</td>
<td>As above for grades 1 and 2</td>
<td>Hold panitumumab until recovery to ≤ grade 2, and then reduce by 1 dose level. A maximum of 2 dose reductions are allowed.</td>
</tr>
</tbody>
</table>

### Keratitis

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Guideline for Management</th>
<th>Panitumumab dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis</td>
<td>1</td>
<td>None</td>
<td>None *</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated.</td>
<td>Hold until recovery to ≤ grade 2** or discontinue at investigator’s discretion. Reduce 1 dose level. A maximum of 2 dose reductions are allowed.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>Discontinue panitumumab</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then resume at the same dose; if dose has been previously held for grade 2 keratitis and grade 2 symptoms recur, hold dose until recovery to ≤ grade 1 and then reduce 1 dose level.

** maximum hold for 21 days; if no recovery to ≤ grade 2 after 21 days, discontinue panitumumab
8.1.12 Other Non-hematologic Toxicity (Arm 2):

Guidelines for dose modification for other non-hematological adverse events are as follows:

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No action</td>
</tr>
<tr>
<td>2</td>
<td>No action</td>
</tr>
<tr>
<td>3</td>
<td>Delay until ≤ grade 2, then resume at one reduced dose level</td>
</tr>
<tr>
<td>4</td>
<td>Discontinue panitumumab permanently</td>
</tr>
</tbody>
</table>

8.1.13 Duration of Therapy (Arm 2):

The first dose of panitumumab will be administered 1 week prior to the commencement of radiotherapy. The subsequent 2 doses will be administered every 3 weeks. A maximum of 3 doses of panitumumab will be administered and with the exception of the first dose, will only be administered the same day as radiotherapy.

If radiotherapy never started, no further panitumumab should be given. If radiotherapy discontinued early, then panitumumab should also be discontinued. If radiotherapy is held and then resumed, panitumumab should be held when radiotherapy is being held. When radiotherapy resumed, panitumumab should fall onto the planned days for panitumumab delivery (i.e. one week prior to and days 15 and 36 of radiotherapy +/- 1 day). It is acceptable if the panitumumab dose does not fall on a Monday or Tuesday. Missed doses will not be made up. For these situations consultation with NCIC CTG and Study Chairs is advised.

8.1.14 Patient Compliance (Arm 2):

All administered doses of panitumumab will be recorded on the case report form.

8.2 Radiation Therapy

Radiation therapy may be delivered with either 3D conformal (3D CRT) or intensity modulated radiation therapy (IMRT). Centers may choose to treat patients with either technique depending on their patterns of practice, expertise, and resources, if they are credentialed for that technique (see section 8.2.2). Radiotherapy technique will be a stratification factor in this study it is therefore mandatory that the treating physician determine the technique (3D CRT or IMRT) to be used prior to the site registering the subject. The selected treatment technique (3D CRT or IMRT) may not be changed after randomization and must be used for the entire course of radiation treatment.
8.2.1  **Glossary for radiotherapy section**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D CRT</td>
<td>Three Dimensional Conformal Radiotherapy Technique</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>CTV70</td>
<td>High Dose Clinical Target Volume (3D CRT and IMRT)</td>
</tr>
<tr>
<td>CTV50</td>
<td>3D CRT Subclinical Dose Clinical Target Volume</td>
</tr>
<tr>
<td>CTV60</td>
<td>3D CRT Intermediate Dose Clinical Target Volume</td>
</tr>
<tr>
<td>CTV56</td>
<td>IMRT Subclinical Dose Clinical Target Volume</td>
</tr>
<tr>
<td>CTV63</td>
<td>IMRT Intermediate Dose Clinical Target Volume</td>
</tr>
<tr>
<td>DRR</td>
<td>Digitally Reconstructed Radiographs</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
</tr>
<tr>
<td>GTV</td>
<td>Gross Tumour Volume</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>modPTV</td>
<td>Modified Planning Target Volumes</td>
</tr>
<tr>
<td>modPTV70</td>
<td>Modified High Dose Planning Target Volume (3D CRT and IMRT)</td>
</tr>
<tr>
<td>modPTV60</td>
<td>3D CRT Modified Intermediate Dose Planning Target Volume</td>
</tr>
<tr>
<td>modPTV63</td>
<td>IMRT Modified Intermediate Dose Planning Target Volume</td>
</tr>
<tr>
<td>modPTV50</td>
<td>3D CRT Modified Subclinical Dose Planning Target Volume</td>
</tr>
<tr>
<td>modPTV56</td>
<td>IMRT Modified Subclinical Dose Planning Target Volume</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>OAR</td>
<td>Organs-at-Risk</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PRV</td>
<td>Planning Organ-at-Risk</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QARC</td>
<td>Quality Assurance Review Centre</td>
</tr>
</tbody>
</table>

8.2.2  **Center Credentialing for delivery of radiotherapy technique:**

All centers participating in the study will require credentialing for the delivery of 3D CRT or IMRT or both prior to local activation. The aim is to demonstrate that an institution posses a minimum standard for use of 3D CRT or IMRT in clinical trials.

Radiation therapy credentialing for this study will be done by the Quality Assurance Review Center (QARC) in Providence, Rhode Island ([www.qarc.org](http://www.qarc.org)). The credentialing process will involve completion of a test case provided by QARC in addition to completing a facility questionnaire. Procedures, information and forms about this credentialing process can be found at [http://www.qarc.org](http://www.qarc.org). Facilities that have been previously credentialled on the head and neck benchmark case with QARC will not have to repeat it. Credentialing will be technique-specific so centres previously credentialled only for 3D CRT that wish to deliver IMRT in the present study will have to perform IMRT specific-credentialing. Likewise centers previously credentialled for IMRT that wish to treat using 3D CRT in the present study will have to perform 3D specific-credentialing. Credentialing is also limited to the planning system used for the benchmark case.
8.2.3 **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 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. In such cases the new plan will be submitted for quality assurance review.

8.2.4 **Equipment**

All patients will be treated on linear accelerators with photon beams of energy 4 MV or greater. Electron beams of energy 6 MeV or greater may be used for components of 3D CRT treatment.

For IMRT, a linear accelerator capable of delivering intensity modulated beams with a multileaf collimator using a step-and-shoot technique or using dynamically moving leaves is required.

3D CRT will be delivered with multiple static photon fields defined with multileaf collimation, and electron fields.

8.2.5 **Treatment Planning**

CT-based treatment planning is mandatory for all patients. Whether 3D CRT or IMRT is utilized, 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 8.2.8). 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 3 mm on a voxel edge.

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

8.2.6 **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.

8.2.7 **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 suprasternal notch inferiorly. CT scan thickness must be ≤ 3 mm through the region that contains the primary target volumes and ≤ 5 mm throughout. The use of intravenous CT contrast agents is permitted when clinically indicated. All specified target volumes and organs-at-risk will be contoured on the planning CT scan. For purposes of contouring, MRI and PET images, if available and clinically indicated, may be fused with the planning CT data set.
8.2.8 Volume Definitions

Nomenclature
All contoured objects will be assigned names according to the descriptions below and/or the appended nomenclature document (see Appendix IX). The volumes listed below will be contoured for all cases whether treatment is delivered with 3D CRT or IMRT.

Gross Tumour Volume (GTV)
The GTV represents grossly involved regions of primary tumour or involved nodes. These regions will be defined based on clinical examination, examination under anesthetic, and CT scan. When indicated and available, MRI and/or positron emission tomography may also be used to define the extent of the GTV. Grossly positive nodes are defined as those greater than 1 cm in axial dimension or any size with evidence of necrosis. Smaller nodes may be determined to be gross disease objects depending on the clinical suspicion.

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 for the various techniques and fractionation schemes are provided in Table 4 and subsequent sections.

CTVs for the Primary Site and Involved Nodes
The primary site GTV and involved nodes will be encompassed by a high dose CTV70 with a minimum margin of 5 mm but should generally not exceed 10 mm in all planes. Exceptions to 5 mm minimum are regions limited by potential barriers to tumour spread as described above. A further expansion of 5 mm on this CTV (1 cm margin around gross disease) will define subclinical dose CTV50 (3D CRT) or CTV56 (IMRT). This subclinical dose CTV will also include neck nodal regions at risk of subclinical disease in relation to primary site defined according to consensus documents [Grégoire 2003, Grégoire 2006]. In cases of uncertainty as to the extent of the primary GTV another CTV delivering an intermediate dose level - CTV60 (3D CRT) or CTV63 (IMRT)- may be used instead of a subclinical dose CTV expansion around this GTV. Necrotic lymph nodes or lymph nodes immediately adjacent to obvious gross nodal disease should be encompassed by CTV70.
**CTVs Intermediate Risk Nodes**

Nodes < 1 cm not thought to harbor gross disease yet thought to be at risk of containing more than subclinical disease may receive an intermediate dose and should be encompassed by CTV60 (3D CRT) or CTV63 (IMRT) representing a 5 mm expansion on these nodes. CTV60 (3D CRT) or CTV63 (IMRT) may include those volumes adjacent to an ill-defined GTV or radiologically visible lymph nodes ≤ 1 cm in axial dimension and < 2 cm in the longitudinal direction. Typically, small suspicious lymph nodes requiring a CTV60 (3D CRT) or CTV63 (IMRT) volume will be located in the lower neck or level 1B so that dose may be kept within tolerance limits to the brachial plexus and mandible.

**CTVs for Neck Regions of Subclinical Disease**

Neck regions thought to harbor nodes at risk of subclinical spread of tumour must be treated. The specific regions treated will depend on the location and extent of the primary site. These must contain a minimum of two nodal levels beyond the primary site. Patients with ipsilateral N2a, N2b or N3 disease must have the contralateral neck treated as well. Patients with N0 or N1 disease may be considered for ipsilateral neck treatment only in the case of well lateralized tonsil primaries. Neck CTVs will be defined according to the anatomic guidelines provided in the consensus documents [Grégoire 2003, Grégoire 2006]. These neck CTVs along with the microscopic CTV at the primary site will comprise the subclinical dose CTV.

**Planning Target Volume (PTV)**

The planning target volumes (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 5 mm expansion of the CTV in all planes. Centres currently using smaller PTV margins of 3-4 mm will be permitted to continue as long as they have their own immobilization data to support this. In instances where the PTV overlaps a critical OAR (Table 1) or its associated PRV, the PTV can be modified to exclude the PRV. The degree of modification will be influenced by a balance between the risks to the OAR and compromise of dose to the CTV. Such instances will be documented for review. Planning target volume doses are defined in Table 4.

**Modified PTVs (modPTV)**

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. PTVs which have been constrained below the skin will be prefixed with mod (e.g. modPTV70). 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. No PTV constraint should be used underneath the bolus.
Organs-at-Risk (OAR)
Critical organs-at-risk 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 structure would be regarded as critical OARs. Other OARs to be contoured include parotid glands, mandible, submandibular glands, glottic larynx, skin 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 1 and dose limits for other OARs in Table 2.

Planning Organ-at-Risk Volume (PRV)
PRVs will represent 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. Critical OARs requiring PRVs include spinal cord, brainstem, optic nerves and chiasm.

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. The limitations of Table 1 apply to all treatment techniques and fractionation schemes. Strict dose limitations are assigned to the critical OARs listed in Table 1 and may not be exceeded under any circumstances. The dose limits of other OARs (Table 2) 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.

Table 1: Critical OAR dose limits:

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Criterion</th>
<th>Dose limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>maximum point dose</td>
<td>54 Gy</td>
</tr>
<tr>
<td></td>
<td>maximum dose to 0.1 cc</td>
<td>50 Gy</td>
</tr>
<tr>
<td>PRV Brainstem</td>
<td>maximum dose to 0.1 cc</td>
<td>60 Gy</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>maximum point dose</td>
<td>48 Gy</td>
</tr>
<tr>
<td></td>
<td>maximum dose to 0.1 cc</td>
<td>45 Gy</td>
</tr>
<tr>
<td>PRV Spinal Cord</td>
<td>maximum dose to 0.1 cc</td>
<td>52 Gy</td>
</tr>
<tr>
<td>Brain</td>
<td>maximum dose to 0.1 cc</td>
<td>70 Gy</td>
</tr>
<tr>
<td>Optic Structures</td>
<td>maximum point dose</td>
<td>45 Gy</td>
</tr>
<tr>
<td>(Chiasm, globes and optic nerves)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2: Other OAR dose limits:

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Criterion</th>
<th>Dose limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid Glands</td>
<td>Mean dose to at least one parotid</td>
<td>&lt; 26 Gy</td>
</tr>
<tr>
<td></td>
<td>Median dose to at least one parotid</td>
<td>&lt; 30 Gy</td>
</tr>
<tr>
<td></td>
<td>At least 20 cc of combined volume both parotids</td>
<td>&lt; 20 Gy</td>
</tr>
<tr>
<td>Mandible</td>
<td>Maximum dose to 0.1 cc</td>
<td>73.5 Gy within overlapping PTV 70 and 70 Gy outside of PTV70</td>
</tr>
<tr>
<td>Glottic Larynx</td>
<td>Maximum dose to 0.1 cc</td>
<td>50 Gy</td>
</tr>
<tr>
<td>Skin and unspecified tissue outside defined OARs/PRVs and PTVs</td>
<td>Max dose to more than 1% or 1 cc</td>
<td>77 Gy</td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>Maximum point dose</td>
<td>60 Gy 3D CRT, 63 Gy IMRT</td>
</tr>
<tr>
<td>Normal midline structures and mucosal surfaces not included in the PTVs</td>
<td>Maximum point dose</td>
<td>60 Gy</td>
</tr>
<tr>
<td>Unspecified normal tissues (external to all PTVs and excluding OARs)</td>
<td>Max dose to 1 cc</td>
<td>77 Gy</td>
</tr>
</tbody>
</table>

### 8.2.10 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 8.2.8) and spare organs-at-risk. Beam arrangements are discretionary and defined to achieve study dosimetric goal specifications.

**Beam modifiers**
Field delineation will be achieved with the use of multileaf collimation. When required, missing tissue compensation may be achieved with either physical methods with wedges, custom-made compensators or beam segmentation to achieve study dose specifications and constraints. Posterior neck volumes may be treated with electrons to achieve spinal cord dose constraints. Bolus may be used as needed to achieve adequate dose to superficial target volumes.

**Beam segmentation**
Beam segmentation is at the discretion of the planner, subject to institutional practice.

**Field junctioning**
Junctions between upper and lower neck fields must be asymmetrically matched (i.e. a nondivergent match) and should not be placed over gross disease. Spinal cord must be shielded throughout treatment in regions of such junctions. Anterior photon fields and posterior neck electron fields will be junctioned at the field edge and must contain an overlap of 5 mm in regions of junction over gross nodal disease. This will be achieved anterior to the posterior edge of the photon field placed no further posterior than midvertebral body defined in the sagittal plane.
Patients with oropharyngeal tumours undergoing IMRT may have the low neck treated with nonIMRT techniques (an AP/PA opposed pair) junctioned to the IMRT treated volume above as long as there is no gross nodal disease in the junction or low neck. Midline shielding should be used in the low neck fields to ensure the spinal cord is shielded at the level of the junction. In these cases 50 Gy in 25 fractions over the first five weeks of treatment will be delivered to the uninvolved low neck.

8.2.11 Dose Reporting

Dose is to be prescribed to an isodose line that encompasses the respective PTV and satisfies the dose heterogeneity criteria in Section 8.2.12.

In the case of parallel opposed photon fields, dose will be prescribed to midplane in the central axis (ICRU 50). Posterior neck electrons will be prescribed to an isodose no less than 95% with the energy chosen sufficient to cover the PTV being treated.

