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CANADIAN CANCER TRIALS GROUP (CCTG)

NEO**A**DJUVANT CHEMOTHERAPY, **E**XCISION AND **O**BSERVATION FOR EARLY RECTAL CANCER: The NEO Trial.

CCTG Protocol Number: **CO.28**

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

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

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

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

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

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

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

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

I attest that all surgeons from our institution who will perform Transanal Endoscopic Microsurgery (TEM) or Transanal Minimally Invasive Surgery (TAMIS) for CO.28 patients have previously performed the procedure in at least 20 previous rectal cancer patients.

_____ _____

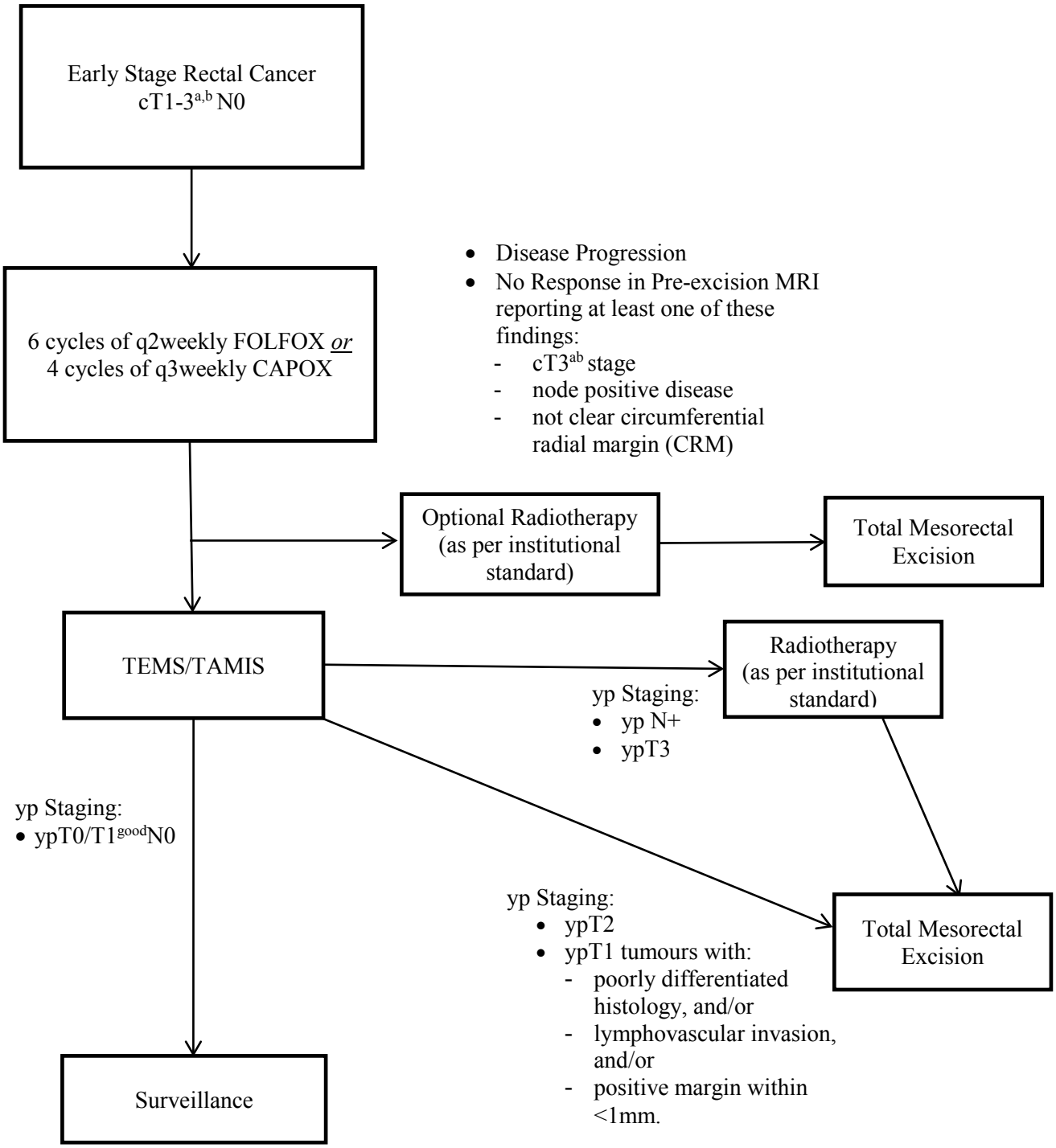
Qualified Investigator Date
(printed name and signature)

Protocol Number: CCTG CO.28

CENTRE: _____

TREATMENT SCHEMA

This is a two staged, single arm phase II trial of chemotherapy (FOLFOX or CAPOX) followed by tumour excision in patients with early stage rectal cancer.



1.0 OBJECTIVES

1.1 Primary Objective

To determine the organ preservation rate in patients with early (cT1-3[a,b]N0) rectal cancer treated with neoadjuvant FOLFOX or CAPOX and TEMS or TAMIS.

1.2 Secondary Objectives

1. To describe the 3-year Locoregional Relapse Rate (LRR) in patients treated with organ preservation.
2. To describe the 3-year Distant Relapse Rate (DRR) in patients treated with organ preservation.
3. To describe the 3-year Disease Free Survival (DFS) rate in patients treated with organ preservation.
4. To evaluate the rate of post-operative complications following neoadjuvant FOLFOX/CAPOX and tumour excision/surgery.
5. To evaluate nature, severity and frequency of acute and long term toxicities in all patients.
6. To evaluate Quality of Life (QoL) in all patients.
7. To evaluate the cost-effectiveness of the neo-adjuvant chemotherapy approach vs. the current standard approach.

1.3 Tertiary Objectives

To evaluate the prognostic value of baseline ctDNA as an independent prognostic value in addition to ypstage and histology.

2.0 BACKGROUND INFORMATION AND RATIONALE

Colorectal cancer is the second most common cause of cancer death in North America, with rectal neoplasms accounting for one third of incident cases. The introduction of provincial colorectal cancer screening programs has led to earlier diagnosis and 35-40% of rectal tumours present with localized disease *[Jemal 2008]*. Current standard therapy for T1-3 tumours includes radical surgery with Total Mesorectal Excision (TME), and preoperative chemoradiation for patients with T3 tumours or N1 tumours. Locoregional relapse rates with modern adjuvant therapy are generally 5% *[Hong 2014; O'Connell 2014; Rodel 2014]*. Even with laparoscopic surgery, surgical complication rates are significant and temporary diverting ostomies are associated with significant morbidity and the requirement for second surgery for reversal *[Alberts 2012]*. In patients treated with radical resection, ongoing issues with bowel function, incontinence, sexual function and depression persist. These are significantly worse in patients treated with neoadjuvant or adjuvant radiotherapy *[Wiltink 2014]*.

Patients with low tumours, < 5 cm from the anal verge, commonly require permanent colostomies and the rates of non-sphincter sparing surgery in phase III trials of stage II/III rectal cancer is consistently 25% *[Gerard 2012; Allegra 2014]*. Loss of the rectum and a permanent colostomy has dramatic effects on quality of life, sexual/urinary and social function and at high economic cost.

Multiple single arm and randomized phase II studies have explored the use of pelvic chemoradiation (chemoXRT) followed by Transanal Endoscopic Microsurgery (TEMS) or Transanal Minimally Invasive Surgery (TAMIS) as a means to increase rectal organ preservation *[Lezoche 2012]*. However, even with minimally invasive surgery like TEMS/TAMIS, neoadjuvant radiation significantly increases wound-healing complications *[Marks 2009]* and adversely affects sphincter *[Hupkens 2015]* and sexual function. Furthermore, patients who develop recurrence with this strategy are difficult to salvage as radiotherapy is no longer an option. Conversely, there is virtually no prospective experience of neoadjuvant FOLFOX/CAPOX chemotherapy and excision/surgery for early rectal tumours.

Population based studies have documented an increasing use of local excision/minimally invasive surgery in the treatment of T1N0 or T2N0 rectal tumours *[Stitzenberg 2013; You 2007]*. In the United States, 2010 rates of local excision (LE) for T1 and T2 tumours were 62% and 21%, respectively *[Stitzenberg 2013]*. The use of adjuvant radiation with LE has decreased between 1998 and 2010 to an estimated frequency of 10% (T1) and 35% (T2) *[Stitzenberg 2013]*. Nevertheless, a significant proportion of clinical T1-2N0 tumours are pathologically node positive and the literature demonstrates an increased rate of local relapse with LE versus surgical resection *[Sgourakis 2011; Sajid 2014]*. Neoadjuvant chemotherapy has been shown to reduce locoregional recurrence in stage II/III rectal cancer (Bosset et al. 2006) and prospective trials are required to establish the role of chemotherapy in T1-T3, N0 rectal tumours treated without proctectomy. Induction chemotherapy is justified as a novel approach to reduce local and distant relapse for rectal tumours treated with excision alone and without the toxicities of pelvic radiation.