8.2.12 Dose Heterogeneity

Dose heterogeneity limits to modified PTVs are illustrated in Table 3. Plan normalization should provide coverage of 95% of the modPTV70 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 modPTV70, modPTV50 (3D CRT)/modPTV56 (IMRT) and modPTV60 (3D CRT)/modPTV63 (IMRT) 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 5).

Table 3: Planning target volume dose limits:

<table>
<thead>
<tr>
<th>Percent Volume</th>
<th>modPTV70 (% of 70Gy)</th>
<th>modPTV50(3D CRT)/modPTV56 (IMRT) (% of 56Gy IMRT or 50Gy 3D CRT)</th>
<th>modPTV60 (3D CRT)/modPTV63 (IMRT) (% of 63Gy IMRT or 60Gy 3D CRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>&lt; 100%</td>
<td>&lt; 100%</td>
<td>&lt; 100%</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>&lt; 93%</td>
<td>&lt; 93%</td>
<td>&lt; 93%</td>
</tr>
<tr>
<td>0%</td>
<td>&gt; 115%</td>
<td>&gt; 125%*</td>
<td>&gt; 120%*</td>
</tr>
<tr>
<td>&lt; 20%</td>
<td>&gt; 110%</td>
<td>&gt; 110%*</td>
<td>&gt; 110%*</td>
</tr>
<tr>
<td>Mean dose</td>
<td>≤ 105%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note 1: These limits are applicable to portions of modPTV56 and modPTV63 which (i) do not overlap higher-dose PTVs and (ii) are not adjacent to higher-dose PTVs

8.2.13 Dose Fractionation Schemes

Patients will be randomized to receive either (1) standard radiation therapy, once-daily radiation therapy to a total dose of 70 Gy in 35 fractions over 7 weeks (with concurrent cisplatin) or (2) accelerated radiation therapy delivered as 70 Gy in 35 fractions over 6 weeks (with concurrent panitumumab).
Clinical target volumes are defined in section 8.2.8; for the purposes of fractionation, they are defined as: CTV70, consisting of primary site gross tumour volume and clinically or radiographically involved nodes only; CTV50 (3D CRT)/CTV56 (IMRT), encompassing both gross and subclinical volumes of disease; and CTV60 (3D CRT)/CTV63 (IMRT), regions thought to harbour gross nodal disease that is not bulky yet thought to be at risk of containing more than subclinical disease. Prescription doses to PTVs associated with these CTVs are presented in Table 4.

Table 4: Prescription Dose to PTV by Regime/Technique:

<table>
<thead>
<tr>
<th>Volume</th>
<th>3D CRT Dose Specifications: Standard Radiation</th>
<th>3D CRT Dose Specifications: Accelerated Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prescription Dose (Gy) to PTV by Regime/Number of fractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>Standard</td>
</tr>
<tr>
<td>modPTV70</td>
<td>70 Gy/35</td>
<td>70 Gy/35</td>
</tr>
<tr>
<td>modPTV50(3D CRT)/modPTV56 (IMRT)</td>
<td>50 Gy/25</td>
<td>56 Gy/35</td>
</tr>
<tr>
<td>modPTV60 (3D CRT)/modPTV63 (IMRT)</td>
<td>60 Gy/30</td>
<td>63 Gy/35</td>
</tr>
</tbody>
</table>

3D CRT Dose Specifications: Standard Radiation
modPTV50 will receive 2 Gy per fraction once daily, five fractions per week to 50 Gy in 25 fractions over 5 weeks for uninterrupted treatment. For interrupted treatment please see section 8.2.15.

Following the treatment of modPTV50, modPTV70 will receive, subsequent to this treatment, 20 Gy over 2 weeks (2 Gy per fraction, five fractions per week). Thus, gross primary and nodal disease (modPTV70) will have received 70 Gy in 35 fractions over 7 weeks, and areas of subclinical disease (modPTV50) 50 Gy in 25 fractions over 5 weeks.

If required following the treatment of modPTV50, modPTV60 will receive an additional 10 Gy in 5 fractions to a total intermediate dose of 60 Gy in 30 fractions over 6 weeks.

3D CRT Dose Specifications: Accelerated Radiation
modPTV50 will receive 2.0 Gy per fraction once daily, five fractions per week to 50 Gy in 25 fractions over 5 weeks for uninterrupted treatment (For interrupted treatment please see section 8.2.15).

modPTV70 will receive a second daily fraction of 2.0 Gy once weekly during weeks 2 to 5. This boost volume radiation should commence during the second week of treatment as a sixth fraction per week. This 6th fraction can either be delivered on a Saturday or as a second fraction on one of the weekdays with a strict minimum 6 hour interfraction interval.

Subsequent to this, during the 6th week, treatment will be delivered to modPTV70 only for 6 further fractions. This can be accomplished by either delivering a second treatment on one of the weekdays or treating on the final Saturday. Thus gross disease (modPTV70) will have received 70 Gy in 35 fractions over 6 weeks, and areas of subclinical disease (modPTV50) 50 Gy in 25 fractions over 5 weeks. See Figure 2 for a schematic representation of the accelerated regimes.

modPTV60 may receive an intermediate dose of 60 Gy in 30 fractions over 5 weeks. This will be achieved by including these regions in modPTV70 to generate a modPTV60, to be treated with 2 Gy per fraction as the sixth fraction on weeks two through five, and the first fraction of the final week. A volume reduction to gross disease only (modPTV70) for the final 5 fractions will bring modPTV70 to 70 Gy.
**IMRT Dose Specifications: Standard Radiation**

A single phase IMRT plan will be given delivering 35 fractions, five fractions per week over 7 weeks.

- modPTV70 will receive 2 Gy per fraction in five fractions a week to 70 Gy in 35 fractions over 7 weeks.
- modPTV56 will receive 1.6 Gy per fraction in five fractions per week to 56 Gy in 35 fractions over 7 weeks.
- modPTV63 will receive 1.8 Gy per fraction in five fractions per week to 63 Gy in 35 fractions over 7 weeks.

**IMRT Dose Specifications: Accelerated Radiation**

A single phase IMRT plan will be given delivering 35 fractions over 6 weeks. This is achieved by adding a sixth fraction per week for the final 5 weeks of the six week plan. The 6th fraction can either be delivered on a Saturday or as a second fraction on one of the weekdays with a strict minimum 6 hour interfraction interval.

- modPTV70 will receive 2 Gy per fraction to 70 Gy in 35 fractions over 6 weeks.
- modPTV56 will receive 1.6 Gy per fraction to 56 Gy in 35 fractions over 6 weeks.
- modPTV63 will receive 1.8 Gy per fraction in five fractions per week to 63 Gy in 35 fractions over 6 weeks.

Graphical representation of the accelerated fractionation schemes are presented in Figure 1:

<table>
<thead>
<tr>
<th>3DCRT</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
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<tbody>
<tr>
<td></td>
<td><img src="image1" alt="3DCRT Week 1" /></td>
<td><img src="image2" alt="3DCRT Week 2" /></td>
<td><img src="image3" alt="3DCRT Week 3" /></td>
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<tr>
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</table>

**IMRT**

<table>
<thead>
<tr>
<th>IMRT</th>
<th>Week 1</th>
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<th>Week 3</th>
<th>Week 4</th>
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</tr>
</thead>
<tbody>
<tr>
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<td><img src="image39" alt="IMRT Week 3" /></td>
<td><img src="image40" alt="IMRT Week 4" /></td>
<td><img src="image41" alt="IMRT Week 5" /></td>
<td><img src="image42" alt="IMRT Week 6" /></td>
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<tr>
<td><img src="image43" alt="IMRT Week 1" /></td>
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<td><img src="image46" alt="IMRT Week 4" /></td>
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<td><img src="image72" alt="IMRT Week 6" /></td>
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</tr>
</tbody>
</table>

Figure 1: Accelerated radiation schemes illustrating timing of bid treatments. If preferred, centers may give a 6th weekly treatment on the Saturday in lieu of this second daily treatment. modPTV70 treatment illustrated as open bars; modPTV60, when used, is indicated by an asterisk. For IMRT, modPTV70, modPTV56 and modPTV63 (if needed) are treated simultaneously with an identical plan for all fractions.
8.2.14 **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. Verification imaging will be done with portal images of all treated fields for 3D CRT or orthogonal fields localizing the isocenter placement for IMRT plans. Alternatively, kV or MV conebeam CT can be used and compared to the planning CT data to verify the patient positioning. Image matching will be based on alignment of regional boney landmarks with offsets of greater than 3 mm requiring patient repositioning and imaging prior to commencement of treatment.

Verification imaging will be done at least weekly commencing on the first day of treatment. More frequent online verification imaging is recommended if possible within the participating treatment centre. This may involve daily image matching of treatment fields, orthogonal portal or kV images with corresponding DRRs or planning CT data volumetrically matched with data acquired by on-board volumetric imaging (cone beam CT scan).

8.2.15 **Corrections For Radiotherapy Treatment Interruptions**

Treatment interruptions of a single day anytime during a standard fractionation course or during the once-daily phase of an accelerated fractionation course 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 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 two such compensatory treatments will be permitted during the course of treatment. In anticipation of long weekends falling during the final 5 weeks of the accelerated course centers may give a second daily treatment once during the first week of treatment. Interruptions not compensated for will be recorded and accounted for in the determination of protocol compliance according to section 8.2.16.

8.2.16 **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 8.2.15 for a maximum of 2 treatment day interruptions.

Any uncompensated treatment break(s) for any 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 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 modPTVs are described relative to dose objectives in Table 5. 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 been deemed as likely to have an adverse impact on patient outcome at the time of central review of the volumes and distributions. Deviations identified at the time of initial rapid central review will be promptly communicated to the managing Radiation Oncologist in order that corrective strategies can be considered.

The reviewers recognize achieving 100% of the dose to 95% of modPTVs will be challenging for cases in which the modPTVs are in close approximation to a critical OAR and/or skin surface however these objectives would be expected to be achieved otherwise. Similarly, achieving doses to modPTVs 50, 56, 60 or 63 below the maximum dose objectives defined in table 3 is not likely in regions of close proximity to modPTV70s. However, such dose limitations would be expected to be achieved in regions distant from modPTV70s.

If the reviewers determine that the volumes have been drawn inappropriately, deviation assessment will be based on the corrected volumes and categorized as minor or major by the reviewers based on an assessment of the potential impact on patient outcome.

Table 5. Major and minor dose delivery deviations for PTVs dose objectives.

<table>
<thead>
<tr>
<th>Percent Volume</th>
<th>modPTV70</th>
<th>modPTV50/ modPTV56</th>
<th>modPTV60, modPTV63</th>
<th>Minor deviation (%) volume</th>
<th>Major deviation (%) volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol (%) of 70Gy</td>
<td>(% of 56Gy IMRT or 50Gy 3D CRT)</td>
<td>(% of 63Gy IMRT or 60Gy 3D CRT)</td>
<td>Minor deviation (%) volume</td>
<td>Major deviation (%) volume</td>
<td></td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>&lt; 100%</td>
<td>&lt; 100%</td>
<td>&lt; 100%</td>
<td>≥ 5%</td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>&lt; 93%</td>
<td>&lt; 93%</td>
<td>&lt; 93%</td>
<td>1-3%</td>
<td>&gt; 3%</td>
</tr>
<tr>
<td>0%</td>
<td>&gt; 115%</td>
<td>See note 1</td>
<td>See note 1</td>
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<tr>
<td>&lt; 20%</td>
<td>&gt; 110%</td>
<td>See note 2</td>
<td>See note 2</td>
<td>See note 2</td>
<td>See note 2</td>
</tr>
<tr>
<td>Mean dose</td>
<td>≤ 105%</td>
<td>105% - 107%</td>
<td>&gt; 107% of mean</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note 1 Where modPTVs of different doses overlap, the dose limits for the higher-dose PTV will be applied. Where a portion of a lower-dose modPTV is adjacent to (e.g., within 10 mm) a higher-dose modPTV, the dose in the lower-dose modPTV should not exceed 110% of the dose to the higher-dose PTV.

Note 2 Regions of the lower dose modPTVs distant from higher dose modPTVs are not to exceed the limits of Table 3.

Non compliance with the dose limitations assigned to the critical OARs listed in Table 1 always will be considered as a major deviation. Non compliance with the dose limits of other OARs (Table 2) will be analyzed case per case by the reviewers and the study chair to define if they should be considered as deviations or not. Cases for which the doses to OARs exceed the limits in table 2 due to the close proximity of PTVs that cannot be underdosed will not be considered deviations. For example exceeding dose limits to parotid glands is acceptable when needed to achieve acceptable dose to an adjacent PTV.
**Treatment Regime/Technique**

All these deviations will be considered as major:

- Delivering a radiotherapy technique (3D CRT or IMRT) not previously credentialed for that center.
- Delivering a radiotherapy technique different to which was intended for purposes of stratification.
- Changing the radiotherapy technique during treatment.
- Changing the assigned fractioned scheme (standard or accelerated).

All other radiotherapy treatment protocol non adherences will be analyzed case per case by the reviewers and the study chair considering the influence over the patient clinical outcome and over the treatment results analysis.

8.2.17 **Central Radiotherapy Quality Assurance Reviews**

Radiotherapy quality assurance reviews will be conducted centrally through the Quality Assurance Review Center (QARC) based in Providence R.I. Please refer to Appendix X for a description of the steps involved in this central radiotherapy quality assurance program.

The radiotherapy quality assurance documentation that has to be submitted could be found at Appendix XI. Data required for plan documentation and quality assurance will be submitted according to QARC guidelines (Appendix XII).

Real time review and final review will be performed for every case.

**Rapid Case Review:**

The treatment plan and supporting documentation (Appendix XI) will be submitted within one week of starting treatment. Feedback from the Rapid Review will be returned to the treating center which will implement corrective action if applicable and respond to QARC recommendations. Planning for the entire course of treatment should be completed up front if possible. If planning for PTV70 or PTV60 is deferred (in 3D CRT), these phases and a composite plan must be submitted in the fourth week of treatment for review.

**Final Review:**

The required documentation (Appendix XI) should be send from treatment centre to QARC within one month of treatment completion. A written report of the Final Review will be created by QARC.

8.2.18 **Concurrent Therapy**

Details of systemic agent administration are outlined in section 8.1.

8.3 **Surgical Treatment Plan Of The Neck For Patients With Nodal Positive Disease At Baseline**

Eight weeks following completion of radiotherapy with cisplatin or panitumumab, patients will have an evaluation of their primary tumour and neck (Section 9.2).

The decision to undertake a neck dissection will be based on the pre-treatment nodal status, the clinical and radiographic examinations at 8 weeks post radiotherapy and institutional policies regarding planned neck dissections.

Planned neck dissection should be completed \( \leq 15 \) weeks following completion of radiotherapy.

For those patients with complete response (CR) (see Section 10.2.1) at the primary site, the following is recommended:
Nodal disease* at Baseline | Nodal disease* at week 8 | Recommendation
--- | --- | ---
N1 | No persistent disease | Follow as per protocol
N2/N3 | No persistent disease | Neck dissection or follow as per protocol
Any | Persistent disease ≤ 2 cm | Neck dissection or follow as per protocol
Any | Persistent disease > 2 cm with evidence of tumour regression | Follow with monthly imaging until 8 months post radiotherapy and then as per protocol. Neck dissection at any time when regression ceases
Any | Persistent disease > 2 cm with no regression compared to baseline | Neck dissection

*on clinical and/or radiographic examinations

For patients undergoing planned bilateral neck dissections staging between lymphadenectomies should be performed.

Regardless of the policy adopted for the management of the neck, any surgical intervention requires that persistent nodal disease be deemed operable by the treating surgeon.

8.4 Concomitant Therapy

8.4.1 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.

8.4.2 Not permitted

Erythropoietic growth factors, pilocarpine, amifostine, other anti-cancer treatment, including cytotoxic agents, biological response modifiers, immunotherapy, anti-cancer hormone therapy, and other investigational drug therapy.

Granulocytic growth factors (e.g. filgrastim) should not be used concurrently during radiation therapy unless radiation therapy has been stopped to allow for recovery of neutropenia and fever.
9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

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

9.1 Evaluation During Protocol Treatment

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical Exam including*:</td>
<td>weekly</td>
</tr>
<tr>
<td>• Weight</td>
<td></td>
</tr>
<tr>
<td>• ECOG PS</td>
<td></td>
</tr>
<tr>
<td>• Mucosal clinical assessment</td>
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</tr>
<tr>
<td>Hematology</td>
<td>Weekly**</td>
</tr>
<tr>
<td>• CBC</td>
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</tr>
<tr>
<td>• Differential</td>
<td></td>
</tr>
<tr>
<td>• Platelets</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Weekly***</td>
</tr>
<tr>
<td>• AST or ALT, bilirubin</td>
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</tr>
<tr>
<td>• Mg, Ca, Na, K, Cl, albumin</td>
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</tr>
<tr>
<td>• Serum creatinine and calculated</td>
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<tr>
<td>creatinine clearance</td>
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</tr>
<tr>
<td>Adverse Events*</td>
<td>weekly</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>last week of radiotherapy ***</td>
</tr>
<tr>
<td>• FACT-H&amp;N **</td>
<td></td>
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<tr>
<td>Swallowing Related Quality of Life</td>
<td>last week of radiotherapy ***</td>
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<tr>
<td>• MDADI</td>
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<td>• SWAL-QOL</td>
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<td>Swallowing Function</td>
<td>last week of radiotherapy</td>
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<tr>
<td>• FOIS</td>
<td></td>
</tr>
<tr>
<td>Economics</td>
<td>last week of radiotherapy +</td>
</tr>
<tr>
<td>• Lost Productivity Questionnaire</td>
<td></td>
</tr>
<tr>
<td>• Resource Utilization Assessment **</td>
<td></td>
</tr>
</tbody>
</table>

* Full staging investigations required if failure documented during treatment.
** Weeks when cisplatin or panitumumab is given tests should be on treatment day or within 72 hours prior.
*** Weeks when cisplatin or panitumumab is given tests should be on treatment day or within 72 hours prior. Biochemistry tests must be within one week of the start of treatment. Repeat biochemistry tests if the pre-randomization tests are done more than one week prior to treatment day 1. Eligibility criteria (as per 5.1.5) must be fulfilled.
* Adverse events will be recorded and graded according to the CTCAE v 3.0.
** The FACT-H&N questionnaire should be completed before the MDADI and the SWAL-QOL.
*** Quality of Life questionnaires are not required in patients not completing the radiotherapy treatment.
+ If radiotherapy terminated early complete on last date of radiotherapy treatment or as soon as possible after completion.
+ To cover the time period from randomization date to the off protocol treatment date.
9.2 Evaluation After Protocol Treatment

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing (from the end of protocol therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and Physical Exam including:</strong></td>
<td></td>
</tr>
<tr>
<td>• Weight</td>
<td>4 weeks, 8 weeks, 4 months, 6 months, then q 3 monthly until 24 months then q 4 monthly until 36 months then q 6 months until 60 months then as clinically indicated.</td>
</tr>
<tr>
<td>• ECOG PS</td>
<td></td>
</tr>
<tr>
<td>• Mucosal clinical assessment</td>
<td></td>
</tr>
<tr>
<td>• Direct or indirect visualization of tumour and surrounding area</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>• CBC</td>
<td>4 weeks, 8 weeks then as clinically indicated</td>
</tr>
<tr>
<td>• Differential</td>
<td></td>
</tr>
<tr>
<td>• Platelets</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>• AST or ALT, bilirubin</td>
<td>4 weeks, 8 weeks, 4 months then as clinically indicated</td>
</tr>
<tr>
<td>• Mg(^+), Ca, Na, K, Cl</td>
<td></td>
</tr>
<tr>
<td>• Serum creatinine and calculated creatinine clearance</td>
<td></td>
</tr>
<tr>
<td><strong>Correlative Science Studies</strong>*</td>
<td></td>
</tr>
<tr>
<td>• Serum, cellular component and plasma</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
</tr>
<tr>
<td>• CT or MRI of head and neck</td>
<td>8 weeks, 6 months then q 6 monthly until 36 months then as clinically indicated</td>
</tr>
<tr>
<td>• CT chest or chest x ray</td>
<td></td>
</tr>
<tr>
<td>• Other radiology exams as clinically indicated</td>
<td>6 months, 12 months then annually until 36 months then as clinically indicated</td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
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</tr>
<tr>
<td>• Audiogram</td>
<td>month 6</td>
</tr>
<tr>
<td>• Biopsy ***</td>
<td>See note below ***</td>
</tr>
<tr>
<td>*<em>Adverse Events</em></td>
<td>4 weeks, 8 weeks, 4 months, 6 months, then q 3 monthly until 24 months then q 4 monthly until 36 months then q 6 months until 60 months</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>8 weeks, 4 months , 6 months, 12 months, 24 months and 36 months</td>
</tr>
<tr>
<td><strong>Swallowing Related Quality of Life</strong></td>
<td>4 months, 6 months, and 12 months</td>
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<td><strong>Swallowing Function</strong></td>
<td>12 months</td>
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<tr>
<td>• FOIS</td>
<td>4 months, 6 months, and 12 months</td>
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<tr>
<td>• MBSImP***</td>
<td>4 months and 12 months</td>
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<tr>
<td>• Videofluoroscopy***</td>
<td>4 months and 12 months</td>
</tr>
<tr>
<td><strong>Economics</strong></td>
<td>8 weeks, 4 months, 6 months, 12 months, 24 months and 36 months</td>
</tr>
<tr>
<td><strong>Phone Contact Follow-ups</strong></td>
<td>Annual contact by phone or equivalent means to verify patient status, disease status and adverse events related to protocol treatment.</td>
</tr>
</tbody>
</table>

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footnotes on next page ...
**9.3 Evaluation Post Recurrence or Local, Regional or Distant Progression**

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing (from the date of first failure)</th>
</tr>
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<tbody>
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<td>q 6 monthly</td>
</tr>
<tr>
<td>• ECOG PS</td>
<td></td>
</tr>
<tr>
<td>• Direct or indirect visualization of tumour and surrounding area</td>
<td>at discretion of the investigator</td>
</tr>
<tr>
<td>Adverse Events*</td>
<td>q 6 monthly</td>
</tr>
<tr>
<td>Radiology</td>
<td>at discretion of the investigator</td>
</tr>
<tr>
<td>* treatment related only</td>
<td></td>
</tr>
</tbody>
</table>
10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS:

10.1 Definitions

10.1.1 Evaluable for toxicity:

All patients will be evaluable for toxicity from the time of their first dose of protocol therapy consisting of cisplatin or panitumumab and/or radiation.

10.1.2 Evaluable for progression free survival:

All patients will be evaluable for assessment of progression free survival from the time of randomization. Subjects not meeting the criteria for failure (see Section 10.3) by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

10.1.3 Evaluable for overall survival:

All patients will be evaluable for assessment of overall survival from the time of randomization. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

10.1.4 Evaluable for quality of life and swallowing related quality of life assessment.

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

10.1.5 Evaluable for swallowing function assessment.

All patients for whom the FOIS scale was completed are evaluable for swallowing function.

10.1.6 Evaluable for Swallowing Impairment Sub-study:

All patients who had a videofluoroscopy and for whom a MBSImP score was completed are evaluable in the Swallowing Impairment Sub-study.

10.2 Response and Evaluation Endpoints

As progression free survival is the primary endpoint in this study, it is vital that it be adequately and precisely documented.

10.2.1 Evidence of Complete Response:

Primary Site: A patient will be considered to have complete response if there is no suspicion of persistent disease either on clinical or radiographic (CT scan or MRI) examinations. (see 10.2.2). Directed biopsies at the site of the index lesions are not required in the absence of suspicion for persistent disease or relapse. Any biopsies performed must be negative for invasive squamous cell carcinoma.

Regional Lymph Nodes: A patient will be considered to have complete response if there is no suspicion of persistent disease (see 10.2.2) either on clinical or radiographic (CT scan or MRI) examinations.
10.2.2 Persistent Disease:

Primary Tumour Site: Defined as palpable or radiographic (CT scan or MRI) evidence of tumour after radiation with cisplatin or panitumumab 8 weeks after completion of radiotherapy. Biopsy for confirmation of persistent disease should be performed when clinically indicated, at week 8 or at a later visit.

Regional Lymph Nodes: For previously involved nodes at baseline persistence of disease is defined as lymph node size > 1 cm in greatest axial dimension, evidence of tumour necrosis or extracapsular spread on clinical examination or radiographic imaging (CT scan or MRI at week 8 after protocol treatment).

10.2.3 Local Recurrence or Progression:

Local recurrence is defined as reappearance of a tumour within the initial or immediate adjoining anatomical regions after complete response on clinical or radiographic (CT scan or MRI) examinations. Local progression is defined as an estimated increase in the size of a tumour (the maximal dimension) of greater than 25%, taking as reference the smallest value of all previous maximal dimensions or appearance of new areas of malignant disease. Confirmation of local recurrence or progression by biopsy is strongly recommended.

10.2.4 Regional Lymph Node Recurrence or Progression:

Regional recurrence is defined as reappearance of tumour in the neck on clinical or radiographic (CT scan or MRI) examinations after complete response in the regional lymph nodes.

Regional progression is defined as any of the following:

a) An estimated increase in the size of any lymph node (the maximal dimension) of greater than 25% and the lymph node is greater than 1 cm, taking as reference the smallest value of all previous maximal dimensions.

b) Appearance of new areas of malignant disease.

Confirmation of regional recurrence or progression by biopsy is strongly recommended.

10.2.5 Distant Metastasis:

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.
10.3 **Primary Endpoint:**

Primary endpoint is progression free survival which is defined by the occurrence of the following events in the table below.

<table>
<thead>
<tr>
<th>First Event</th>
<th>Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Censored</td>
</tr>
<tr>
<td>Local-regional progression or recurrence</td>
<td>Failure</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Failure</td>
</tr>
<tr>
<td>Non-protocol RT, chemotherapy, or biologic therapy without documentation of the site of failure</td>
<td>Failure</td>
</tr>
<tr>
<td>Surgery of primary site with tumour present/unknown</td>
<td>Failure</td>
</tr>
<tr>
<td>Neck dissection with tumour present/unknown, &gt; 15 weeks from end of RT</td>
<td>Failure</td>
</tr>
<tr>
<td>Death due to study cancer or from unknown causes</td>
<td>Failure</td>
</tr>
<tr>
<td>Death due to any other reason</td>
<td>Failure</td>
</tr>
</tbody>
</table>

*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 ≤ 15 weeks from end of RT;
- Neck dissection > 15 weeks from end of RT with no tumour on pathology specimen.

10.3.1 **Capture of Failures and Work-up at Detection of First Failure:**

Only the first event experienced will determine a patient’s failure status. However, in order to fully capture the patterns of failure in this study population, a detailed work-up at the time of the first failure is required, and sites of failures should be documented in the CRF.

For instance, if a patient first develops local, or regional, or local-regional progression, then a work-up for distant metastasis will be performed at the same time. If the distant metastatic work-up reveals the presence of distant metastasis, then all sites of failure will be documented, even though the time of the first detected failure event will be used to determine the progression free survival. Similarly, if a patient is first found to have distant metastasis, then a work-up for local and regional progression should be performed at the same time. If the local-regional work-up does not reveal progression at the same time, then this patient is considered to only have distant failure.
11.0 SERIOUS ADVERSE EVENT REPORTING

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 3.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

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 NCIC CTG SAE form. The term ‘reportable SAE’ is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to NCIC CTG.

11.1 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 11.2 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 investigator brochure.
- 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 judgment 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.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported as follows:

Within 24 hours: FAX preliminary Serious Adverse Event Form to:

Wendy Parulekar MD
or Alexander Montenegro, Study Coordinator
NCIC Clinical Trials Group
Fax: 613-533-2941

Within 14 days: Mail Serious Adverse Event form (signed by the investigator and updated as much as possible)
11.3 Reporting Malignancies or Myeloid Dysplasia

Malignancies or myeloid dysplasia that are unexpected AND related to protocol treatment in the opinion of the investigator must be reported as Serious Adverse Events as described in Section 11.0 and 11.2, within 15 working days of when diagnosis is known to the investigator. Other malignancies occurring or recurring during the trial, which are considered unrelated or expected should only be reported on the case report form.

11.4 NCIC CTG Responsibility for Reporting Serious Adverse Events to Health Canada (Office of Clinical Trials)

The NCIC CTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) 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 can not be ruled out).

11.5 NCIC CTG Reporting Responsibility to Amgen

Amgen will be notified of all regulatory reportable serious adverse events within 1 Canadian working day of submission to Health Canada. SAEs will be faxed to Amgen Canada for forwarding to Amgen Thousand Oaks safety group.

Spring Meeting reports including all adverse event data will also be provided to Amgen.

11.6 Amgen Reporting Responsibilities

Amgen will provide to NCIC CTG Quarterly Safety Update Reports and other safety information deemed relevant to the conduct of HN.6.

11.7 Reporting Safety Reports to Local Research Ethics Boards

NCIC CTG will notify all Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials via a Quarterly Safety Update Report) that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Drug Brochure. The date of REB Submission for SAEs and SUs will need to be entered into the NCIC CTG trial HN.6 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:
- this letter must be either printed on institutional letterhead or contain the centre identification/REB name;
- the date of REB submission must be provided;
- this form must be signed by one of the approved participants (according to the participants list) for this trial.

The submission of these events to your ethics board should be done as soon as possible. The suggested timeframe is 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.
12.0  PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Tumour progression or disease recurrence as defined in Section 10.0.
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. 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.

12.2 Therapy After Protocol Treatment is Stopped

Therapy will be administered at the discretion of the investigator.

12.3 Follow-up Off Protocol Treatment

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.
13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

There will be no central radiology review for this study. Radiology films documenting sites of disease at baseline and progression will be stored in a central archive located at the QARC facilities. These will be archived for future research purposes. See Appendix XIV for submission guidelines.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Tissue and Blood Collection

The collection of a representative specimen of the diagnostic tumour tissue and whole blood, serum, cellular component and plasma samples are an important and optional part of this trial. Blocks and samples will be carefully banked as part of the NCIC CTG Tissue/Tumour Bank at Queen’s University in Kingston, Ontario. These will optimize the amount of tissue and whole blood, serum, cellular component and plasma samples available to investigators. If, at any time, the submitting hospital requires the block and samples to be returned for medical or legal concerns, it will be returned by courier on request.

Tumour samples from each patient will be collected according to the following hierarchy list:
1. One tumor block.
2. If it is the policy of the submitting institution not to release blocks, NCIC CTG Tissue/Tumour Bank will ask the institution permission to create tissue microarrays from the material. This would involve NCIC CTG Tissue/Tumour Bank taking one to four 0.6mm cores from areas of the block that contain tumour prior to returning the material to the centre. Every effort will be made to ensure that the diagnostic value of any submitted block is maintained.
3. 20 unstained slides (4 microns) (if < 20 slides available, please send maximum).
4. If fine needle aspirate is the only diagnostic specimen available, please send cell block.

The tissue and serum, cellular component and plasma samples may be used by researchers now or in the future to better understand the nature of head and neck cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue and samples will be by a patient study number assigned at the time of randomization 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.

Details about the cellular component sample preparation will be provided in the *Serum, Plasma and Cellular Component Collection Manual*.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen’s Department of Pathology to pathology departments for a representative tumour sample.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.
All patients on whom a diagnostic tumour block and whole blood, serum, cellular component and plasma samples are collected will be aware of this retrieval and will have given their consent.