This two staged phase II trial will determine if patients with stage 1-2 rectal tumours will have better outcomes if they are treated with chemotherapy (FOLFOX or CAPOX) followed by minimally invasive surgery (TEMS or TAMIS). The primary objective of the study is to determine the rate of organ preservation and the trial will be a success if more than 65% of patients treated in the study end up having a rectum-sparing surgery. Similar studies in Europe use chemoradiation, which has a higher surgical complication rate and more long-term toxicity. If this study's primary endpoint is met, a randomized trial of radical surgery versus induction chemotherapy and organ preservation would be justified.

The shortened duration of induction FOLFOX chemotherapy proposed by this study reduces toxicity and is similar in duration to the ongoing phase III CRC.7 "PROSPECT" study to evaluate the role of induction chemotherapy as a means to avoid pelvic radiation. Pathologic stage after induction therapy (ypStage) remains the strongest and most consistent prognostic factor in rectal cancer and allows the safe stratification to observation after minimally invasive surgery or to radical surgery for those with ypT2 or higher stage tumours. The combination of reduced local recurrence and less radical surgery will substantially benefit patients while decreasing surgical and hospital resources and complications. The NEO Trial builds on the concept established by CRC.7 of neoadjuvant FOLFOX chemotherapy without pelvic irradiation as an experimental treatment for early rectal tumours.

Radical surgery for invasive rectal cancer aims to remove the primary tumour and locoregional nodes and tumour deposits. While local excision can successfully remove the primary tumour, complete nodal clearance is not possible with this technique. The role of neoadjuvant chemotherapy is to treat locoregional tumour spread and improve locoregional tumour control. In table I, the frequency of pathologic node involvement in cT1-3 tumours is summarized, and both standard and exploratory treatment approaches are listed.

Table 1. Pathologic node involvement (pN+) in cT1-3 tumours, with standard and exploratory treatment approaches.

Clinical Stage	pN+Rate	Standard Treatment	Exploratory Therapy
cT1N0	11-15%	TME	Excision/TEMS/TAMIS in low risk
cT2N0	22-28%	TME	Chemoradiation + TEMS = Chemoradiation + TME post (Randomized Phase II)
cT3N0	>30%	ChemoRT + TME	"Watch & Wait": multiple retrospective case series report a 50% organ preservation rate among patients with cT3+ tumours with a clinical response to induction chemoRT +/- chemotherapy.
[Verseveld 2015; Perez 2014; Minsky 1989; Brodsky 1992; Salinas 2011; Lezoche 2012; Habr-Gama 2013] Abbreviations: c: clinical; pN+: pathologic node positive; TME: total mesorectal excision (radical surgery); LE: local excision; ChemoRT: chemoradiation; TEMS: transanal excisional microsurgery.			

T1N0 Tumours

While proctectomy remains the standard for patients with T1N0 rectal cancer, a significant proportion of patients are treated with local excision alone due to lower morbidity and to allow organ preservation [Ptok 2007]. In 2010, 62% of T1 tumours were treated with LE of which < 10% received adjuvant radiation *[Stitzenberg 2013]*. The overall rate of nodal positivity for T1 tumours is reported to be 11-15% and predictors of lymph node metastasis include tumour size > 3 cm, high tumour grade (i.e. poorly differentiated), depth of tumour invasion into the lower third of the submucosa, the presence of lymphovascular invasion and lesions in the lower third of the rectum *[Nascimbeni 2004; Salinas 2011; Minsky 1989; Brodsky 1992; Nascimbeni 2002*]. Local excision is considered an appropriate treatment modality for carefully selected T1 rectal cancer patients without high-risk features who want to avoid surgery *[Monson 2013]*.

T1 tumours treated with LE are at increased risk of locoregional relapse and optimal adjuvant therapy for disease control and long-term organ preservation is not established. Numerous retrospective studies have described pelvic relapse rates of 6-14% among patients with T1 tumours *[You 2007; Endreseth 2005; Ptok 2007; Borschitz 2008]* and distal rectal tumours are at increased risk of both local and distant relapse *[Nascimbeni 2004]*. CALGB 8984 was a prospective study in which 59 patients with T1 rectal tumours were treated with local excision alone and had an observed locoregional relapse rate of 8% and a 10 year DFS of 75% *[Greenberg 2008]*.

T2N0 Tumours

A National Cancer Database study described that 17% of T2 tumours were treated with LE in 2010, of which an estimated 40% of patients received adjuvant radiation *[Stitzenberg 2013]*. The overall rate of nodal positivity in T2 tumours is reported to be 22-28% *[You 2007; Salinas 2011; Minsky 1989; Brodsky 1992]* and LE alone is not considered an acceptable standard among patients eligible for proctectomy. In CALGB 8984, 51 patients with T2 rectal tumours were treated with local excision and pelvic chemoradiation, and an 18% local relapse rate was observed *[Greenberg 2008]*. A randomized trial of 100 patients with clinical T2N0 tumours treated with chemoradiation compared subsequent modified TEMS (including significant perirectal fat/lymph node harvest) to laparoscopic TME. This RCT demonstrated pathological downstaging to ypT0/1 stage in half of patients. Rates of local and distant disease control were similar between the two arms, suggesting a combination of neoadjuvant therapy and expert TEM/TAMIS could be oncologically acceptable *[Lezoche 2012; Lezoche 2005]*.

T3N0 Tumours

Standard therapy for patients with T3N0 rectal tumours is trimodality therapy with radical surgical resection plus combination 5-fluorouracil chemotherapy and external beam radiation therapy (EBRT). Patients with pathologic high-risk features are considered for post-operative chemotherapy. Retrospective case series have reported favourable outcomes among highly select groups of stage II/III rectal cancer after complete clinical response to induction therapy. Survival outcomes of patients treated with local excision after complete clinical or pathologic response (excisional biopsy) to induction chemoradiation were similar to patients treated with surgical resection *[Smith 2012; Belluco 2011; Callender 2010]*. One centre reported an actuarial local recurrence rate of 11% among 47 clinical T3, N0/N+ patients treated with full-thickness excision and EBRT. In this cohort, 49% had achieved a pCR and an additional 36% a complete clinical response after EBRT and excision. The reports have demonstrated that response to induction EBRT may be used as a means to select T3 patients for non-surgical management of rectal cancer.

Other studies are currently exploring the role of induction chemotherapy with FOLFOX (NCT01515787) as a means to avoid the toxicities associated with pelvic radiation for stage II/III rectal tumours that do not approach the circumferential radial margin on MRI. A prior phase II study demonstrated a R0 resection rate of 100% and a pCR rate of 25% (8 of 32 patients) using a similar approach *[Schrag 2014]*. The current study similarly aims to evaluate the ability of induction FOLFOX/CAPOX chemotherapy and minimally invasive surgery to allow organ sparing therapy of early stage rectal cancer.

A further approach to management of stage T3N0/N+ rectal cancer is a "watch-and-wait" strategy whereby patients with a complete clinical response to induction chemoradiotherapy with or without chemotherapy are treated with close surveillance. Retrospective studies have documented high salvage rates for patients with recurrent tumours and disease specific survival rates that are similar to patients treated with initial surgical resection *[Habr-Gama 2013; Glynne-Jones 2012; Callender 2010]*. The rate of surgery avoidance is reported to be 50% *[Habr-Gama 2013]*. A study of FOLFOX/CAPOX chemotherapy and chemoradiation followed by surveillance for patients with significant clinical response is underway to prospectively document 3-year disease free survival in patients with T3-4N1-2 low rectal tumours treated with non-operative management (ClinicalTrials.gov Identifier: NCT02008656). A "watch-and-wait" approach does not generally include the planned excision of the primary tumour and requires an intensive surveillance strategy.

ypT0/T1 as a Surrogate of Local Control

Multiple studies have demonstrated a very low risk of lymph node positivity and locoregional recurrence if downstaging to ypT0/T1 is achieved after chemoradiation. These risks significantly increase with ypT2 or more advanced tumours *[Mignanelli 2010; Kim 2006; Belluco 2011]*. The concept of ypT0/T1 as a surrogate of locoregional tumour control has been applied in multiple prospective phase II studies including the Dutch CARTS study in which patients with T1-3N0 low rectal tumours were treated with pelvic chemoXRT and those without clinical regression or with yp>T1 tumours after TEMS were recommended for radical surgical resection. Patients with ypT0-1 tumours were treated with TEMS only *[Bökkerink 2011; Callender 2010]*. The study did not proscribe systemic therapy, and tumour excision occurred after irradiation of the tumour bed, which has been shown to be associated with increased toxicity (see below).