All patients consenting to tumour sample and whole blood, serum, cellular component and plasma samples will also complete a correlative science questionnaire, with their consent.

13.4 Central Radiotherapy Review:

Central radiotherapy review will be required for all patients randomized onto the study. See section 8.2.17 for details.

13.5 Central Swallowing Impairment Sub-study Interpretation

Results will be captured digitally and sent via password protected discs to Dr. Martino’s Swallowing Lab at the University of Toronto. Interpretation of results will be made by two blinded speech-language pathologists using the MBSImP tool (Appendix XIII).
14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this study is to compare the progression free survival of patients with locally advanced squamous cell carcinoma of the head and neck randomized to receive standard fractionation radiotherapy with high dose cisplatin (Arm 1) or accelerated fractionation radiotherapy with panitumumab (Arm 2). Secondary objectives include comparisons of overall survival, local progression free survival, regional progression free survival, distant metastasis, adverse events, quality of life, swallowing related quality of life, functional swallowing outcome and economic and health utilization resources between the two treatment arms. In addition, predictive and prognostic biomarkers in this patient population will be identified. Eligible patients will be randomized in a 1:1 ratio to one of the two treatment arms using the minimization method and the following stratification factors: T categorization: 1-3 versus 4; nodal stage: N0/N1 versus N2 versus N3, radiotherapy delivery modality (3D CRT versus IMRT) and anatomic location: hypopharyngeal versus oral cavity versus oropharynx versus larynx. Participation in the Swallowing Impairment Sub-study, this will be added as a stratification factor for the purpose of achieving balance in participation between the two arms.

14.2 Endpoints and Analysis

Progression free survival (PFS), the primary endpoint of this study, is defined as the time from randomization to the time when a failure defined in 10.3 is observed. If a patient has not developed a failure at the time of final analysis, PFS will be censored on the date of the last disease assessment. The PFS experience of patients in both treatment groups will be described by the Kaplan-Meier method. All patients will be included in the analyses in the arms to which they are randomized regardless of whether they receive the assigned treatment (intention-to-treat). The following stepwise test (S-NI) procedure [Wang 2001] which controls the overall type 1 rate at 5% will be used to analyze PFS: In the first step, whether Arm 2 is superior to Arm 1 will be tested using a stratified log-rank test adjusting for the stratification factors: T categorization: 1-3 versus 4; nodal stage: N0/N1 versus N2 versus N3, radiotherapy delivery modality (3D CRT versus IMRT) and anatomic location: hypopharynx versus oral cavity versus oropharynx versus larynx at the time of randomization as the primary method of analysis. Secondary analyses based on stratified Cox proportional hazards model will also be performed. T categorization: 1-3 versus 4; nodal stage: N0/N1 versus N2 versus N3, radiotherapy delivery modality (3D CRT versus IMRT) and anatomic location: hypopharynx versus oral cavity versus oropharynx versus larynx will be the stratification factor to define the stratified Cox proportional hazards model. Stratified Cox model with single treatment covariate will be used to estimate the hazard ratio and associated 95% confidence interval between two treatment arms. Exploratory Cox proportional hazards models adjusting treatment effect for other potential prognostic factors and/or seeking to identify other factors significantly related to the PFS outcomes may also be conducted. If the two-sided p-value of stratified log-rank test is higher than 0.05 (i.e. superiority of Arm 2 to Arm 1 is not demonstrated), a test for the non-inferiority of Arm 2 to Arm 1 will be performed which includes also all randomized patients. Non-inferiority of Arm 2 to Arm 1 will be claimed when the upper limit of a two-sided 95% confidence interval for the hazard ratio of Arm 2 to Arm 1 is lower than or equal to 1.15. The non-inferiority margin 1.15 for hazard ratio is corresponding to a margin of 5% for the 2 year PFS between two arms. It is calculated from the data in a phase III trial of standard radiation therapy and two schedules of concurrent chemoradiotherapy [Adelstein 2003] that the hazard ratio in PFS of standard radiotherapy to Arm 1 in our study was 1.65. Therefore, from the definition of Rothmann et al. [Rothmann 2003], if Arm 2 is demonstrated non-inferior to Arm 1 based on a non-inferiority margin of 1.15, it preserves at least 72% of the Arm 1 effect. A sensitivity analysis based on only eligible patients who have received at least one dose of study treatment and analyzed based on arms they are treated will also be performed for non-inferiority testing.
Secondary efficacy endpoints include (1) overall survival, defined as time from randomization to the time of death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last contact date. (2) local and regional progression free survival, defined as time from randomization to the time of first documented local (primary site) or regional (lymph node) recurrence. Patients who developed distant metastasis or died before the documentation of local or regional recurrence will be censored at the time of first documented distant metastasis or death. Patients who are alive without any progression at the time of the final analysis will be censored at their last disease assessment dates. (3) distant metastasis free survival, defined as time from randomization to the time of first documented distant metastasis. Patients who developed local or regional progression or died before the documentation of distant metastasis will be censored at the time of first documented local or regional progression or death. Patients who are alive without any progression at the time of the final analysis will be censored at their last disease assessment dates. Analyses for these secondary efficacy endpoints will be done using similar methodology for PFS.

All patients who have received at least one dose of study treatment will be included in the safety analysis based on arms they are treated. Toxicities will be graded using the NCI Common Toxicity Criteria Version 3.0. The incidence of toxicities will be summarized by type of adverse event and severity. A Fisher’s exact test will be used as needed to compare toxicities between the two arms.

**Safety Review**
A comprehensive real-time review of the adverse event experience and compliance with radiotherapy will be performed. The review will be based on data from the first 30 randomized patients who receive at least one dose of protocol therapy. The time period will encompass from the first dose of protocol therapy until 4 weeks after the last dose of protocol therapy. The data set will be submitted for review by the independent NCIC Clinical Trials Group Data Safety Monitoring Committee (DSMC) as necessary. Unless otherwise specified, accrual will continue during the review period. In addition, the current NCIC Clinical Trials Group policies and procedures related to oversight of safety on phase III clinical trials will be followed (Section 14.7).

14.3 **Analysis of Quality of Life**
QOL is a secondary outcome of the study. We anticipate 80% of patients would be eligible for QOL (able to speak or read English or French). This will provide approximately 256 patients available for QOL analysis.

14.4 **Analysis of Swallowing Outcomes**
Swallowing outcome as measured in this study will be analyzed descriptively. We anticipate 256 patients available for swallowing QOL questionnaire analysis, and 50 available for description of videofluoroscopy outcomes.

In keeping with the objectives and feasibility issues of Swallowing Impairment Sub-study, we will have the capacity to enroll 50 patients from participating centres with equal distribution in the two treatment arms. This sample size is sufficient to assess the reliability of the MBSImP in a test-retest design, assuming an Intraclass Correlation (ICC) of at least 0.75 between 2 raters with significance set at 0.05 [Streiner 2003]. In addition, it will be sufficient to assess the feasibility of capturing swallowing impairment measures over time in patients with head and neck cancer. It will be sufficient to perform descriptive, non comparative analyses between both treatment groups.
14.5 Analysis of Biomarker and Health Economics

The analysis plan for biomarker and health economics evaluation will be detailed in separate documents before these analyses are performed.

14.6 Sample Size and Duration of Study

It is estimated that 2 year PFS for the Arm 1 is around 45%. In order to detect a 12.2% difference in 2-year PFS between two treatment arms, which is corresponding to a hazard ratio of 0.7 between Arms 2 and 1, with two-sided 0.05 level and 80% power, a total of 246 events in PFS are required to observe before final analysis would be performed. Assuming that enrollment rate is 100 patients/year and all patients will be followed for additional 3 years after last patient randomized, we will need to enroll 320 patients in 3.2 years in order to observe the required number of events at the time of final analysis. The final analysis will be performed when 246 events in PFS are observed and the total expected duration will be 6.2 years.

With 246 events observed at the time of final analysis for this study, we would have 80% power to claim non-inferiority at 5% alpha level if the true hazard ratio of Arm 2 to the Arm 1 is not higher than 0.81 (which is corresponding to a difference not lower than 7.6% in 2 year PFS between experimental arm and the control arm). That is, if the true hazard ratio of Arm 2 to Arm 1 is lower than or equal to 0.7 (equivalent to an improvement of 12.2% or higher in 2 year PFS by Arm 2), this study will have 80% power to demonstrate superiority of Arm 2 to Arm 1; if the true hazard ratio of Arm 2 to Arm 1 is higher than 0.7 but lower than or equal to 0.81 (equivalent to an improvement between 7.6% and 12.2% in 2 years PFS by Arm 2), this study will have 80% power to claim non-inferiority of Arm 2 to Arm 1.

2014 Update

Based on external data and the observed trends in number of PFS events over time in HN.6, the primary efficacy analysis will be time based with a clinical cut-off date of October 31, 2014, corresponding to a median follow of 38 months (see Section 2.1 Background).

Based on the 100 PFS events currently observed using a clinical cut-off date of October 31, 2014, the power for the superiority analysis will be 43%; the power for non-inferiority analysis will be 42%.

14.7 Safety Monitoring

Adverse events will be monitored on an ongoing basis by Central Office. Their frequencies will be reported annually at investigators’ meetings. In addition adverse events will be reviewed by the DSMC every 6 months and also by the Safety Conference Committee according to NCIC CTG policy.
14.8 Interim Analysis

One interim analysis is planned when at least half of required number of events (> 123) in PFS is observed to allow early termination of the study if the results are extreme. We expect to have 123 events approximately at the end of accrual. Since primary interest of this study is to demonstrate the superiority of Arm 2 to Arm 1, a group sequential closed test (GSC) procedure proposed by Wang et al. [Wang 2001] will be used for the interim analysis, which allows termination of study in the interim analysis only when the superiority of Arm 2 to Arm 1 is demonstrated. A stratified log-rank test for the PFS adjusting stratification factors at randomization will be performed in the interim analysis. Early termination will be considered when the p-value of stratified log-rank test is less than the nominal p-value calculated based on number of events observed at the time of interim analysis using O’Brien-Fleming alpha spending function with stopping boundaries as proposed by Lan and DeMets to maintain the significance level of overall study at two-sided 5% level. For example, if exactly 123 events were observed at the time of interim analysis, the nominal p-value would be 0.005.

Results of the interim analysis will be supplied to the DSMC who will communicate their recommendation regarding continuation of the trial to the Director of the NCIC CTG.

2014 Update

The study design has been changed to a time based primary analysis using a clinical cut-off date of October 31, 2014 (See Sections 2.1 and 14.6). No interim analysis will be performed.
15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 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 NCIC Clinical 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 quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee, similarly for economic outcomes and the Working Group on Economic Analysis (WGEA).

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

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

15.2 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.

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Amgen, the NCIC CTG 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.
16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Institution Eligibility for Participation

Selected member centres in good standing of the NCIC CTG are eligible to participate in this study. Any centre joining the NCIC CTG is required to sign a Participating Centre Study Agreement and have Standard Operating Procedures regarding the conduct of clinical trials.

The NCIC CTG will submit via fax to Health Canada for each participating Canadian centre prior to local activation a completed Health Canada Clinical Trial Site Information Form.

16.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the NCIC CTG:

- A current curriculum vitae, updated and submitted within two years at the time of randomization.
- Documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate).
- Completion of the required NCIC CTG GCP training modules.

For the principal investigator only:

- A Health Canada Qualified Investigator Undertaking Form must be completed and signed by the principal investigator of the study at participating Canadian centres and received by the NCIC CTG central office before that centre can be locally activated.

16.3 REB (Research Ethics Board) Approval for Protocols

Each participating centre will have on file with the NCIC CTG central office, as part of its membership/agreement documents, a description of its ethics review process and composition of its REB.

**REB Composition**

Membership of an REB approving this protocol must be consistent with Canadian regulatory requirements, summarized as follows:

- at least 5 members;
- majority of members are Canadian citizens or permanent residents;
- includes 2 members whose primary expertise and experience are in a scientific discipline with broad experience in the methods and areas of research to be approved (1 of these is from a medical discipline);
- includes 1 member knowledgeable in ethics;
- includes 1 member knowledgeable in Canadian laws relevant to the biomedical research to be approved;
- includes 1 member whose primary experience and expertise are in a non-scientific discipline;
- includes 1 member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the NCIC CTG or the centre where the clinical trial is to be conducted.
A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation to the following may be included in the signed local ethics approval document:

- The membership of the Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations;
- The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice; and
- The Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified investigator named at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

This documentation must be received by the NCIC CTG central office before the centre can be locally activated.

**Initial Approval**
Member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB.

**Annual Re-Approvals**
Annual re-approval must continue until NCIC CTG informs you that they are no longer required.

**Amendments/Administrative Updates**
All amendments or administrative updates to the protocol must undergo review by local REBs. Amendments/administrative updates will be circulated to all participating sites in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified.

Amendments will be reviewed and approved by Health Canada prior to central implementation of the amendment, and by REBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects. Amendments may be distributed with Health Canada REB attestation forms; if so they must be completed. For each amendment NCIC CTG will collect documentation of REB approval, a completed REB attestation form (if applicable), and the date the amendment is locally implemented.

**REB Refusals**
If an REB refuses to approve this protocol (or an amendment/administrative update to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

**Serious Adverse Events, Safety Updates, Investigator Brochure Updates and Product Monograph Updates**
During the course of the study serious adverse events, safety updates, investigator brochure updates or product monographs may be sent to you for reporting to your REB. The date of REB submission for these documents will need to be entered into the NCIC CTG trial HN.6 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.
16.4 Informed Consent

_Informed Consent Document_

The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

It is essential that the consent form contain a clear statement which gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the NCIC CTG and other agencies as necessary. The consent form must include all ICH-GCP consent elements. In addition, the consent form should include all elements required by NCIC CTG policy, and centres receiving funding from NCEHR, SSHRC and/or CIHR should include elements from the Tri Council Policy Statement (TCPS).

Informed consent forms that do not contain all ICH-GCP required elements will require an amendment and will lead to the delay of local activation. A complete list of the elements required by regulations, guidelines and NCIC CTG policy can be found by accessing the NCIC CTG website at [http://www.ctg.queensu.ca/private/ethics/consent_RE_Checklists.html](http://www.ctg.queensu.ca/private/ethics/consent_RE_Checklists.html).

_Consent Process/Patient Eligibility_

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

16.5 Retention of Patient Records and Study Files

ICH Good Clinical Practice guidelines apply to NCIC CTG studies. It is the responsibility of NCIC CTG to inform the investigator/institution as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

NCIC CTG will notify all the trial investigators/institutions and all the regulatory authorities if clinical development of an investigational product discontinues or when trial related records no longer need to be retained.

16.6 Centre Performance Monitoring

This trial is eligible for inclusion in the Centre Performance Index. There are minimum standards for performance.

Forms are to be submitted according to the schedule in Appendix IV (Documentation for Study).
16.7 On-Site Monitoring/Auditing

In addition to the routine review of case report forms submitted electronically and supporting documents sent to the central office, NCIC CTG site monitoring 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 document binders, standard operating procedures (including electronic information), as well as ethics and pharmacy documentation.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

16.8 Case Report Forms (CRFs)

This trial will use a web-based Electronic Data Capture (EDC) system for most data collection forms. For details of accessing the EDC system and completing the online forms please refer to the "Randomization and Data Management Guidebook" posted on the HN.6 area of the NCIC CTG website (www.ctg.queensu.ca).