Excision Strategies

Tumour excision can be performed via transanal excision or by transanal endoscopic microsurgery (TEM) approach. Transanal endoscopic microsurgery may have transanal approach in terms of visualization and resection of higher lesions. TAMIS is an alternative to TEMS that uses the same surgical principles of endoscopic illumination/magnification of the endoluminal operative field and minimally invasive instruments for tumour excision. A recent metanalysis demonstrated superiority of TEMS techniques over conventional transanal excision. The authors reported higher rates of R0 resection (OR 5.281; 95% CI, 3.201–8.712; $p < 0.001$) and fewer lesion recurrences (OR, 0.248; 95% CI, 0.154–0.401; $p < 0.001$) with TEM compared to transanal excision *[Clancy 2015]*. Despite the demonstrated superiority of minimally invasive techniques for locoregional control, a recent US Database study revealed that traditional LE is still performed in up to 34% of all patients treated by local excision *[Stitzenberg 2013]*. This may explain the higher than expected local recurrence rates observed on a population level. While the introduction of MIS techniques for transanal excision have made classic approaches to local excision obsolete, there is a role for the traditional approach with anal retractors and direct visualization in very low tumours that extend below the anorectal junction. In these patients, once the dissection has extended above the anorectal junction, the MIS platform can be introduced to complete the procedure.

Standard TEMS/TAMIS approach for early rectal malignancy includes a full-thickness excision of the lesion down to the perirectal fat and a 1 cm mucosal margin to achieve best results *[Monson 2013]*. However, Lezoche et al recommend a more extensive resection of mesorectal fat with the specimen, termed "endoluminal locoregional resection" (ELRR) *[Lezoche 2012]*. With this approach, the authors demonstrated similar outcomes to radical resection in patients with T2 tumours after chemoXRT. These data suggest inclusion of some mesorectal fat in the local excision specimen may improve local control.

Several studies have demonstrated the importance of individual surgeon skill on both perioperative and oncologic outcomes. *[Yeo, 2016; Massarotti, 2016; McColl, 2015]*. Thus, control of this factor is crucial in the assessment of a novel oncologic strategy. Two established strategies to ensure surgeon ability are minimum volume thresholds and, where possible, video assessment of surgeon performance *[Stevenson, 2015; Fleschman, 2015; Bonjer, 2015]*. Helewa et al. have demonstrated that surgeons overcome the learning curve for TEM/TAMIS technique after performing 16 procedures *[Helewa, 2016]*. Large, randomized control trials involving minimally invasive techniques have utilized minimum experience thresholds of 20 procedures for enrollment of patients, in addition to a surgeon evaluation of an unedited video of the performance of a single procedure *[Stevenson, 2015; Bonjer, 2015; Fleschman, 2015]*.

Correlative Studies

Few validated prognostic biomarkers have been established in rectal cancer. Prognostic multi-gene signatures such as Coloprint® and the Oncotype Recurrence Score® were developed to estimate prognosis and facilitate decision-making in the adjuvant setting *[Salazar 2011; O'Connell 2010; Gray 2011; Venook 2013; Sanz-Pamplona 2012]*. More recently, the utility of the Oncotype Recurrence Score (RS) has also been defined in a randomized phase III trial of oxaliplatin-containing adjuvant chemotherapy *[Yothers 2013]* and in the setting of rectal cancer *[Reimers 2014]*. However there is a lack of predictive biomarkers that can be used to predict whether colorectal subtypes will benefit from adjuvant FOLFOX chemotherapy.

The Nanostring PanCancer Pathways and Immune Panels® include a set of 700 genes representing major cancer pathways and key driver genes and can be used to score and rank each gene in 13 pathways and immune cell-types and relate these to prior therapy. This study offers the unique opportunity to prospectively collect diagnostic and centrally reviewed TEM surgical specimen for Ncounter® based gene-expression studies. Matched pair analysis of rectal tumours prior to, and after FOLFOX/CAPOX chemotherapy will be characterized with the PanCancer Pathways and Immune Panels to characterize key cancer pathways and the most important immune-related genes altered by chemotherapy.

ctDNA is a promising prognostic marker in early stage colon cancer *[Diehl 2008; Diaz 2014; Lin 2014]*, but limited data has described its utility in rectal cancer. In a small study, the decrease of cell-free DNA levels after chemoradiation was associated with tumour downstaging to ypT0-T2 while ctDNA levels increased in nonresponders with ypT3-T4 tumours *[Zitt 2008]*. The utility of ctDNA to risk stratify patients with stage I/II rectal tumours has not yet been described. Measuring ctDNA after neoadjuvant therapy may serve as an early surrogate of response to FOLFOX therapy and 3 year locoregional relapse rate and disease free survival.

Quality of Life

Rectal cancer treatment can adversely affect functional outcomes and quality of life. Total mesorectal excision (TME) and the use of chemoradiation have negative impact on short and long term function and QoL. Fourteen years following TME, patients who undergo TME have more sexual dysfunction and reduced quality of life. The addition of radiation therapy in addition to TME led to inferior bowel function *[Wiltink 2014]*. We anticipate that organ sparing therapy may result in better functional and quality of life outcomes than radical surgical resection with the potential for temporary or permanent stoma formation.

Quality of life will be evaluated by European Organization for Research and Treatment in Cancer (EORTC) Quality of Life Questionnaire QLQ-30 and EORTC QLQ-CR29 subscale. The EORTC QOL-C30 is a multidimensional, 30-item questionnaire which assesses five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a global health /QOL scale, as well as 6 single items *[Groenvold 1997; Aaronson 1993]*.

The EORTC QLQ-CR29 subscale supplements the core questionnaire with 29 items specific for patients with colorectal cancer. There are 18 items that deal with gastrointestinal symptoms, separate items for those with stomas and four sexual function items. These items comprise 6 scales and 11 individual items *[Gujral 2007; Whistance 2009]*. The EORTC core and subscale have been validated in various patient groups and translated into several languages.

Two rectal cancer specific functional scales will be used by this trial, the Fecal Incontinence Quality of Life (FIQL) and the Low Anterior Resection Syndrome (LARS) instruments *[Rockwood 2000; Juul 2014]*. These instruments have been developed to follow patients undergoing standard rectal surgery (i.e. TME) and have been previously reported for patients undergoing organ sparing transanal procedures *[Planting 2013]*.

3.0 BACKGROUND THERAPEUTIC INFORMATION

The chemotherapy agents that may be used for patients enrolled on this trial are commercially available.

3.1 Oxaliplatin

3.1.1 *Background Drug Information*

See the current oxaliplatin Product Monograph for details and up to date information.

3.1.2 *Chemical Structure*

Oxaliplatin is a platinum alkylating agent, which contains platinum complexed to oxalate and diaminocyclohexane (DACH) complex. Its full chemical name, oxalate(trans-l-1,2-diaminocyclohexane)platinum. The molecular weight of oxaliplatin is 397.3. It is slightly soluble in water, less so in methanol, and almost insoluble in ethanol and acetone.

3.1.3 *Mechanism of Action*

Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.

3.1.4 *Human Toxicology*

The most common adverse reactions associated with the combination oxaliplatin/5-FU/LV were peripheral sensory neuropathies, fatigue, myelosuppression, GI toxicity and increased transaminases.

The acute, reversible, primarily peripheral, sensory neuropathy associated with oxaliplatin is of early onset, and can occur within hours or one to two days of dosing. It usually resolves within 14 days, and frequently recurs with further dosing. Symptoms include sensory dysesthesia, paresthesia and hypoesthesia of the limbs, mouth, throat and larynx. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed.

Pharyngolaryngeal dysesthesia is common, with severe symptoms in 1-2% of patients shortly after drug infusion. Symptoms usually resolve within hours of onset. The feeling of difficulty in breathing or swallowing may be distressing to the patient. Cold avoidance should be exercised. Treatment is usually not needed, although antihistamines and bronchodilators have been used. To prevent recurrence, infusion time should be extended to 6 hours with subsequent treatments.

The persistent (>14 days), primarily peripheral, sensory neuropathy is usually characterized by paresthesias, dysesthesias, hypoesthesias and altered proprioception. It can interfere with daily activities (e.g. buttoning clothing, holding objects, writing) and occurs in most patients receiving oxaliplatin with 5-FU/LV. Lhermittes sign and urinary retention are seen rarely. Persistent neuropathy can occur without prior acute neuropathy event. Symptoms may improve in some patients upon discontinuation of oxaliplatin. Calcium gluconate 1 g and magnesium sulphate 1 g infusions pre ± post-oxaliplatin did not appear to be effective neuroprotective agents in a randomized study.

Anaphylaxis has been reported, including severe events in 2-3% of patients, and can occur during any cycle. Patients should not be re-challenged.

Pneumonitis has been reported rarely, and presents with cough, dyspnea, crackles and pulmonary infiltrates; oxaliplatin should be held pending investigation and discontinued if pneumonitis is confirmed.

Incidences of adverse events are generally similar between oxaliplatin used as single agent or with fluorouracil and leucovorin, although severe (grades 3-4) diarrhea, nausea and vomiting, and neurotoxicity are more common with combination therapy.

Hepatotoxicity, transaminitis, veno occlusive disease and nodular regenerative hyperplasia have been reported.

Oxaliplatin is fetotoxic, mutagenic, clastogenic, teratogenic, genotoxic and is probably carcinogenic, and can affect fertility. It is contraindicated in pregnancy. Adequate contraception for both sexes is mandatory during treatment and for at least 6 months after the last dose. Breast feeding is contraindicated due to the potential secretion into breast milk.

3.1.5 *Pharmacokinetic Studies*

Approximately 15% of the administered platinum is present in the systemic. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. It does not cross blood brain barrier. Oxaliplatin has more than 90% irreversible plasma protein binding, primarily albumin and gamma globulin. It also binds irreversibly to erythrocytes. It has a rapid and extensive non-enzymatic (no cytochrome P450-mediated metabolism) biotransformation to reactive platinum complexes which are both active and inactive metabolites. It has a triphasic elimination with terminal half-time of 391 hours. The major elimination route of platinum and its metabolites is renal excretion (54% within 5 days). Renal clearance of ultrafilterable platinum is significantly related to glomerular filtration rate.

3.1.6 *Pharmaceutical Data*

Refer to the package insert.

3.2 Leucovorin Calcium (CF)

3.2.1 *Background Drug Information*

See the current leucovorin calcium Product Monograph for details and up to date information.

3.2.2 *Chemical Structure*

Leucovorin calcium (folinic acid) is a reduced form of folic acid.

3.2.3 *Mechanism of Action*

Leucovorin is used to enhance the activity of fluorouracil by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of thymidylate.

3.2.4 *Human Toxicology*

Deaths from severe enterocolitis, diarrhea and dehydration have been reported in elderly or debilitated patients receiving leucovorin and fluorouracil. Seizures or syncope have been reported rarely, usually in combination with fluorouracil and in patients with cerebral metastases, although a causal relationship has not been confirmed. Immediate allergic reactions and anaphylaxis can occur. Diarrhea and mucositis are common in combination with fluorouracil. Hand-foot syndrome and myelosuppression also occur in this combination.

3.2.5 *Pharmacokinetic Studies*

It is rapidly and extensively converted to 5-methyltetrahydrofolate derivatives in the intestine prior to abruption. 5-methyltetrahydrofolate is an active metabolite and inactive metabolites are also formed. It rapidly absorbs with 97% absorption at a 25 mg dose. Leucovorin has a 35 – 45 % of plasma protein binding. It distributes to all tissues with maximum accumulation in liver and CSF. Leucovorin crosses the blood brain barrier. Volume of distribution is 3.2 L/kg. It is mainly eliminated in urine (80 – 90 %) and small amounts in feces. Elimination half-life is 32 min for parent drug and 227 min for active metabolite with a clearance of 3.9 mL/min/kg.

3.2.6 *Pharmaceutical Data*

Refer to the package insert.

3.3 Fluorouracil

3.3.1 *Background Drug Information*

See the current fluorouracil Product Monograph for details and up to date information.

3.3.2 *Fluorouracil Chemical Structure*

Its chemical name is 5-Fluoro-1*H*,3*H*-pyrimidine-2,4-dione, chemical formulae is $C_4H_3FN_2O_2$ with a molar mass of 130 g/mol.

3.3.3 *Mechanism of Action*

Fluorouracil was developed based on the observation that tumour cells utilized the base pair uracil for DNA synthesis more efficiently than did normal cells of the intestinal mucosa. It is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase).

3.3.4 *Human Toxicology*

Following longer IV infusions, *mucositis, hand-foot syndrome and diarrhea* occur most commonly. Diarrhea may be profuse and life-threatening following administration of leucovorin with fluorouracil. *Leukopenia* is the usual dose-limiting toxicity after IV bolus administration

Patients with dihydropyrimidine dehydrogenase deficiency (DPD) are at risk of severe lifethreatening toxicity with fluorouracil. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency.

Excessive lacrimation occurs frequently. Transient blurring of vision, eye irritation and excessive nasal discharge have also been reported. The onset of eye symptoms may occur at any time during treatment. Fluorouracil has been demonstrated in tear fluid causing acute and chronic conjunctivitis that can lead to tear duct fibrosis.

Acute cerebellar syndrome is manifested as ataxia of the trunk or extremities, disturbance of gait and speech, coarse nystagmus and dizziness. The ataxia syndrome is related to peak plasma levels of the drug rather than to cumulative dose, and is therefore more common with bolus doses than with infusions. It usually resolves after treatment is discontinued, but may persist in some cases.

Palmar-plantar erythrodysesthesia or hand-foot syndrome has been noted with protracted and high dose continuous infusion (23-82%). The syndrome begins with dysesthesias of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot. The syndrome resolves gradually over 5 to 7 days with cessation of drug infusion.

Cardiotoxicity has been reported and may be caused by coronary vasospasm, endothelial cell damage or increased thrombogenicity. It occurs in less than 10% of patients, of which up to 8% may be fatal. Cardiac effects include ECG changes, angina, arrhythmias, myocardial infarction, heart failure and are usually reported within 72 h of the first cycle of fluorouracil. Cardiotoxicity is independent of dose or underlying cardiac risk factors, but may be more common with infusions. Patients should be rechallenged only when there are no other treatment options.

Fluorouracil has the potential to enhance radiation injury to tissues. While often called radiation recall reactions, the timing of the radiation may be before, concurrent with or even after the administration of the fluorouracil. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Hemolytic-uremic syndrome has been reported when used in combination with mitomycin C.

Brivudine, sorivudine or their chemically related analogues irreversibly inhibit DPD, resulting in a significant increase in fluorouracil exposure. This may lead to increased fluoropyrimidinerelated toxicities with potentially fatal outcome. Therefore, either a different antiviral therapy may be used or there should be an interval of at least 4 weeks between the administration of brivudine, sorivudine, or the analogues and the start of fluorouracil treatment. In the case of accidental administration of nucleoside analogues that inhibit DPD activity to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalization is recommended.

Treatment with cimetidine for several weeks before initiation of fluorouracil treatment may increase plasma fluorouracil concentrations. This effect is probably due to both inhibition of hepatic enzymes and reduction of hepatic blood flow. Caution should be taken if the patient receives fluorouracil and cimetidine concurrently.

Metronidazole may enhance the toxicity of fluorouracil. The mechanism of interaction is presumed to be reduced clearance of fluorouracil by metronidazole. Concurrent administration should be avoided.

Elevated INR levels and occasional episodes of bleeding have been reported during concomitant use of warfarin and fluorouracil or its analogues. In these cases, fluorouracil has usually been administered as one component of an antineoplastic combination regimen. Adequate anticoagulant response to warfarin and other coumarin-derivative therapy should be monitored regularly in patients taking fluorouracil.

3.3.5 *Pharmacokinetic Studies*

Fluorouracil distributes into all body water by passive diffusion, crosses placenta and blood brain barrier, reaches high and persistent concentration in malignant effusions and has only 10% plasma protein binding. Eighty percent of the dose is degraded in liver by dihydropyrimidine dehydrogenase to active and inactive metabolites. It is mainly excreted as respiratory CO_2 (60 – 80 %), with 15 -20% excreted in the urine as intact drug within 6 hours after administration and 2-3% by biliary system. Higher clearance occurs in IV infusions than IV injections, due to saturation of metabolic or transport processes at higher drug concentrations. Elimination half-life is 6 – 20 mins dose dependent.

3.3.6 *Pharmaceutical Data*

Refer to the package insert.

3.4 Capecitabine

3.4.1 Background Drug Information

See the current capecitabine calcium Product Monograph for details and up to date information.

3.4.2 *Chemical Structure*

Capecitabine is an antimetabolite, belonging to the fluoropyrimidine carbamate class. The molecular formulae is $C_{15}H_{22}FN_3O_6$ and molecular weight is 359 g/mol.