The following ELECTRONIC CRFs will be used for this trial:
- Eligibility Checklist
- Baseline Report
- Treatment Report
- 4 weeks Follow-up Report
- 8 weeks Follow-up Report
- Follow-up Report (Form 5)
- Short Follow-up Report (Form 5s)
- Follow-up of Ineligible Patients
- Recurrence/Progression Report
- Death Report (Form 6)
- QARC’s Final Review Summary Report

The following PAPER CRFs will be used for this trial:
- Archival Tumour Tissue Submission
- Quality of Life Questionnaire (FACT H&N)
- Swallowing Quality of Life Questionnaires (MDADI, SWAL-QOL)
- Lost Productivity Questionnaire
- Correlative Sciences Questionnaire
- Serious Adverse Event (SAE) Report

A list of all forms (electronic or paper) that need to be completed together with expectation dates and details of required supporting documentation is given in Appendix IV.
17.0 REFERENCES


American Cancer Society Cancer Facts & Figures 2008; Atlanta: American Cancer Society; 2008


Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, Garden AS, Ridge JA, Cooper JS, Ang KK. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003.


## APPENDIX I - PATIENT EVALUATION FLOW SHEET

<table>
<thead>
<tr>
<th>Required Investigations</th>
<th>Pre-study</th>
<th>DURING protocol treatment (weekly (weeks 1-7))</th>
<th>last week of radiotherapy</th>
<th>AFTER Protocol Treatment (from the end of protocol therapy)</th>
<th>Post First Failure (from the date of first failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X¹</td>
<td>X</td>
<td></td>
<td>X X X X X²</td>
<td>q6 monthly</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>X¹</td>
<td>X</td>
<td></td>
<td>X X X X X²</td>
<td>q6 monthly</td>
</tr>
<tr>
<td>BSA</td>
<td>X¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal clinical assessment</td>
<td>X¹</td>
<td>X</td>
<td></td>
<td>X X X X X²</td>
<td>at discretion of investigator</td>
</tr>
<tr>
<td>Direct or indirect visualization of tumour and surrounding area</td>
<td>X⁸</td>
<td></td>
<td></td>
<td>X X X X X²</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X³</td>
<td>X</td>
<td>X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differential</td>
<td>X³</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>X³</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST or ALT, Bilirubin, Mg, Ca, Na, K, Cl, Serum creatinine and calculated creatinine clearance</td>
<td>X³</td>
<td>X³,6</td>
<td></td>
<td>X X X²</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>X³</td>
<td>X³,6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiology *</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CT or MRI of head and neck</td>
<td>X⁸</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>CT scan of chest **</td>
<td>X⁸</td>
<td></td>
<td></td>
<td>X X X³</td>
<td>at discretion of investigator</td>
</tr>
<tr>
<td>Other tests as clinically indicated</td>
<td>X⁸</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other Investigations</td>
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<td>Pregnancy test ***</td>
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<tr>
<td>Audiogram</td>
<td>X⁸</td>
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<tr>
<td>Biopsy</td>
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<tr>
<td>Tumour HPV status</td>
<td>X²⁰</td>
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<tr>
<td>Correlative Studies</td>
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<tr>
<td>Archival tumour collection *</td>
<td>X¹³</td>
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<td></td>
</tr>
<tr>
<td>Plasma, cellular component and serum samples *</td>
<td>X¹³</td>
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<td></td>
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</tr>
<tr>
<td>Correlative Sciences Questionnaire *</td>
<td>X¹⁴</td>
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<tr>
<td>Adverse Events</td>
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<td></td>
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<tr>
<td>Graded according to CTCAE v3</td>
<td>X³</td>
<td>X</td>
<td>X X¹⁵</td>
<td>X¹⁵ X²,¹⁵</td>
<td>q6 monthly¹⁵</td>
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<tr>
<td>Quality of Life</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>FACT-H&amp;N ☳</td>
<td>X³</td>
<td>X¹⁶</td>
<td>X X X X X¹⁷</td>
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Table and footnotes continued on next page ...
### Required Investigations

<table>
<thead>
<tr>
<th></th>
<th>Pre-study</th>
<th>DURING protocol treatment</th>
<th>AFTER Protocol Treatment (from the end of protocol therapy)</th>
<th>Post First Failure (from the date of first failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>weekly (weeks 1-7)</td>
<td>last week of radiotherapy</td>
<td>week 4</td>
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<tr>
<td>Swallowing QOL</td>
<td></td>
<td>X^3</td>
<td>X^{16}</td>
<td>X</td>
</tr>
<tr>
<td>MDADI</td>
<td></td>
<td>X^3</td>
<td>X^{16}</td>
<td>X</td>
</tr>
<tr>
<td>SWAL-QOL</td>
<td></td>
<td>X^3</td>
<td>X^{16}</td>
<td>X</td>
</tr>
<tr>
<td>Swallowing Function</td>
<td></td>
<td>X^3</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FOIS</td>
<td></td>
<td>X^3</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MBSImP ***</td>
<td></td>
<td>X^{19}</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Video Fluoroscopy ***</td>
<td></td>
<td>X^{19}</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Economics</td>
<td></td>
<td></td>
<td></td>
<td>X^{18}</td>
</tr>
<tr>
<td>Lost Productivity</td>
<td></td>
<td></td>
<td></td>
<td>X^{18}</td>
</tr>
<tr>
<td>Questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resource Utilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone Contact Follow-ups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*footnotes continued on next page ...*
1. Within 4 weeks prior to randomization.
2. After month 6: q 3 monthly until 24 months then q 4 monthly until 36 months then q 6 months until 60 months then as clinically indicated.
3. Within 2 weeks before randomization.
4. Weeks when cisplatin or panitumumab is given tests should be on treatment day or within 72 hours prior.
5. After week 8: as clinically indicated.
6. Biochemistry tests must be within one week of the start of treatment. Repeat biochemistry tests if the pre-randomization tests are done more than one week prior to treatment day 1. Eligibility criteria (as per 5.1.5) must be fulfilled.
7. After month 4: as clinically indicated. Patients with abnormal Mg should be followed and supplemented as indicated till resolved.
8. Within 8 weeks prior to randomization.
9. After month 12: q 6 monthly until 36 months then as clinically indicated.
10. Within 72 hours prior to randomization.
11. After patient’s tissue and blood collection and banking consent obtained.
12. Biopsy is required for confirmation of primary tumor site persistent disease. Biopsy for confirmation of persistent disease should be performed when clinically indicated, at week 8 or at a later visit. Recommended for confirmation of first recurrence, first distant metastases or first local/regional progression.
13. After patient’s tissue and blood collection and banking consent obtained.
14. Should be completed after patient consent obtained.
15. Treatment related only.
16. Quality of Life questionnaires are not required in patients not completing the radiotherapy treatment.
17. After month 12: then at 24 months and 36 months.
18. If radiotherapy terminated early complete on last date of radiotherapy treatment or as soon as possible after completion.
19. After the Swallowing Impairment Sub-study consent is signed and prior to commencement of protocol therapy.
20. Tumour HPV status for all patients. Participants who refused tumour banking and for whom the tumour HPV status is unknown must be re-consented with the participant information letter to obtain consent to test tumour HPV status and to collect the results.
21. Annually after 60 months.

* Full staging investigations required if failure documented.
** After protocol treatment CT chest or chest x-ray is permitted
*** For women of childbearing potential.
♦ Optional for consenting patients only.
★★ The FACT-H&N questionnaire should be completed before the MDADI and the SWAL-QOL.
★★★ For institutions participating in swallowing impairment substudy.
+ To cover the time period between the Resource Utilization Assessments logs.
## APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

### PERFORMANCE STATUS CRITERIA

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

<table>
<thead>
<tr>
<th>ECOG (Zubrod)</th>
<th>Karnofsky</th>
<th>Lansky*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score Description</td>
<td>Score Description</td>
<td>Score Description</td>
</tr>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or do active work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Severely disabled, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly.</td>
</tr>
</tbody>
</table>

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.
APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution
Panitumumab will be manufactured and packaged by Amgen. A shipment of labeled and packaged panitumumab will be shipped to the Investigational Drug Research Service (IDRS), Kingston General Hospital Pharmacy, and distributed from IDRS to participating centres.

Each vial of panitumumab will contain 10 mL of a sterile, colorless, preservative-free protein solution containing a 20-mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Boxes of panitumumab will contain 12 vials of panitumumab.

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

Drug Labelling
Panitumumab for this study has been labelled in accordance with Health Canada regulations.

Initial Drug Supply
At the time of local activation of a centre (after receipt and review of all required documentation), the NCIC CTG will authorize a start-up supply of panitumumab to be shipped directly to the centre. The drug will be shipped to the centre within 3 working days of local activation.

Drug accountability forms will be posted on the trial website.

Drug Ordering (Re-supply)
Subsequent requests for more panitumumab should be directed to Tony Pascoal at IDRS by faxing the drug reorder form to 613-544-9560. (Tel: 613-544-3400 x 2013). Drug accountability and drug re-order forms will be posted on the trial website for pharmacists to download. Please allow sufficient time for shipment of drug.

Drug Accountability
The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction
At the end of the study, it must be possible to reconcile delivery records with records of usage by completion of the study drug accountability form. Any discrepancies must be accounted for. All unused study medication, after accountability and reconciliation may be destroyed locally, per institutional guidelines.

** PLEASE NOTE **

DRUG FROM THIS SUPPLY IS TO BE USED ONLY
FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.
Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life and SAE reporting. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Randomization and Data Management Guidebook" posted on the HN.6 area of the NCIC CTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial are as follows:

<table>
<thead>
<tr>
<th>Electronic Form</th>
<th>To be Completed</th>
<th>To be submitted electronically</th>
<th>Supporting Documentation to be sent by MAIL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Report</td>
<td>Within 2 weeks of randomization</td>
<td>Within 6 weeks of randomization</td>
<td>Copies of signed consent form, tissue and blood banking consent, swallowing impairment Sub-study consent, relevant pathology, operative, radiology reports, correlative science questionnaire (if applicable).</td>
</tr>
<tr>
<td>Treatment Report</td>
<td>1 week after the end of all protocol treatment has been completed</td>
<td>Within 4 weeks of completion</td>
<td>Clinic notes detailing physical examinations, relevant radiology reports (if applicable).</td>
</tr>
<tr>
<td>4 week Follow-up Report</td>
<td>PRIOR to first failure: at week 4 after all protocol treatment has been completed</td>
<td>Within 8 weeks of follow up visit</td>
<td>Clinic notes detailing physical examinations, relevant radiology reports (if applicable).</td>
</tr>
<tr>
<td>8 week Follow-up Report</td>
<td>PRIOR to first failure: at week 8 after all protocol treatment has been completed</td>
<td>Within 8 weeks of follow up visit</td>
<td>Clinic notes detailing physical examinations , relevant radiology reports</td>
</tr>
<tr>
<td>Follow-up Report</td>
<td>PRIOR to Progression: After all protocol treatment has been completed at 4 months, 6 months, then q 3 monthly until 24 months then q 4 monthly until 36 months then q 6 months until 60 months</td>
<td>Within 8 weeks of follow up visit</td>
<td>Clinic notes detailing physical examinations, relevant radiology reports (if applicable).</td>
</tr>
<tr>
<td>Short Follow-up Report</td>
<td>AFTER first failure: Every 6 months</td>
<td>Within 8 weeks of follow up visit.</td>
<td></td>
</tr>
<tr>
<td>Death Report</td>
<td>When patient dies</td>
<td>Within 8 weeks of patient’s death</td>
<td>Autopsy report, if done.</td>
</tr>
<tr>
<td>Progression / Recurrence Report</td>
<td>Upon disease progression / recurrence (but only if it is the first failure)</td>
<td>Within 8 weeks of progression / recurrence</td>
<td>Relevant radiology and pathology reports.</td>
</tr>
<tr>
<td>QARC’s Final Review Summary Report</td>
<td>Upon final radiotherapy review</td>
<td>Within 24 hours of receipt documentation</td>
<td></td>
</tr>
<tr>
<td>Archival Tumour Submission</td>
<td>Within 2 weeks of randomization</td>
<td>Within 6 weeks of randomization</td>
<td></td>
</tr>
<tr>
<td>Follow-up of Ineligible Patients Report</td>
<td>Annually from the time when the patient is identified to be ineligible.</td>
<td>Within 8 weeks of follow up visit</td>
<td>Clinic notes detailing physical examinations, relevant radiology reports (if applicable).</td>
</tr>
<tr>
<td>Phone Contact Follow-ups</td>
<td>Annually after 60 months.</td>
<td>Within 8 weeks of contact.</td>
<td>Relevant clinic notes detailing physical examinations, radiology reports and pathology reports (if applicable).</td>
</tr>
</tbody>
</table>

* Supporting documents should be mailed immediately after the form they refer to has been submitted electronically.
The PAPER CRFs to be used in this trial are as follows:

<table>
<thead>
<tr>
<th>Paper Form</th>
<th>To be Completed</th>
<th>Due in NCIC CTG Central Office/EORTC Data Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Event Report Form</td>
<td>At the time of event</td>
<td>To be FAXED within 24 hours of knowledge of event. Paper copy to be mailed within 14 working days</td>
</tr>
<tr>
<td>Correlative Sciences Questionnaire</td>
<td>After patient consent obtained</td>
<td>Mail as soon as the Baseline Report has been submitted electronically</td>
</tr>
<tr>
<td>Quality of Life (FACT-H&amp;N)</td>
<td>See sections 6.0 and 9.0</td>
<td>Mail as soon as the corresponding form (Baseline Report, Treatment Report, 8 week Follow-up Report, Follow-up Report) has been submitted electronically</td>
</tr>
<tr>
<td>Swallowing Quality of Life (SWAL-QOL, MDADI)</td>
<td>See sections 6.0 and 9.0</td>
<td>Mail as soon as the corresponding form (Baseline Report, Treatment Report, Follow-up Report) has been submitted electronically</td>
</tr>
<tr>
<td>Economic Evaluation (Lost Productivity Questionnaire)</td>
<td>Last week of radiotherapy</td>
<td>Mail as soon as the Treatment Report has been submitted electronically</td>
</tr>
<tr>
<td>Swallowing Function Report (MBSImP)</td>
<td>To be completed by the central interpretation Lab.</td>
<td>Mail within one month of receipt digital data at the central interpretation Lab.</td>
</tr>
</tbody>
</table>
APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 3.0 (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) for adverse events and serious adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page: http://ctep.cancer.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.
APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

This study will use three questionnaires:

FACT-H&N is a core quality of life questionnaire and subscale specific for head and neck cancer

MDADI assesses swallowing related quality of life and is specific for head and neck cancer

SWAL-QOL also assesses swallowing related quality of life but is not specific for head and neck cancer

While these three questionnaires are being used for the first time on HN.6, their mode of administration is similar to familiar questionnaires and so the general instructions for collecting quality of life, as described below, apply. However, please be aware of these additional instructions.

The three questionnaires are formatted as separate documents. Accordingly, 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 and SWAL-QOL have been completed, on the last week of radiotherapy. See Appendix VII.

As indicated in the following table, the FACT-H&N is to be completed at every scheduled assessment. Sometimes the MDADI and SWAL-QOL are also completed, and sometimes the MDADI is also completed. This is because the design of the quality of life component of this study does not require all three questionnaires to be completed at every scheduled assessment. Please make every effort to have the patient complete the correct questionnaires in order at the scheduled assessment.

<table>
<thead>
<tr>
<th>Scheduled Assessment</th>
<th>Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 2 weeks prior to randomization</td>
<td>FACT-H&amp;N, MDADI, SWAL-QOL</td>
</tr>
<tr>
<td>Last week of radiotherapy</td>
<td>FACT-H&amp;N, MDADI, SWAL-QOL</td>
</tr>
<tr>
<td>8 weeks</td>
<td>FACT-H&amp;N</td>
</tr>
<tr>
<td>4 months</td>
<td>FACT-H&amp;N, MDADI</td>
</tr>
<tr>
<td>6 months</td>
<td>FACT-H&amp;N, MDADI</td>
</tr>
<tr>
<td>12 months</td>
<td>FACT-H&amp;N, MDADI, SWAL-QOL</td>
</tr>
<tr>
<td>24 months</td>
<td>FACT-H&amp;N</td>
</tr>
<tr>
<td>36 months</td>
<td>FACT-H&amp;N</td>
</tr>
</tbody>
</table>

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 questionnaire.