3.4.3 *Mechanism of Action*

It causes cell injury via RNA- and DNA-related mechanisms. It is an orally administered precursor of 5- fluorouracil (5FU). Capecitabine is converted to 5FU by carboxyesterase, cytidine deaminase and thymidine phosphorylase (present in the liver and in tumours). Docetaxel appears to upregulate thymidine phosphorylase. The daily oral administration of capecitabine mimics the continuous intravenous infusion of 5-FU.

3.4.4 *Human Toxicology*

The most common side effects for capecitabine include hand-foot syndrome, diarrhea, nausea, vomiting, mucositis, abnormal liver function tests, fatigue, abdominal pain, anorexia, weight loss, edema and headache.

The median time to onset of diarrhea, a dose-limiting adverse effect of capecitabine, is 34 days. The diarrhea may respond to standard anti-diarrheal therapy (e.g. loperamide). Patients with severe diarrhea should be closely monitored and given fluid and electrolyte replacement for dehydration as indicated. Dehydration may result in acute renal failure, particularly with other risk factors (preexisting renal dysfunction, concomitant nephrotoxic agents). Capecitabine should be held and the dose reduced after recovery. Older patients (≥ 65 years) may be at higher risk.

Palmar-plantar erythrodysesthesia (commonly referred to as hand-foot syndrome) is characterized by numbness, dysesthesia or paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering, and severe pain of the hands and/or feet and is more common in patients also receiving docetaxel. The median time to onset was 79 days. Dosage interruption/adjustment is required according to severity. In addition to dose interruption and subsequent dose reduction, topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine. Current evidence indicates that oral pyridoxine may not be effective in ameliorating hand-foot syndrome in patients receiving capecitabine. (Kang 2010).

Severe rashes have been reported (Stevens-Johnson syndrome, Toxic Epidermal Necrolysis). Capecitabine must be permanently discontinued and the patient treated appropriately.

Hyperbilirubinemia associated with capecitabine therapy occurs more frequently in patients with hepatic metastases.

Patients with very low or absent dihydropyrimidine dehydrogenase (DPD) deficiency (ratelimiting enzyme of 5-fluorouracil catabolism) are at increased risk of severe or lifethreatening toxicity (i.e. neutropenia, GI and neurotoxicity, including fatalities) and should not receive capecitabine. In patients with partial DPD deficiency, capecitabine should be used with extreme caution, where the benefits outweigh the risks of treatment.

Cardiac toxicity is similar to that reported for other fluorinated pyrimidines and includes ECG changes, angina, infarction, EKG changes, dysrhythmias and cardiac failure. The risk may be increased in patients with prior coronary artery disease.

Very rare cases of leukoencephalopathy have been reported.

3.4.5 *Pharmacokinetic Studies*

It has 70% oral absorption reaching Cmax in 1.5 hours. Pharmacokinetics is largely dose proportional with insignificant food effect. The pharmacokinetics is altered with advanced age and renal function but nor with gender, race, performance status, liver function and albumin. It is widely distributed with less than 60% plasma protein binding, primary to albumin (35%). Capecitabine is extensively bioactivated and metabolized in the liver. Elimination is mainly in the urine (70%) with a terminal half-life of 45 – 60 mins.

3.4.6 *Pharmaceutical Data*

Refer to the package insert.

4.0 STUDY POPULATION

This study population includes patients with stage I-II (cT1-3^{ab}/N0) rectal cancer.

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

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of enrollment. Questions about eligibility criteria should be addressed prior to enrollment.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy and to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar disease.

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

4.1.1 Histologically confirmed invasive well-moderately differentiated rectal adenocarcinoma diagnosed within 90 days prior to enrollment.

Note: it is recommended that surgeons take a biopsy of the tumour during sigmoidoscopy / colonoscopy to ensure tissue availability and adequate pathology report confirming invasive well-moderately differentiated rectal adenocarcinoma and no evidence of pathologic high risk factors.

4.1.2 Tumour stage cT1-T3^{ab}N0 based on pelvic MRI:

- cT1N0– tumour invasion into submucosa, no radiographic evidence of mesorectal nodal metastasis, tumour deposits or vascular invasion.
- cT2N0 – tumour invasion into muscularis propria, no radiographic evidence of mesorectal nodal metastasis, tumour deposits or vascular invasion.
- cT3a,bN0– tumour invasion through the muscularis propria no more than 5 mm into the subserosa/perirectal tissue and clear of the circumferential radial margin (CRM). Absence of radiographic evidence of mesorectal nodal metastasis, tumour deposits or lymphovascular invasion *[Glimelius 2010]*.

Note: If the tumour is not visualized in the MRI but there is histological confirmation of rectal adenocarcinoma the patient is eligible.

4.1.3 cN0 stage based on pelvic MRI. Any nodes ≥ 10 mm in longest dimension are considered malignant, regardless of nodal morphology. For pelvic nodes < 10 mm in longest dimension, if nodes are seen and are deemed to be morphologically benign in the opinion of the radiologist and surgeon, the patient is eligible. Patients with visible pelvic sidewall nodes are excluded.

4.1.4 M0 stage based on no evidence of metastatic disease by CT imaging.

4.1.5 Mid to low-lying tumour eligible for local tumour excision in the opinion of the treating surgeon.

4.1.6 Age of at least 18 years.

4.1.7 Medically fit to undergo radical surgery as per treating surgeon's discretion.

4.1.8 No contraindications to protocol chemotherapy.

4.1.9 Adequate normal organ and marrow function as defined below (must be done within 30 days prior to enrollment):

- ANC ≥ 1.5 x 109/L
- platelet count ≥100 x 109/L
- bilirubin < 1.5 ULN, excluding Gilbert's syndrome
- Calculated creatinine clearance of ≥ 50 ml/min.
- Clearance to be calculated using Cockcroft formula:

Males: $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (µmol/l)}}$

Females: $\frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (µmol/l)}}$

4.1.10 The patient must have an ECOG performance status of 0, 1.

4.1.11 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life and health utility questionnaires. The baseline assessment must be completed within required timelines prior to enrollment. Inability (illiteracy, 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.

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

4.1.13 Must be accessible for treatment and follow-up. Patients enrolled on this trial must be treated with chemotherapy and followed at the enrolling centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. The patient's city of residence may be required to verify their geographical proximity. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, follow-up and response assessments.

Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial.

4.1.14 Protocol treatment is to begin within 5 working days of patient enrollment.

4.1.15 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method during and for 6 months after completion of chemotherapy. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

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

4.2 Ineligibility Criteria

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

4.2.1 Patient has pathologic high risk factors on either the initial biopsy specimen report or follow up biopsy (if done): high histologic grade, mucinous histology, lymphatic or vascular invasion.

4.2.2 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.

4.2.3 Synchronous cancer.

4.2.4 Prior treatment for rectal cancer.

4.2.5 Previous pelvic radiation for any reason.

4.2.6 Patients with known dihydropyrimidine dehydrogenase deficiency

4.2.7 Treatment with other investigational drugs or anti-cancer therapy within 28 days prior to enrollment.

4.2.8 Clinically significant (i.e. active) cardiovascular disease for example cerebro vascular accidents (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, New York Heart Association (NYHA) grade II or higher, congestive heart failure, serious cardiac arrhythmia requiring medication.

4.2.9 Any contra-indications to undergo MRI imaging.

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

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

Required Investigations	Prior To Enrollment: Within 90 days	Prior To Enrollment: Within 30 days	During Protocol Treatment Prior to each FOLFOX or CAPOX cycle	Pre-Excision 2 weeks (FOLFOX) or 3 weeks (CAPOX) after last injection in last cycle of chemotherapy	Excision within 3 weeks after pre-excision visit	After Excision [1]: 30 d	After Excision [1]: Months 6, 12, 18, 24, 30 and 36.	After Excision [1]: Months 48 and 60 (phone contacts acceptable)	First Disease Relapse [2]	After First Disease Relapse (Phone Contacts Acceptable)[3]
History and Physical Exam										
Including: height (baseline only), weight, ECOG performance status		X	X[4]	X		X	X			
Concomitant Medications		X	X[4]	X	X	X				
Hematology										
CBC, differential (including lymphocytes), platelets		X	X[4]	X						
Coagulation										
PTT, PT/INR		X		X						
Biochemistry										
ALT, serum creatinine, total bilirubin		X	X[4]	X						
Creatinine Clearance (calculated)		X	X[4]	X						
Serum CEA		X		X			X			
Correlative Studies										
Tumour tissue specimen banking [5]	X				X					
Whole blood (for ctDNA), whole blood, serum and plasma [5, 6]		X		X			12, 24 and 36[7]		X [7, 8]	
Radiology										
MRI pelvis	X			X			6, 18 and 30[7]		X	
CT pelvis [9] *(optional if pelvic MRI performed)*	X						12, 24 and 36		X	
CT chest [9]	X						12, 24 and 36		X	
CT abdomen with contrast [10]	X						12, 24 and 36		X	
Sigmoidoscopy/Colonoscopy [11]	X			X			X [12]		X	
Other Investigations										
Biopsy confirming invasive well-moderately differentiated rectal adenocarcinoma	X [13]				X				X [14]	
Pregnancy test [13]		X								
Submission of tumour tissue for retrospective central ypstaging confirmation (mandatory)					X					
Capecitabine patient diary			Daily [16]							
Adverse Events										
Adverse event assessment [17]		X	X	X	X	X	X [18]	X [18]	X [18]	X [18]

table continues on next page

Required Investigations	Prior To Enrollment		During Protocol Treatment Prior to each FOLFOX or CAPOX cycle	Pre-Excision 2 weeks (FOLFOX) or 3 weeks (CAPOX) after last injection in last cycle of chemotherapy	Excision within 3 weeks after pre-excision visit	After Excision [1]			First Disease Relapse [2]	After First Disease Relapse (Phone Contacts Acceptable)[3]
	Within 90 days	Within 30 days				30 d	Months 6, 12, 18, 24, 30 and 36.	Months 48 and 60 (phone contacts acceptable)		
Quality of Life										
EORTC QLQ-30 and EORTC QLQ-CR29		X		X			6, 12, 24 and 36			
LARS and the Fecal Incontinence Quality of Life Instrument		X		X			6, 12, 24 and 36			
Health Economics										
EQ-5D-5L		X	X [19]	X		X	6, 12, 24 and 36			
Phone Contact										
Survival information								X		X

1. Timing for visits after excision are scheduled from last tumour excision date:
   a. For patients having TME as first protocol excision: from TME date
   b. For patients having TEMS/TAMIS as first protocol excision: from TEMS/TAMIS date
   c. For patients having TEMS/TAMIS as first protocol excision and then having a TME: from TME date
2. See protocol section 8 for definitions.
3. Phone contacts or visits after first disease relapse are required every 6 months from date of relapse.
4. Tests may be done on the date of treatment or, if not possible, the previous working day before treatment day. If treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment).
5. Please also see protocol Section 12.0 and details for collection, processing, storing, and shipping these samples provided in the CO.28 Correlative Studies Manual.
6. Whole blood (that is *not* for ctDNA testing) will only be collected prior to enrollment.
7. Not required for patients that had a TME.
8. To be obtained within 28 days as close to the time of relapse as possible. Blood for correlatives done within 28 days PRIOR to date of relapse does not need to be repeated.
9. For CT pelvis and chest, a CT scan with contrast is preferred but not mandated. Patients with contrast allergies may undergo chest X-ray and /or Chest MRI.
10. Contrast is REQUIRED for the CT scan of the abdomen. Patients with contrast allergies may undergo liver ultrasound and /or MRI.
11. Rectal exam and proctoscopy are ideally to be performed by the primary surgeon. Proctoscopy should be performed $\leq$ 90 days prior to enrollment. Ideally, the surgeon should perform pre and post induction treatment proctoscopies. A gastroenterologist may perform proctoscopy in lieu of the surgeon, but then must also perform the follow-up exam. Proctoscopy may be accomplished using rigid proctoscopy or as part of a flexible sigmoidoscopy or colonoscopy.
12. For patients that had a TME it is only required at month 36.
13. If a rectal tumour tissue biopsy was performed within 90 days prior to enrollment, a repeat biopsy is not necessary. It is recommended that surgeons take a biopsy of the tumour during sigmoidoscopy/colonoscopy to ensure tissue availability and adequate pathology report confirming invasive well-moderately differentiated rectal adenocarcinoma and no evidence of pathologic high risk factors.
14. It is strongly encouraged that suspicious or unequivocal evidence of first local relapse be confirmed definitively by either biopsy (preferred) or by repeat/confirmatory imaging. Where imaging evidence of first local relapse is, in the opinion of the investigator and radiologist, absolutely unequivocal and not requiring subsequent confirmation by either biopsy or follow-up imaging, this must be clearly indicated in supporting documentation
15. Urine pregnancy test in women of childbearing potential and if a false-positive is suspected this may include an ultrasound to rule-out pregnancy.
16. To be completed daily for patients receiving Capecitabine.
17. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0) (see Appendix III).
18. Only protocol chemotherapy or surgery related adverse events have to be reported after the 30 days post-excision visit.
19. After 3 cycles of FOLFOX or after 2 cycles of CAPOX.

5.1 Follow-up for Ineligible Patients

The follow-up requirement for ineligible patients who have received no protocol chemotherapy and have not had excision procedure only includes submission of the Baseline Report.

Ineligible participants who have received at least one dose of protocol chemotherapy and/or have had TEMS/TAMIS procedure should be followed as per protocol requirements to allow for treatment and adverse event assessment.

6.0 ENTRY/ENROLLMENT PROCEDURES

6.1 Entry Procedures

All enrollments will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and enrolling patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the CO.28 trial specific web-site. If sites experience difficulties accessing the system and/or enrolling patients please contact the help desk (link in EDC) or the CO.28 Study Coordinator.

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

The following information will be required:

- trial code (CCTG CO.28)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking/optional consent version date
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- BSA, height and weight

6.2 BSA Calculation

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

6.3 Enrollment

Enrollment will be provided electronically.

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

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

All enrolled patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are outlined in Section 5.1.

7.0 TREATMENT PLAN

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

In accordance with CCTG policy, protocol treatment is to begin within 5 working days of patient enrollment.

7.1 Chemotherapy Treatment Plan

FOLFOX or CAPOX is selected based on investigator discretion.

7.1.1 *Drug Administration*

7.1.1.1 ***FOLFOX*** *(5-fluorouracil + leucovorin + oxaliplatin)*

Agent(s)	Dose	Route	Duration	Schedule
Oxaliplatin	85 mg/m^2	IV over 2 hours	Day 1	Repeat every 14 days for a total of 6 cycles
Leucovorin	400 mg/m^2 bolus	IV over 2 hours	Day 1	Repeat every 14 days for a total of 6 cycles
5FU	400 m/m^2 bolus over 5 - 15 minutes then 2400 mg/m^2 continual infusion over 46 - 48h total dose	IV	Days 1 to 2	Repeat every 14 days for a total of 6 cycles

1. Oxaliplatin could be administered first, prior to leucovorin; or concurrently with leucovorin administered via separate infusion containers.
2. If necessary to accommodate holidays, patient schedule or other justified circumstance, the schedule may be delayed up to 7 days.
3. Patients who cannot tolerate six cycles of FOLFOX or those that require dose modification below dose level -2 (see Section 7.1.3.1) may receive preoperative 5FU chemoradiotherapy based on investigator decision. If chemoradiotherapy is given, it should be given according to local institutional guidelines for FOLFOX administration. There are no restrictions on dose modifications for the 6th cycle of neoadjuvant FOLFOX.
4. Alternate folinic acids (i.e. levo-leucovorin) may be substituted for Leucovorin if not available. Note: Levo-leucovorin is twice as potent as leucovorin; dosages should be adjusted accordingly. Dosages are at the discretion of the treating physician. Dose modifications of leucovorin up to and including omission of leucovorin or its analogues imposed by drug shortages will not constitute protocol violations.
5. The dose modification schema for FOLFOX (see Section 7.1.3.1) is suggested. Oncologists may use clinical judgment in making dose modifications that deviate from the suggested schema. These will not constitute protocol violations.

7.1.1.2 ***CAPOX*** *(capecitabine + oxaliplatin)*

Agent(s)	Dose	Route	Duration	Schedule
Capecitabine	1000 mg/m^2 BID	PO	14 days starting on Day 1	Repeat every 21 days for a total of 4 cycles
Oxaliplatin	130 mg/m^2	IV over 2 hours	Day 1	Repeat every 21 days for a total of 4 cycles

1. Patients must be counseled about the importance of compliance with capecitabine. Compliance, with mention of missed doses, must be documented in the patient's medical record by site study personnel.
2. Missed doses must be documented on the appropriate CRF and by patients on their provided diary.
3. Patients should take their doses of capecitabine orally daily, one dose in the morning and one dose in the evening, approximately 12 hours apart. Patients should swallow capecitabine tablet(s) whole with a full glass of water, about 8 ounces, within 30 minutes after a meal. Patients should not try to make up a missed or vomited dose, never double up on a dose and tell their doctor if they miss a dose. Patients must return any remaining capecitabine tablets at their next study visit.