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-randomization or 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. Pretreatment 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, 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. 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.
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 is not literate in either English or French (or other languages that the questionnaire may be available in). 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 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

NCIC CTG Trial: **HN.6**

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

<table>
<thead>
<tr>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC CTG Patient Serial No: ___________</td>
</tr>
<tr>
<td>Institution: ___________________________________________</td>
</tr>
</tbody>
</table>

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

☐ Prior to randomization

**During Treatment:**

☐ Last week of radiotherapy

**Off Treatment - prior to progression only:**

☐ week 8

then ☐ mth 4 ☐ mth 6 ☐ mth 12 ☐ mth 24 ☐ mth 36

The FACT-H&N questionnaire should be completed before the MDADI and the SWAL-QOL.

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.

NCIC CTG use only

Logged: _______ Study Coord: _______ Res Assoc: _______ Data Ent’d: _______

______-____-____  ______-____-____  ______-____-____  __________  ________
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.

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

<table>
<thead>
<tr>
<th>SOCIAL/FAMILY WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1 I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS2 I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS3 I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS4 My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS5 I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS6 I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS7 I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE1 I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE2 I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE3 I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE4 I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE5 I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE6 I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GF1 I am able to work (include work at home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF2 My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF3 I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF4 I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF5 I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF6 I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF7 I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
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.

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

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

NCIC CTG Trial: **HN.6**

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

**Patient Information**

NCIC CTG Patient Serial No: ___________  Patient Initials: ____________________________ (first-middle-last)

Institution: ____________________________________________________________________________ Investigator: ______________________________

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

☐ Prior to randomization

**During Treatment:**

☐ Last week of radiotherapy

**Off Treatment - prior to progression only:**

☐ mth 4  ☐ mth 6  ☐ mth 12

The FACT-H&N questionnaire should be completed before the MDADI and the SWAL-QOL.

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.

**NCIC CTG use only**

Logged: _______  Study Coord: _______  Res Assoc: _______  Data Ent’d: _______  Verif: _______
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.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My swallowing ability limits my day to day activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2. I am embarrassed by my eating habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1. People have difficulty cooking for me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2. Swallowing is more difficult at the end of the day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E4. I am upset by my swallowing problem.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P6. Swallowing takes great effort.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E5. I do not go out because of my swallowing problem.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F5. My swallowing difficulty has caused me to lose income.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P7. It takes me longer to eat because of my swallowing problem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Statement</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>P3</td>
<td>People ask me, “Why can’t you eat that?”</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>E3</td>
<td>Other people are irritated by my eating problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>P8</td>
<td>I cough when I try to drink liquids.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>F3</td>
<td>My swallowing problems limit my social and personal life.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>F2</td>
<td>I feel free to go out to eat with my friends, neighbors, and relatives.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>P5</td>
<td>I limit my food intake because of my swallowing difficulty.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>P1</td>
<td>I cannot maintain my weight because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>E6</td>
<td>I have low self-esteem because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>P4</td>
<td>I feel that I am swallowing a huge amount of food.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
<tr>
<td>F4</td>
<td>I feel excluded because of my eating habits.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No opinion</td>
<td>Disagree</td>
</tr>
</tbody>
</table>

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.
**SWAL-QOL**
Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **HN.6**

This [page] to be completed by the Clinical Research Associate

<table>
<thead>
<tr>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC CTG Patient Serial No: ___________</td>
</tr>
<tr>
<td>Institution: _____________________________</td>
</tr>
</tbody>
</table>

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

☐ Prior to randomization

During Treatment:

☐ Last week of radiotherapy

Off Treatment - prior to progression only:

☐ mth 12

The FACT-H&N questionnaire should be completed before the MDADI and the SWAL-QOL.

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.**

**NCIC CTG use only**

<table>
<thead>
<tr>
<th>Logged: _______</th>
<th>Study Coord: _______</th>
<th>Res Assoc: _______</th>
<th>Data Ent’d: _______</th>
<th>Verif: _______</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______ - _______ - _______</td>
<td>_______ - _______ - _______</td>
<td>_______ - _______ - _______</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>
The SWAL-QOL Survey

Instructions for Completing the SWAL-QOL Survey

This questionnaire is designed to find out how your swallowing problem has been affecting your day-to-day quality of life.

Please take the time to carefully read and answer each question. Some questions may look like others, but each one is different.

Here’s an example of how the questions in the survey will look.

1. In the last month how often have you experienced each of the symptoms below.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feel weak</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Thank you for your help in taking part in this survey!

IMPORTANT NOTE: We understand that you may have a number of physical problems. Sometimes it is hard to separate these from swallowing difficulties, but we hope that you can do your best to concentrate only on your swallowing problem. Thank you for your efforts in completing this questionnaire.

1. Below are some general statements that people with swallowing problems might mention. In the last month, how true have the following statements been for you.

   (circle one number on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Very much true</th>
<th>Quite a bit true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dealing with my swallowing problem is very difficult.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My swallowing problem is a major distraction in my life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. Below are aspects of day-to-day eating that people with swallowing problems sometimes talk about. In the last month, how true have the following statements been for you?

   (circle one number on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Very much true</th>
<th>Quite a bit true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most days, I don’t care if I eat or not.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>It takes me longer to eat than other people.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I’m rarely hungry anymore.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>It takes me forever to eat a meal.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I don’t enjoy eating anymore.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
3. Below are some physical problems that people with *swallowing problems* sometimes experience. In the last month, **how often** you have experienced each problem as a result of your swallowing problem? (circle one number on each line)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Almost always</th>
<th>Often</th>
<th>Sometimes</th>
<th>Hardly ever</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Choking when you eat food</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Choking when you take liquids</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Having thick saliva or phlegm</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Gagging</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Drooling</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Problems chewing</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Having excess saliva or phlegm</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Having to clear your throat</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Food sticking in your throat</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Food sticking in your mouth</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Food or liquid dribbling out of your mouth</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Food or liquid coming out your nose</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Coughing food or liquid out of your mouth when it gets stuck</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. Next, please answer a few questions about how your *swallowing problem* has affected your diet and eating in the last month. (circle one number on each line)

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Uncertain</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figuring out what I can and can't eat is a problem for me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>It is difficult to find foods that I both like and can eat.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5. In the last month, **how often** have the following statements about communication applied to you because of your *swallowing problem*? (circle one number on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>People have a hard time understanding me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>It’s been difficult for me to speak clearly.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
6. Below are some concerns that people with swallowing problems sometimes mention. In the last month, how often have you experienced each feeling?  

(circle one number on each line)

<table>
<thead>
<tr>
<th>Concern</th>
<th>Almost always</th>
<th>Often</th>
<th>Sometimes</th>
<th>Hardly ever</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>I fear I may start choking when I eat food.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry about getting pneumonia.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I am afraid of choking when I drink liquids.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I never know when I am going to choke.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

7. In the last month, how often have the following statements been true for you because of your swallowing problem?

(circle one number on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Always true</th>
<th>Often true</th>
<th>Sometimes true</th>
<th>Hardly ever true</th>
<th>Never true</th>
</tr>
</thead>
<tbody>
<tr>
<td>My swallowing problem depresses me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Having to be so careful when I eat or drink annoys me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I've been discouraged by my swallowing problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My swallowing problem frustrates me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I get impatient dealing with my swallowing problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

8. Think about your social life in the last month. How strongly would you agree or disagree with the following statements?

(circle one number on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Uncertain</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not go out to eat because of my swallowing problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My swallowing problem makes it hard to have a social life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My usual work or leisure activities have changed because of my swallowing problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Social gatherings (like holidays or get-togethers) are not enjoyable because of my swallowing problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My role with family and friends has changed because of my swallowing problem.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
9. In the last month, how often have you experienced each of the following physical symptoms? (circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feel weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have trouble falling asleep?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have trouble staying asleep?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Feel exhausted?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

10. Do you now take any food or liquid through a feeding tube? (circle one)

   No...................................................................................................................................................... 1
   Yes.................................................................................................................................................... 2

11. Please circle the letter of the one description below that best describes the consistency or texture of the food you have been eating most often in the last week.

   Circle one:
   
   A. Circle this one if you are eating a full normal diet, which would include a wide variety of foods, including hard to chew items like steak, carrots, bread, salad, and popcorn.
   
   B. Circle this one if you are eating soft, easy to chew foods like casseroles, canned fruits, soft cooked vegetables, ground meat, or cream soups.
   
   C. Circle this one if you are eating food that is put through a blender or food processor or anything that is like pudding or pureed foods.
   
   D. Circle this one if you take most of your nutrition by tube, but sometimes eat ice cream, pudding, apple sauce, or other pleasure foods.
   
   E. Circle this one if you take all of your nourishment through a tube.
12. **Please circle the letter** of the one description below that best describes the consistency of liquids you have been drinking most often in the last week.

**Circle one:**

A. Circle this if you drink liquids such as water, milk, tea, fruit juice, and coffee.

B. Circle this if the majority of liquids you drink are thick, like tomato juice or apricot nectar. Such thick liquids drip off your spoon in a slow steady stream when you turn it upside down.

C. Circle this if your liquids are moderately thick, like a thick milkshake or smoothie. Such moderately thick liquids are difficult to suck through a straw, like a very thick milkshake, or drip off your spoon slowly drop by drop when you turn it upside down, such as honey.

D. Circle this if your liquids are very thick, like pudding. Such very thick liquids will stick to a spoon when you turn it upside down, such as pudding.

E. Circle this if you did not take any liquids by mouth or if you have been limited to ice chips.

13. In general, would you say your health is:

(Circle One)

- Poor.................................................................................................................................................... 1
- Fair ..................................................................................................................................................... 2
- Good .................................................................................................................................................. 3
- Very Good.......................................................................................................................................... 4
- Excellent............................................................................................................................................. 5

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

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

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, 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.

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.

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.

4. What If...

4A. 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.
4B. 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.

4C. 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 randomization 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.

5. 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.

6. 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.

7. 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

NCIC CTG Trial: HN.6

This page only to be completed by the Clinical Research Associate

Patient Information

| NCIC CTG Patient Serial No: _____________ | Patient Initials: ____ ____ ____ (first-middle-last) |
| Institution: _____________________________ | Investigator: _____________________________ |

Scheduled time to obtain this Lost Productivity Questionnaire: Last week of radiotherapy

Date questionnaire completed: __ __ __ __ - __ __ __ - __ __ yyy yyy mmm dd

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

NCIC CTG use only

| Logged: _______ | Study Coord: _______ | RA: _______ | Data Ent’d: | Verif: |
| ______ - _____ - ___ | ______ - _____ - ___ | ______ - _____ - ___ | ______ | ______ |
HN.6   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: ______________________________
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
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
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) ______________________
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
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: $ _______________
   □ 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 - 6TH EDITION OF THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 6th 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/cstage/CSManual010400.pdf). These staging criteria should be used for new trials.
APPENDIX IX - NOMENCLATURE

Tumour and Target Volumes
Volume naming is to be done in accordance with the system below.

Primary Site
The gross extent of the primary will be contoured and named “GTV” without additional prefix or suffix.

Gross Lymph nodes
All visible nodes > 1cm, or a node of any size thought to be at risk of harboring disease, are to be contoured and named according to the system below.

An individual node will be named “R” or “L” according to its laterality right or left.

This will then be followed by a number or numbers to indicate the anatomic nodal level or levels according to the consensus guidelines documents [Grégoire 2003; Grégoire 2006]. Alphanumeric scripting will be used to denote the nodal level.

For example, a left neck node extending from zone 2 into zone 3 would be named “L23” a right neck node occupying zone 1b would be named “R1b”. Multiple distinct nodes at a given level may be distinguished by use of a roman numeral prefix. For example 2 nodes in left zone 3 would be named “IL3” and “IIL3” respectively. In cases of nodal confluence, these can be contoured and labelled as one volume.
Normal Tissue Volumes
Normal tissue volume nomenclature should comply with the following naming. Only those volumes relevant to
the treatment plan should be included in the plan.

<table>
<thead>
<tr>
<th>Structure name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPAROTID</td>
<td>left parotid gland</td>
</tr>
<tr>
<td>RPAROTID</td>
<td>right parotid gland</td>
</tr>
<tr>
<td>LSUB</td>
<td>left submandibular gland</td>
</tr>
<tr>
<td>RSUB</td>
<td>right submandibular gland</td>
</tr>
<tr>
<td>CORD</td>
<td>spinal cord</td>
</tr>
<tr>
<td>BRSTEM</td>
<td>brainstem</td>
</tr>
<tr>
<td>BRAIN</td>
<td>brain</td>
</tr>
<tr>
<td>NEURO</td>
<td>brainstem and spinal cord</td>
</tr>
<tr>
<td>CANAL</td>
<td>spinal bone canal</td>
</tr>
<tr>
<td>REYE</td>
<td>right globe</td>
</tr>
<tr>
<td>LEYE</td>
<td>left globe</td>
</tr>
<tr>
<td>RLENS</td>
<td>right lens</td>
</tr>
<tr>
<td>LLENS</td>
<td>left lens</td>
</tr>
<tr>
<td>RCHAMBER</td>
<td>includes right lens and vitreous canals</td>
</tr>
<tr>
<td>LCHAMBER</td>
<td>includes left lens and vitreous canals</td>
</tr>
<tr>
<td>ROPTIC</td>
<td>right optic nerve</td>
</tr>
<tr>
<td>LOPTIC</td>
<td>left optic nerve</td>
</tr>
<tr>
<td>CHIASM</td>
<td>optic chiasm</td>
</tr>
<tr>
<td>OPTIC</td>
<td>chiasm/right and left optic nerves</td>
</tr>
<tr>
<td>RIEAR</td>
<td>right inner ear</td>
</tr>
<tr>
<td>LIEAR</td>
<td>left inner ear</td>
</tr>
<tr>
<td>RMEAR</td>
<td>right middle ear</td>
</tr>
<tr>
<td>LMEAR</td>
<td>left middle ear</td>
</tr>
<tr>
<td>RACOUSTIC</td>
<td>middle and inner ear</td>
</tr>
<tr>
<td>LACOUSTIC</td>
<td>middle and inner ear</td>
</tr>
<tr>
<td>LARYNX</td>
<td>larynx</td>
</tr>
<tr>
<td>MANDIBLE</td>
<td>mandible</td>
</tr>
<tr>
<td>RMANDIBLE</td>
<td>right mandible</td>
</tr>
<tr>
<td>LMANDIBLE</td>
<td>left mandible</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>esophagus</td>
</tr>
<tr>
<td>RLUNG</td>
<td>right lung</td>
</tr>
<tr>
<td>LLUNG</td>
<td>left lung</td>
</tr>
<tr>
<td>RPLEXUS</td>
<td>right brachial plexus</td>
</tr>
<tr>
<td>LPLEXUS</td>
<td>left brachial plexus</td>
</tr>
<tr>
<td>POSTCRICOID</td>
<td>posterioric pharynx</td>
</tr>
</tbody>
</table>
APPENDIX X - STEPS IN THE CENTRAL RADIOTHERAPY QUALITY ASSURANCE PROGRAM

1. QARC facility questionnaire: treatment centres complete the HN6 facility questionnaire available on QARC website.

2. Credentialing test notification: QARC will notify the treatment centre either to complete the credentialing test case or that they are exempted based on a prior approval status.

3. Credentialing submission: test case provided by QARC; documentation sent from treatment centre to QARC.

4. QARC written credentialing report to treatment centre: sent via email letter from QARC to treatment centre. All centers participating in the study will require credentialing for the delivery of 3D CRT or IMRT or both prior to local activation.

5. QARC written credentialing report to CTG: from treatment centre to CTG as part of the local activation documentation.

6. Rapid review submission to QARC: Radiotherapy Quality Assurance Documentation sent from treatment centre to QARC within one week of starting treatment (Appendices XI and XII).

7. Rapid review results to treatment centers: sent via email letter from QARC to treatment centre within 24 hours of receipt documentation. This will detail whether or not revisions to make the plan compliant with protocol are needed.

8. Submission to QARC of treatment center’s rapid review response: If revisions are needed, treatment centre sends comments about changes requested by the reviewer and other supporting documents if requested to QARC within 72 hours of receipt of the rapid review results.

9. Revisions of Treatment center’s rapid review response: QARC will decide whether or not the deviations will be reversed within 24 hours of receipt of comments and new supporting documentation. Sent via email letter from QARC to treatment centre.

10. Final review submission to QARC: Radiotherapy Quality Assurance Documentation sent from treatment centre to QARC within one month of treatment completion (Appendices XI and XII).

11. Final review summary report to treatment centers: sent via email from QARC to treatment centre within 24 hours of receipt documentation. QARC indicates if protocol deviations are present and signs form.

12. Signed Final Review Summary to QARC: treatment centre sends a signed Final Review Summary to QARC as a confirmation that the reported information is accurate.

13. Final summary review report to CTG: QARC final summary report data transferred to the NCIC CTG.

NOTE: 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. In such cases the new plan will be submitted for QARC review.
5. Confirmation Credentialing

1. QARC Facility Questionnaire
2. Credentialing Test Notification
3. Credentialing Submission
4. Credentialing Report
5. 
6. Rapid Review Submission
7. Rapid Review Results
8. Rapid Review Response
9. Rapid Review Results
10. Final Review Submission
11. Final Review Summary Report
APPENDIX XI - RADIOTHERAPY QUALITY ASSURANCE DOCUMENTATION

This study requires the submission of the treatment planning data in digital format. Submission of the plan in either DICOM RT or RTOG format is preferred. Sites that have a treatment planning system that cannot export data in DICOM RT or RTOG formats may create screen capture images of the required documentation. For submission instructions for DICOM RT or RTOG format files see Appendix XII.

**Required documentation and Timelines:**

**Real-time (rapid) Review:**
Within one week of the start of radiotherapy for each patient, the following data for real-time review shall be submitted:

**Diagnostic Imaging Data to be submitted:**
Copies of the pre-study diagnostic imaging used to define the GTV and CTV. DICOM format files can be copied to a CD and submitted to QARC. Multiple studies for a patient may be included on a CD, but please include only one patient per CD.

**Radiotherapy Data to be submitted:**

- **Digital data submission** shall include:
  - Planning CT images
  - Target volumes and normal structures
  - Beam geometry
  - 3D dose distributions in absolute dose for each phase of treatment (concurrently treated beams) and for the total treatment
  - DVHs for the total treatment for all PTVs and for any required critical normal structures in these volumes. If IMRT is used, a DVH shall also be submitted for a category of tissue called “unspecified tissue,” which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

- Hardcopy isodose distributions for the total dose plan in the axial, sagittal and coronal planes, which includes the isocenter of the planning target volume, must be submitted along with total dose DVHs for digital data validation. These may be sent to QARC as screen captures (FTP, e-mailed or mailed on a CD).

- **Additional data** to accompany digital submissions shall include the following. These may be sent to QARC as screen captures and/or scanned documents (FTP, e-mailed or mailed on a CD).
  - For 3D CRT, copies of simulator films and/or digitally reconstructed radiographs (DRRs) for each field. It is strongly encouraged that the GTV, CTVs and PTV70, optPTV50/ optPTV56 be displayed on the films or DRRs.
  - First day portal films (or hard copy of real time portal images) if achievable.
  - One set of orthogonal anterior/posterior and lateral DRRs and portal films/images for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
  - Centers utilizing cone beam imaging for verification should submit day one orthogonal films matched to similar anterior/posterior and lateral DRRs on which the isocenter is indicated.
  - Prescription for the ENTIRE treatment.
  - RT-1 or IMRT Dosimetry Summary Form.
  - Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
• Beam eye’s views (BEVs) of portals showing collimator, beam aperture, target volume and critical structures.
• A room eye's view (REV), i.e. a composite illustration of all the fields and their angles, if available from your planning system.

Final Review:
Within one month of the completion of radiotherapy the following data for each patient shall be submitted:

• RT 2 - Radiotherapy Total Dose Record form.
• A copy of the patient’s radiotherapy record including prescription, and the daily and cumulative doses to all required areas and critical organs.
• If the patient’s treatment plan was modified subsequent to the reporting of the real-time data, submit data as specified under the real time review for the modified plan.

Data copied on to a CD should be forwarded to:

ATTN: NCIC HN.6
Quality Assurance Review Center
272 West Exchange St., Suite 101
Providence, Rhode Island 02903-1025
Phone: (401) 454-4301
FAX: (401) 454-4683

E-mailed data can be sent to: NCIC@QARC.org.

Please see Appendix XII for Digital Data Submission via FTP.

Questions regarding the dose calculations, documentation or data submission should be directed to: NCIC@QARC.org.

Or contact the QARC at the number above.
APPENDIX XII - DIGITAL DATA SUBMISSION PROCEDURES TO QARC

A  DIGITAL DATA FORMAT

For digital data submission, an institution’s treatment planning system must have the capability of exporting data in one of two formats:

- RTOG Data Exchange Format, Version 3.20 or later (specifications at http://itc.wustl.edu/exchange_files/tapeexch400.htm ); or
- DICOM 3.0 in compliance with the ATC's DICOM 3.0 Conformance Statement

The commercial systems that are known to have this capability are listed on the ATC website (http://atc.wustl.edu/credentialing/atc_compliant_tps.html).

The capability for QARC to accept digital RT data using the method described below has been developed with the Advanced Technology Consortium (NIH grant CA81647).

Institutions may submit treatment planning data in one of these formats on a CD or electronically via ftp to QARC. Institutions must obtain a username and password for submission of data via ftp. To request an FTP account, please complete the FTP Account Request Form (available at www.qarc.org/DigitalData/FTPAccountRequest.pdf) and email it to ATCDICOMRT@QARC.org. Please include your name and your institution’s name and address as well as the best way to contact you (i.e. phone number, e-mail address, etc.). Allow 3 business days to process your account request.

Contact QARC at ATCDICOMRT@QARC.org or 401-454-4301 if you have any questions.

B  SUBMITTING DIGITAL DATA VIA THE INTERNET

Digital treatment planning data in RTOG Data Exchange or DICOM RT format can be submitted to QARC over the Internet using FTP. Effective April 9, 2007, the QARC FTP server uses Secure FTP (SFTP). Secure FTP (SFTP) uses the SSH network protocol and offers several advantages over FTP, including secure (encrypted) transport of usernames, passwords, and data, and compatibility with most firewall configurations.

Please use the following steps to submit data via SFTP:

1. Complete the FTP Account Request Form and e-mail it to ATCDICOMRT@QARC.org to obtain an FTP account.
2. QARC’s SFTP address is ftpatc.qarc.org (current IP address 204.17.95.243).
3. For many users, the SFTP upload procedure is essentially the same as for FTP, except that a new SFTP client may be needed. SFTP client software, both commercial and open-source, is broadly available. Windows clients include WS_FTP Professional (commercial), FileZilla (free/open-source) and WinSCP (free/open-source). For Linux systems, both graphical (gftp) and command-line (sftp) programs are included with most distributions.
5. Problems in connecting to the QARC SFTP server, may be caused by your institution's firewall configuration. An outbound connection from your computer to TCP Port 22 on host ftpatc.qarc.org is required. (Although allowing such a connection is considered safe, it is sometimes disallowed by default.) Please consult you local firewall/network administrator.
6. Instructions for Specific Treatment Planning Systems are linked below:
   
   
   • Philips/Pinnacle - Contact Philips support for help in installing command-line SFTP client.

7. Once you are connected to the QARC SFTP server, change to the “incoming” directory. (CD incoming)

8. Create a new sub-directory within “incoming” with a name that is pertinent to the data that you are submitting (mkdirCase01423totalplan). Please do not use spaces in directory names or filenames.

9. Send e-mail to ATCDICOMRT@QARC.org to indicate that you have uploaded protocol case data. Please identify the study group, protocol, and case number for the submission as well as your contact information.

10. In order for QARC to confirm that your data has been received and imported correctly, please send images showing structures and the dose distribution in three orthogonal planes along with total dose DVHs. These may be screen dumps sent via e-mail as jpeg, bitmap, or tiff files or they may be hardcopies mailed to the QARC.

Please see Appendix XI for the complete list of quality assurance materials to be submitted and the required timelines.

C- SUBMITTING DIGITAL DATA VIA CD

Digital patient treatment planning data may be written to CD and the CD mailed to QARC. Most scanners have the option to write patient studies to CDs in DICOM. If you have a PACS system, you should be able to choose to export studies to a CD in DICOM format; this is the preferred method of submission. Some PACS systems may export studies only in their proprietary format; these are acceptable only if the viewer is also included on the CD.

Please follow the next instructions to submit data via CD:

1. Be sure to label the CD with the study group, protocol, and case number.

2. Include only one patient per CD. You may send multiple studies for one patient on each CD.

3. Do not send diagnostic imaging as .jpg, .bmp, power point, or any other non-DICOM format, as the ability to window, level and measure is lost.

4. In order for QARC to confirm that your data has been imported correctly; please include hardcopies showing structures and the dose distribution in three orthogonal planes along with total dose DVHs and send to the QARC. These may be sent to QARC (FTP, e-mailed or mailed on a CD) as screen captures saved as an image file (jpeg, bitmap, tiff) and/or scanned documents.

Please see Appendix XI for the complete list of quality assurance materials to be submitted and the required timelines.
APPENDIX XIII - SWALLOWING IMPAIRMENT SUB-STUDY PROCEDURES.

Digital Data Capture:

The data will be recorded using a digital video imaging (computer movie file recording). A high resolution videofluoroscopic recording device will be used for signal acquisition and digital storage and retrieval of these swallowing data. Each swallow study will be recorded directly to computer storage media for instantaneous retrieval and playback of the exams at full video resolution. Video recordings will be made with a resolution of 30 frames per second.

Digital Data Submission:

Results will be captured digitally and sent via password protected discs to this address:

Rosemary Martino, MA MSc PhD
Assistant Professor, Department of Speech Language Pathology
University of Toronto
160-500 University Ave.,
Toronto, ON Canada M5G 1V7

Be sure to label the CD with the study group, protocol, and case number. Include only one patient per CD. Participating centers should submit digital data to the central interpretation Lab within one week after the videofluoroscopy was performed.

Central Interpretation:

Interpretation of results will be made by 2 blinded speech language pathologists using the MBSImP tool. Speech Language Pathologist will score the de-identified studies.

All swallow studies will be converted from the native uncompressed format to a universal, compressed digital video format (.mpg) prior to distribution to Speech Language Pathologist raters for analysis. All converted studies will be collected and de-identified for protection of personal information.

The central interpretation Lab will make the interpretation of results and will complete the MBSImP within one month the digital data was received.

All digitally recorded videos will be saved on the computer following completing of the swallow study and will be saved to DVD and stored in the Swallowing Lab at the University of Toronto. One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams.
APPENDIX XIV - CENTRAL RADIOLOGY ARCHIVING

For all patients we are going to have central radiology archiving. Submit the following studies with their corresponding reports to the address below.

- CT or MRI of head and neck done within 8 weeks prior to randomization.
- All positive images to document first progression or recurrence.

Hard copies or digital data DICOM format (preferred) will be submitted for central archiving to:
  Quality Assurance Review Center  
  272 West Exchange Street, Suite 101  
  Providence, Rhode Island 02903-1025  
  Phone: (401) 454-4301  
  Fax: (401) 454-4683

Submission of Diagnostic Imaging data in digital format is preferred over hard copies of films. Digital files must be in DICOM format. These files can be burned to a CD and mailed to QARC.

Please follow the next instructions to submit data via CD:

- Be sure to label the CD with the study group, protocol, and case number.
- Include only one patient per CD. You may send multiple studies for one patient on each CD.
- Do not send diagnostic imaging as .jpg, .bmp, power point, or any other non-DICOM format, as the ability to window, level and measure is lost.
- Some PACS systems may export studies only in their proprietary format; these are acceptable only if the viewer is also included on the CD.

Institutions with PACS systems can contact QARC regarding installation of the COG Dicommunicator software that manages e-mailing studies securely to QARC. Information about this software could be found at: www.qarc.org/dicommunicator.htm. There is a one-time cost per workstation to install Dicommunicator on one workstation. Contact COG@QARC.org for further information.

All demographic data and patient identifiers should be removed from films, images, digital data and reports and should be replaced with the NCIC CTG Study Number, NCIC CTG Patient Serial Number, Patient Hospital Chart Number, Patient Initials and Date of Scan. The Dicommunicator software scrubs demographic (patient name) data from the images and replaces it with the protocol and patient registration number.

All images will be collected retrospectively and should be submitted to QARC within 3 months of their realization.
APPENDIX XV - CORRELATIVE SCIENCES QUESTIONNAIRE

Instructions for Administration of the Correlative Science Questionnaire

The instructions below are intended as a guide for the administration of the Correlative Science Questionnaire.

1. **Preamble**

   Correlative science 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 series of questions which should be completed from the patient’s perspective.

   The scheduled time to obtain the questionnaire is:

   • After patient consent obtained.

   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 the questionnaire has not been completed, please document the reason(s) on the appropriate case report form.

2. **Assessment**

   It should be explained to the patient that the purpose of the questionnaire is to collect information such as race and ethnicity, family history, smoking and alcohol exposure, vitamin and medication use as well as demographic data to analyze its relation with the results of the tested treatment.

   This questionnaire will be completed by all patients who consent to participate in the specimen banking portion of the study and will be completed after randomization and prior to start of treatment.

   The Correlative Science Questionnaire should be given to the patient to be completed at his/her home or at the clinic.

   The Clinical Research Associate (CRA) should collect the questionnaire at the next patient clinic visit.

3. **What If...**

   The patient leaves the clinic and someone forgets to give the questionnaire to the patient.

   Contact the patient by phone informing him or her that the questionnaire will be mailed.

   Mail a blank questionnaire to the patient with instruction to be completed with instructions to return the completed questionnaire at the next clinic visit.

4. **Inability to Complete the Correlative Science Questionnaire**

   Assistance may be used to complete the questionnaire.
Correlative Sciences Questionnaire – ENGLISH

NCIC CTG Trial: HN.6

This page only to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____________  Patient Initials: _____________ (first-middle-last)
Institution: ___________________________________________  Investigator: ______________________________

THIS QUESTIONNAIRE COULD BE TAKEN BACK TO PATIENT’S HOME TO BE COMPLETED, NOT AT THE CLINIC.

Scheduled time to obtain this Correlative Sciences Questionnaire:
After patient consent obtained.

Date questionnaire completed: __ __ __ __ - __ __ __ - __ __
            yyyy    mmm     dd

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

Comments: _____________________________________________________

_________________________________________________________________

_________________________________________________________________

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

NCIC CTG use only

Logged: _______  Study Coord: _______  RA: _______  Data Ent’d: _______
            - - -   - - -   - - -   - - -   - - -

Verif: _______
Correlative Sciences Questionnaire HN6

INSTRUCTIONS

- Answer by marking the correct box or filling in the spaces provided.  
  Example:  ☐ Yes  
  ☒ No
- You may skip any question that you do not want to answer
- Some questions have a follow-up question.
  Example:  11. Have you ever tried to quit smoking?
  ☐ No (go to question 12)
  ☐ Yes
  a) How many times?
     ____ ___ # times

HELPFUL INFORMATION: Some information is used to help describe the patients in our study as a whole. No individual’s information will be analyzed alone.