7.1.2 *Premedication*

All patients should be pre-medicated as per institutional guidelines.

7.1.3 *Dose Adjustments*

Doses will be reduced 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 (CTCAE) (see Appendix III).

The major toxic effects which limit dose are hematologic. 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.

7.1.3.1 *FOLFOX*

The precise dose modification schema used and the symmetry of dose modification (e.g., reduce both 5FU and oxaliplatin symmetrically, or one preferentially) may be left to the discretion of the treating oncologist. **The modification schema in Table *Dose levels of FOLFOX* is a guideline.** Leucovorin dose may be decreased in concert with bolus 5-FU dose. If 5-FU is not administered, leucovorin should not be administered.

1. **Dose reduction:** If a patient requires a dose reduction below level -2 during cycles 1-5 preoperative therapy, consider discontinuing FOLFOX and referring the patient for TME. This does not apply for cycle 6.
2. **Dose delay:** If FOLFOX is held due to toxicity for more than 30 days from planned next cycle date consider discontinuing FOLFOX and referring the patient for TME. This does not apply for cycle 6.

Dose levels of FOLFOX

Dose Level*	5-FU infusion	5-FU bolus	Oxaliplatin
0	1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours)	400 mg/m^2	85 mg/m^2
-1	960 mg/m^2/day x 2 days (1920 mg/m^2 over 46-48 hours)	320 mg/m^2	65 mg/m^2
-2	800 mg/m^2/day x 2 days (1600 mg/m^2 over 46-48 hours)	270 mg/m^2	50 mg/m^2
-3**	680 mg/m^2/day x 2 days (1360 mg/m^2 over 46-48 hours)	230 mg/m^2	40 mg/m^2

* Dose level 0 refers to the starting dose.

** If dose reduction below level -2 is required during cycles 1-5 of neoadjuvant therapy for a Group 1 patient, FOLFOX should be discontinued and the patient referred for standard surgical therapy. Dose reduction to level -3 is only permitted during cycle 6.

Suggested FOLFOX Dose Modifications Based on Interval Adverse Events

The following describe actions in the Dosage Change column:

- Omit = Treatment is not given for this cycle
- Hold = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

SYSTEM/ORGAN/ CLASS (SOC)	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT (Occurring before Day 1 of Cycle)			
Other Non-hematologic	Grade ≥ 2 (excluding alopecia)	5-FU Oxaliplatin	Hold treatment until ≤ grade 1 then resume at next lower dose level.

Dose Modifications Based on Retreatment (days 2-14 during previous cycle)

SYSTEM/ORGAN /CLASS (SOC)	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT (occurring at Days 2-14 during cycle)			
Gastrointestinal disorders	Nausea grade 2	Oxaliplatin	Intensify antiemetic therapy and proceed with FOLFOX at current dose level. Maximal antiemetic therapy includes a 5HT inhibitor (i.e. granisteron, ondansetron, palonestron) as well as compazine, lorazepam, aprepitant, and decadron
	Nausea grade 3		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. May decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Nausea grade 4		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. Decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Vomiting grade 2	5-FU Oxaliplatin	Intensify antiemetic therapy and proceed with FOLFOX at current dose level. Maximal antiemetic therapy includes a 5HT inhibitor (i.e. granisteron, ondansetron, palonestron) as well as compazine, lorazepam, aprepitant, and decadron.
	Vomiting grade 3		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. May decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Vomiting grade 4		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. Decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Diarrhea grade 2		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX at current dose level. If not resolved to < grade 2, HOLD FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX when resolved to < grade 2.
	Diarrhea grade 3		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX, decreasing 5FU and oxaliplatin one dose level. If not resolved to < grade 2, HOLD FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX decreasing 5FU one dose level when resolved to < grade 2
	Diarrhea grade 4		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX, decreasing 5FU and oxaliplatin one dose level. If not resolved to < grade 2, HOLD FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX decreasing 5FU and oxaliplatin one dose level when resolved to < grade 2

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SYSTEM/ORGAN /CLASS (SOC)	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT (occurring at Days 2-14 during cycle) - CONTINUED			
Gastrointestinal disorders *continued*	Oral mucositis, Esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 3	5-FU Oxaliplatin	Hold FOLFOX until mucositis improves to < grade 2 then resume with one dose level reduction of 5-FU and the previous dose level of oxaliplatin
	Oral mucositis, Esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 4		Hold FOLFOX until mucositis improves to < grade 2 then resume with two dose level reduction of 5-FU and the previous dose level of oxaliplatin
AT TIME OF RETREATMENT (occurring at Days 11-14 during cycle)			
Blood and lymphatic system disorders	Neutropenia ANC 1.0 to 1.199 x 10^9/L	5-FU Oxaliplatin	Hold FOLFOX until ANC ≥ 1200 then resume at previous dose levels.
	Neutropenia ANC < 1.0 x 10^9/L		Hold FOLFOX until ANC ≥ 1200 then resume with one dose level reduction of both 5-FU and oxaliplatin for all subsequent cycles or at same dose level with GCSF at standard doses.
	Febrile neutropenia ANC < 1.0 x 10^9/L and temp ≥ 38.5° C		Hold FOLFOX until fever has resolved and ANC ≥ 1200 then resume with one dose level reduction of both 5-FU and oxaliplatin for all subsequent cycles or at same dose level with GCSF at standard doses.
	Thrombocytopenia Platelets 50 to 74.999 x 10^9/L		Hold FOLFOX until platelets ≥ 75,000 then resume at previous dose levels. except bolus 5-FU which is reduced by one dose level.
	Thrombocytopenia Platelets < 50 x 10^9/L		Hold FOLFOX until platelets ≥ 75,000 then resume FOLFOX with one dose level reduction of both 5-FU and oxaliplatin for all subsequent cycles
ENT	Pharyngolaryngeal dysesthesia	Oxaliplatin	Increase the duration of oxaliplatin infusion to six hours for all subsequent cycles. See section 8.4
Pulmonary disorders	Cough, dyspnea, hypoxia, pneumonitis or pulmonary infiltrates, grade ≥ 3.	5-FU Oxaliplatin	Hold oxaliplatin until interstitial lung disease is ruled out. Continue 5-FU/leucovorin. Discontinue study if interstitial lung disease is confirmed.
Thrombotic microangiopathy	Hemolytic uremic syndrome (HUS) ≥ grade 3	5-FU Oxaliplatin	Discontinue oxaliplatin. Continue 5-FU/leucovorin.

table continues on next page

SYSTEM/ORGAN /CLASS (SOC)	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT (occurring at Days 11-14 during cycle) CONTINUED			
Immune system disorders	Allergic reaction grade 1	Oxaliplatin Leucovorin	Decrease infusion rate by 50% until symptoms resolve, then resume at initial planned rate.
	Allergic reaction grade 2		Stop FOLFOX infusion. Administer H_1 and/or H_2 blockers and/or steroids according to local medical site policy. Restart infusion when symptoms resolve and pretreat before all subsequent doses. Treat according to local medical site policy.
	Allergic reaction grade 3 or 4		Stop the infusion. Discontinue FOLFOX. Treat according to local medical site policy.
Skin and subcutaneous tissue disorders	Extravasation	Oxaliplatin	Extravasation of oxaliplatin has been associated with necrosis. If extravasation is suspected, stop the FOLFOX infusion and restart at another site. Treat according to local medical site policy. DO NOT apply COLD.
Other Non-hematologic	Grade 3 or Grade 4	5-FU Oxaliplatin Leucovorin	Hold FOLFOX until toxicity ≤ grade 1 then resume with one dose level reduction of both 5-FU and oxaliplatin
Neurological	Neurotoxicity grade 2 persisting between treatment cycles	Oxaliplatin	Continue FOLFOX with previous dose level of 5-FU and one dose level reduction of oxaliplatin for all subsequent cycles.
	Neurotoxicity grade 3 resolving to ≤ grade 2 between treatment cycles		Continue FOLFOX with previous dose level of 5-FU and one dose level reduction of oxaliplatin for all subsequent cycles.
	Neurotoxicity grade 3 persisting between treatment cycles		Discontinue oxaliplatin. Continue 5-FU/leucovorin. Reassign to 5FUCMT if has not completed at least 5 cycles of FOLFOX.
	Neurotoxicity grade 4		Discontinue oxaliplatin. Continue 5FU/leucovorin. Reassign to 5FUCMT if has not completed at least 5 cycles of FOLFOX.
Cardiovascular	Cardiac ischemia or infarction grade 3 or 4		Discontinue all study therapy.
	Cerebrovascular ischemia grade 3 or 4		Discontinue all study therapy.