YOUR BACKGROUND

1. In what country were you born?  
   Name of country

2. What is your race? Mark all that apply.
   ☐ White
   ☐ Black or African origin
   ☐ First Nations or North American Indian or Indigenous Peoples
   ☐ East or South Asian, Native Hawaiian or other Pacific Islander
   ☐ Spanish, Latino, or Hispanic (please specify): ______________________________________________________
   ☐ Some other race (please specify):________________________________________________________________
   ☐ Don’t Know

3. What was your weight before illness? ___ ___ pounds or ___ ___ kg

4. What is (or was) your primary occupation (job) for most of your life?

   Primary Occupation/Job
FAMILY HISTORY

5. **Are you adopted?**
   - ☐ Yes
   - ☐ No

6. **Can you answer questions about your blood (natural) relatives?**
   - ☐ Yes
   - ☐ No (go to question 8)

7. **Please answer the following questions about your natural parents, brothers or sisters, and children.**
   **Fill in the table.**
   
   *Do not include aunts, uncles, grandparents or grandchildren, adopted, step or half relatives.*

<table>
<thead>
<tr>
<th>Relationship (e.g. mother, father, sister, brother, son, daughter)</th>
<th>Are they still Alive?</th>
<th>How old are they now (or how old were they when they died)?</th>
<th>Did they ever have cancer?</th>
<th>What type(s) of cancers, and their (approximate) age(s) of diagnosis?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Example: Brother #1</td>
<td>☒</td>
<td>☐</td>
<td>49 yrs</td>
<td>☐</td>
</tr>
<tr>
<td>Mother</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
</tr>
<tr>
<td>Father</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
</tr>
<tr>
<td>Daughter # ____</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
</tr>
<tr>
<td>Daughter # ____</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
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<tr>
<td>Daughter # ____</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
</tr>
<tr>
<td>Son # ____</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
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<tr>
<td>Son # ____</td>
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<td>____ yrs</td>
<td>☐</td>
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<tr>
<td>Son # ____</td>
<td>☐</td>
<td>☐</td>
<td>____ yrs</td>
<td>☐</td>
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</table>

continued on next page …
**Question continued from previous page:**

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<thead>
<tr>
<th>Relationship (e.g. mother, father, sister, brother, son, daughter)</th>
<th>Are they still Alive?</th>
<th>How old are they now (or how old were they when they died)?</th>
<th>Did they ever have cancer?</th>
<th>What type(s) of cancers, and their (approximate) age(s) of diagnosis? If you don’t know which type, write “Don’t know”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: Brother #1</td>
<td>Yes</td>
<td>49 yrs</td>
<td>No</td>
<td>Examples include: Breast, Ovarian, Uterus, Lung, Colon or Rectal, Bladder, Prostate, or Pancreas Cancer, Melanoma, Leukemia or Lymphoma, Sarcoma</td>
</tr>
<tr>
<td>Brother # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td>colon cancer, 46 yrs</td>
</tr>
<tr>
<td>Brother # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td>Lymphoma, 30’s</td>
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<tr>
<td>Brother # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
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<td>No</td>
<td>____ yrs</td>
<td>No</td>
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<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
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<tr>
<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Sister # _____</td>
<td>No</td>
<td>____ yrs</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
SMOKING AND EXERCISE

8. Have you ever smoked at least 100 cigarettes (5 packs) in your entire life?
   □ Yes (go to question 9)
   □ No (go to question 18)
   □ Don’t Know (go to question 18)

9. How old were you when you first started smoking cigarettes on a regular basis (at least 5 cigarettes per week)?
   ___ ___ Age started smoking cigarettes regularly

10. In the year before you were diagnosed, did you smoke cigarettes?
    □ Yes (go to question 11)
    □ No not at all
    
    a) At what age did you last stop smoking cigarettes?
       ___ ___ Age stopped smoking
    
    b) Excluding all the times you may have quit, how many years did you smoke cigarettes?
       ___ ___ Years
       □ Don’t Know

11. Have you ever tried to quit smoking?
    □ No (go to question 12)
    □ Yes
    
    a) How many times? ___ ___ # times

12. On average, how many cigarettes do/did you smoke each day? If you are now ill, think about the average amount you smoked before your current illness.
    ___ ___ Cigarettes per day

13. How soon after you wake up do you / did you smoke your first cigarette?
    □ after 60 minutes
    □ 31-60 minutes
    □ 6-30 minutes
    □ within 5 minutes

14. Do you/did you find it difficult to refrain from smoking in places where it is forbidden, e.g. in the hospital or on the bus?
    □ Yes
    □ No

15. Is the first cigarette that you smoke in the morning the one that you hate to give up the most?
    □ Yes
    □ No
16. Do you/did you smoke more frequently during the first hours after waking than the rest of the day?
   - Yes
   - No

17. Did you ever smoke when you were so ill that you are in bed most of the day?
   - Yes
   - No

18. We are interested in your exposure to smoke from other people’s cigarettes and tobacco products. Please complete the table below.

<table>
<thead>
<tr>
<th>Were you exposed to smoke from other people’s cigarettes or tobacco products during:</th>
<th>Yes</th>
<th>No</th>
<th>For how many hours per day? (Best guess)</th>
<th>For how many years? (Best guess)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood at home</td>
<td></td>
<td></td>
<td>___ hours</td>
<td>___ years</td>
</tr>
<tr>
<td>Adulthood at home</td>
<td></td>
<td></td>
<td>___ hours</td>
<td>___ years</td>
</tr>
<tr>
<td>Adulthood at work</td>
<td></td>
<td></td>
<td>___ hours</td>
<td>___ years</td>
</tr>
</tbody>
</table>

19. How many days per week did you exercise for 20 minutes or more, 1 year prior to diagnosis? (Best estimate)
   - None
   - 1-2 days
   - 3-4 days
   - 5 or more days

20. How many days per week do you exercise for 20 minutes or more, now?
   - None
   - 1-2 days
   - 3-4 days
   - 5 or more days

VITAMINS:

21. Since you were 18 years old, have you ever taken any of these supplements at least once a week for a year? Fill in the table.

<table>
<thead>
<tr>
<th>Vitamin(s)</th>
<th>At least once a week for a year?</th>
<th>If yes, total years taken since age 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin (that contains ten or more vitamins and/or minerals). An example of a multivitamin is Centrum®</td>
<td>□ Yes □ No</td>
<td>1-4 □ □ □ □ □ □</td>
</tr>
<tr>
<td>Vitamin C (not in a multivitamin)</td>
<td>□ Yes □ No</td>
<td>5-9 □ □ □ □ □ □</td>
</tr>
<tr>
<td>Vitamin E (not in a multivitamin)</td>
<td>□ Yes □ No</td>
<td>10-14 □ □ □ □ □</td>
</tr>
<tr>
<td>Calcium (not in a multivitamin)</td>
<td>□ Yes □ No</td>
<td>15-24 □ □ □ □ □</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25+ □ □ □ □ □ □</td>
</tr>
</tbody>
</table>
### 22. If you took a multivitamin, how often did you take it?
- [ ] No I never took a multivitamin or I took a multivitamin less often than once a week
- [ ] 1-3 days per week
- [ ] 4-6 days a week
- [ ] every day (7 days a week)

### 23. Since you were 18 years old, did you take any of the following medications?
*Fill in the table. Mark all that apply.*

<table>
<thead>
<tr>
<th>Did you ever take these drugs for at least once a week for at least one year?</th>
<th>If Yes, for how long (approximately)?</th>
<th>For how many days every week on average (approximately)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid Such as aspirin, Anacin®, Bufferin®</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
<tr>
<td>Acetaminophen Such as Tylenol®, Panadol®, Tempra®</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
<tr>
<td>Ibuprofen Such as Advil®, Motrin®, Rufen®, Medipren®, Nuprin®</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
<tr>
<td>Naproxen Such as Aleve®</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
<tr>
<td>Other Anti-Inflammatory Drugs Such as Indocin®, Lodine®, Voltaren®, Relafen®, Clinoril®</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
<tr>
<td>Cox-2 Inhibitors Such as Celebrex®, Vioxx®, Bextra®</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
<tr>
<td>Cholesterol Statin Medications Such as Lipitor®, Zocor, Mevacor, Pravachol, or Crestor</td>
<td>☐ Yes, at least once a week for at least one year ☐ No, not that often</td>
<td>__ __ __ years</td>
</tr>
</tbody>
</table>
24. Have you ever drank at least 1 glass of alcohol per month for at least one year of your life?
   □ Yes (go to question 25)
   □ No (go to question 28, page 8 if you are a woman, and page 9, question 33 if a man)
   □ Don’t Know (go to question 28, page 8 if a woman, and page 9, question 33 if a man)

25. How old were you when you first started drinking at least 1 glass of alcohol per month for at least one year of your life?
   ___ ___ age started drinking alcohol (in years)

26. In the year before you were diagnosed with cancer, did you drink at least 1 glass of alcohol per month for at least one year of your life?
   □ Yes (go to question 27)
   □ No, not at all

   a) At what age did you stop drinking alcohol?
      ___ ___ Age stopped drinking alcohol (in years)

27. Please fill in table. Fill in the period of time using your age, and the average amount you drank for that period. You may use multiple age ranges if your drinking habits have changed over the years. If you are still drinking fill in your current age as the “ending age”.

   One drink means one can/bottle/mug of beer, one 6 ounce glass of wine, or one ounce of hard liquor.

<table>
<thead>
<tr>
<th>Type of alcohol</th>
<th>Time period Starting age (years)</th>
<th>Time period Ending age (years)</th>
<th>Average weekly consumption of drinks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>Age ___ years to Age ___ years</td>
<td></td>
<td>[ ] 0  [ ] 1-2  [ ] 3-5  [ ] 6-11 [ ] 12-23 [ ] 24+</td>
</tr>
<tr>
<td>Wine</td>
<td>Age ___ years to Age ___ years</td>
<td></td>
<td>[ ] 0  [ ] 1-2  [ ] 3-5  [ ] 6-11 [ ] 12-23 [ ] 24+</td>
</tr>
<tr>
<td>Hard Liquor (e.g. gin, vodka)</td>
<td>Age ___ years to Age ___ years</td>
<td></td>
<td>[ ] 0  [ ] 1-2  [ ] 3-5  [ ] 6-11 [ ] 12-23 [ ] 24+</td>
</tr>
</tbody>
</table>
WOMEN’S HISTORY:

Fill in only if you are a woman. If you are a man, proceed to question 33.

28. How old were you when you had your first menstrual period?
   ___ ___ Age in years.
   □ Never had a period
   □ Don’t know

29. Have you ever given birth to a child? Do not include miscarriages in the first 5 months of pregnancy
   □ Yes
   □ No (go to question 30)
   a) How old were you when your first child was born?
      ___ ___ Age in years.
   b) How many times have you given birth?
      ___ ___ times in your lifetime

30. Have you had periods in the last year? Mark only one.
   □ Yes (go to question 31)
   □ Yes, but not regularly (go to question 31)
   □ Yes, because I take hormones (go to question 31)
   □ No
   a) How old were you when your periods permanently stopped?
      ___ ___ age periods stopped (best guess)
   b) Why did your periods stop?
      □ Natural menopause (Change in life)
      □ Surgery (such as having your ovaries or uterus removed)
      □ Other ________________________________

31. Have you ever used pills, shots, patches or hormone implants for birth control or to regulate periods?
   □ Yes
   □ No (go to question 32)
   □ Don’t Know (go to question 32)
   a) How many years (total) did you use pills, shots, patches or hormone implants for birth control or to regulate periods?
      ___ ___ years (best guess)
32. Have you ever used estrogen (hormone) replacement therapy (HRT) to help with menopausal symptoms? Only include pills, shots, patches or hormone implants that require a doctor’s prescription. Do not include birth control pills.
   □ Yes
   □ No (go to question 33)
   □ Don’t Know (go to question 33)
   a) How old were you when you first used HRT?
      __ __ age you used HRT (hormones)
   b) How many years (total) have you used (or did you use) HRT?
      __ __ years that you used hormones
   c) Do you take HRT now?
      □ Yes
      □ No

33. 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.)

34. What is your marital status?
   □ Married
   □ Living as married
   □ Widowed
   □ Separated
   □ Divorced (or annulment)
   □ Single, never married or never lived as married
   □ Don’t Know

35. Who filled in this questionnaire?
   □ Patient
   □ Patient’s family member (specify relationship, e.g. wife, etc.) ____________________________
   □ Study personnel (specify) __________________________________________________________
   □ Other (specify) _________________________________________________________________

38. Date this questionnaire was completed __ __ __ __ / __ __ __ / __ __
   Comments:
   ____________________________________________________________
   ____________________________________________________________

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 for completing this questionnaire!
# LIST OF CONTACTS

<table>
<thead>
<tr>
<th>Contact</th>
<th>Tel. #</th>
<th>Fax #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADMINISTRATIVE QUERIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May Mak</td>
<td>613-533-6430</td>
<td>613-533-2941</td>
</tr>
<tr>
<td>Clinical Trials Assistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCIC CTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Email:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="mailto:mmak@ctg.queensu.ca">mmak@ctg.queensu.ca</a></td>
<td></td>
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<tr>
<td><strong>STUDY SUPPLIES</strong></td>
<td></td>
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</tr>
<tr>
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<td>613-533-6430</td>
<td>613-533-2941</td>
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<tr>
<td>Forms, Protocols</td>
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<tr>
<td>Available on NCIC CTG Website:</td>
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<td><a href="http://www.ctg.queensu.ca">http://www.ctg.queensu.ca</a></td>
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<td><strong>PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES</strong></td>
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<tr>
<td></td>
<td>613-533-6430</td>
<td>613-533-2941</td>
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<tr>
<td>(including eligibility questions and protocol management)</td>
<td></td>
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</tr>
<tr>
<td>Alexander Montenegro</td>
<td></td>
<td></td>
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<tr>
<td>Study Coordinator</td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>Email:</td>
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<tr>
<td><a href="mailto:amontenegro@ctg.queensu.ca">amontenegro@ctg.queensu.ca</a></td>
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<tr>
<td>or</td>
<td></td>
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<tr>
<td>Dr. Wendy Parulekar</td>
<td></td>
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<tr>
<td>Senior Investigator</td>
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<td><a href="mailto:wparulekar@ctg.queensu.ca">wparulekar@ctg.queensu.ca</a></td>
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<tr>
<td><strong>STUDY CO-CHAIRS</strong></td>
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<tr>
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<tr>
<td>Dr. Lillian Siu</td>
<td></td>
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<td>Study Co-Chair</td>
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<td><a href="mailto:lillian.siu@uhn.on.ca">lillian.siu@uhn.on.ca</a></td>
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<td>or</td>
<td></td>
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<tr>
<td>Dr. John Waldron</td>
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<td><a href="mailto:john.waldron@rmp.uhn.on.ca">john.waldron@rmp.uhn.on.ca</a></td>
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<td><strong>MEDICAL PHYSIC CONTACT</strong></td>
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<td>Stephen Breen</td>
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<td>Medical Physic Contact</td>
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<td><a href="mailto:stephen.breen@rmp.uhn.on.ca">stephen.breen@rmp.uhn.on.ca</a></td>
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<td><strong>SERIOUS ADVERSE EVENT REPORTING</strong></td>
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<td>See protocol Section 11.0 for details of reportable events.</td>
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<td>Dr. Wendy Parulekar</td>
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<td>Senior Investigator</td>
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<td>Alexander Montenegro</td>
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<td>See Appendix III for full details.</td>
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<td>Tony Pascoal</td>
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<td>Investigational Drug Research Services (IDRS)</td>
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