7.1.3.2 *Oxaliplatin-Induced Pharyngolaryngeal Dysesthesia*

Oxaliplatin can induce an acute syndrome of pharyngolaryngeal dysesthesia (grades 3/4) characterized by subjective sensations of dysphagia or dyspnea, feeling of suffocation, without any evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing) occurs in 1-2% of the patients.

If a patient develops this oxaliplatin-induced pharyngolaryngeal dysesthesia, proceed to evaluate the oxygen saturation with a pulse oximeter and if confirmed as normal, an anxiolytic agent may be given and the patient observed in clinic until the episode has resolved. The duration of the oxaliplatin infusion should be increased to six hours for all subsequent treatment cycles.

Pharyngolaryngeal dysesthesia may appear similar to a hypersensitivity reaction. The table below compares the two.

Comparison of the symptoms and treatment of pharyngolaryngeal dysesthesias and platinum hypersensitivity:

Clinical Symptoms	Pharyngolaryngeal dysesthesias	Platinum hypersensitivity
Dyspnea	present	present
Bronchospasm	absent	present
Laryngospasm	absent	present
Anxiety	present	present
O_2 saturation	normal	decreased
Difficulty swallowing	present (loss of sensation)	absent
Pruritis	absent	present
Urticaria/rash	absent	present
Cold-induced symptoms	yes	no
Blood pressure	normal or increased	normal or decreased
Potential treatments	anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

7.1.3.3 *CAPOX*

The precise dose modification schema used and the symmetry of dose modification may be left to the discretion of the treating oncologist. The modification schema in Table Dose levels of CAPOX is a guideline.

CAPOX Dose Levels for NON-neurologic toxicity:

Dose Level*	Oxaliplatin	Capecitabine
0	130 mg/m^2	1000 mg/m^2 bid
-1	100 mg/m^2	750 mg/m^2 bid
-2	85 mg/m^2	500 mg/m^2 bid
-3	Discontinue Therapy	Discontinue Therapy
** Dose level 0 refers to the starting dose.*		

Suggested CAPOX Dose Modifications Based on Interval Adverse Events

SYSTEM/ORGAN/ CLASS (SOC)	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT (Occurring before Day 11 -14 of Cycle)			
Blood and lymphatic Systemic disorders	Neutropenia ANC (x 10^9/L) 1000-1199	Capecitabine Oxaliplatin	If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. If ANC is greater than or equal to 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). If ANC remains less than 1.2 after 2 weeks, discontinue treatment.
	ANC (x 10^9/L) 500 - 999		Follow steps in first box above and if resumed, with one dose level reduction.
	ANC (x10^9/L) less than 500		Follow steps in first box above but resume with two dose level reduction.
	Platelets (x 10^9/L) 50 – 74.9	Capecitabine Oxaliplatin	If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). If platelets remain less than 75 after 2 weeks, discontinue treatment.
	Platelets (x 10^9/L) 10 – 49.9		Follow steps in first box above and if resumed, with one dose level reduction from the lowest platelets result of the delayed week(s).
	Platelets (x 10^9/L) Less than 10.0		Follow steps in first box above but resume with two dose level reduction from the lowest platelets result of the delayed week(s).

The following describe actions in the Dosage Change column:

- Omit = Treatment is not given for this cycle
- Hold = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

7.1.4 *Duration of Therapy*

In the absence of unacceptable toxicities or disease progression, as defined in Section 10.1, or intolerable toxicity, chemotherapy will continue until completion of 6 cycles for FOLFOX and 4 cycles for CAPOX.

7.1.5 *Patient Compliance*

Trained medical personnel will administer protocol chemotherapy. Treatment compliance will be recorded in the patient's medical record and case report form (CRF).

Capecitabine treatment compliance will be monitored by review of the patient diary.

7.2 Radiation Treatment Plan

Pelvic radiation is recommended for patients when the excisional specimen demonstrates ypT3+ or N+ disease and requires radical TME surgery. Patients should be treated with standard preoperative chemoradiation or short course pelvic radiation according to standard institutional pre-operative protocol.

Optional preoperative pelvic radiation could be deliver as per institution standard to patients with pre-excision MRI reporting at least one of these findings:

- $cT3^{ab}$ stage
- node positive disease
- not clear circumferential radial margin (CRM)

Patients with yp staging as T1 (high risk) and T2 tumours do not require pre-operative pelvic radiation and should proceed directly to radical TME surgery.

Patients who cannot tolerate six cycles of FOLFOX or those that require dose modification below dose level -2 (see Section 7.1.3.1) may receive preoperative 5FU chemoradiotherapy based on investigator decision. If chemoradiotherapy is given, it should be given according to local institutional guidelines for FOLFOX administration.

7.3 Surgical Treatment Plan

Tumour excision should be performed within 2-5 weeks (FOLFOX) or 3-6 weeks (CAPOX) after first dose of last cycle of chemotherapy.

Step/Indication	Result	Surgical Treatment Plan
Pre-excision MRI/Endoscopy (post-chemotherapy)	• Disease Progression OR • No Response demonstrated by at least one of these findings on pre-excision MRI - $cT3^{ab}$ stage - node positive disease - not clear circumferential radial margin (CRM)	Total Mesorectal Excision (TME) or optional radiotherapy (per institution standard) followed by TME
	• No Disease Progression • Pre-excision MRI not meeting the "no response" criteria	TAMIS/TEMS
TEMS/TAMIS	yp Staging : • ypN+ OR • ypT3	Radiotherapy (per institution standard) followed by TME
	yp Staging: • ypT2 OR • ypT1 tumours with: - poorly differentiated histology and/or - lymphovascular invasion and/or - positive margin within < 1 mm	TME
	yp Staging: • ypT0 N0 • $ypT1^{good}$ N0	Surveillance

Lesions that on pre-excision (post-chemotherapy) MRI and/or endoscopy show evidence of progression or no response to chemotherapy (see protocol section 8.2) should be treated with immediate TME surgery as progression of local disease in spite chemotherapy is an established poor prognostic factor.

Local pathology ypstaging review determines subsequent therapy. Patients with ypstage T0/T1^{good}N0 tumours are treated with surveillance while patients with tumours with ypT2, N+ or ypT1 tumours with poor prognostic features or are treated with radical TME surgery within 6-8 weeks after local excision. Poor prognostic features include poorly differentiated histology, lymphovascular invasion and/or positive margin within < 1 mm. ypT1^{good} are those tumours that do not have poor prognostic factors.

For information about retrospective ypstaging confirmation by central pathology review refer to section 11.1 of this protocol.

Surgeons performing TEMS/TAMIS in this trial should have performed these procedures in at least 20 previous rectal cancer cases *[Stevenson 2015; Bonjer, 2015; Fleschman, 2015]*. Each surgeon should submit an unedited video of a TEMS/TAMIS procedure with sutured defect closure for central review. A video of the 1st patient enrolled in CO.28 is acceptable.

Surgeon trainees are not excluded from performing TME but their cases must be performed under supervision of a qualified surgeon and cancer-specific surgery must be ensured.

As per protocol, transanal, endoscopic tumour excision is permitted for low rectal tumours that approach or involve the anal sphincter if complete excision is feasible.

Lesions that on pre-excision (post-chemotherapy) MRI and/or endoscopy show evidence of progression or no response to chemotherapy (see protocol Section 8.2) should be treated with immediate TME surgery as progression of local disease in spite chemotherapy is an established poor prognostic factor.

Prior to surgery, all patients will have pretreatment with mechanical bowel preparation, with the specific bowel cleansing regimen at the discretion of the treating surgeon. Patients will be usually admitted to hospital on the day of surgery. Appropriate antibiotics for gram positive, negative and anaerobic coverage, and taking patient allergies/sensitivities into considerations will be administered as per institutional guidelines preoperative or at the start of the procedure. Heparin will not be administered.

The operating surgeon will use the minimally invasive transrectal platform of their choice. If the tumour encroaches into the anal canal, the surgeon can start the procedure using conventional transanal technique and complete the procedure with the transanal platform inserted using minimally invasive techniques. Where possible, the procedure will be video recorded. Excision of the tumour will include a minimum of 1 cm gross margin *[Monson et al. 2013]*. and a full thickness rectal excision, including a cuff of mesorectal fat. *[Lezoche 2012]*. After specimen extraction, vigorous irrigation with water will be recommended to minimize the risk of tumour implantation. The preferred management of the rectal defect will be sutured closure.

If the tumour has progressed and is no long appropriate for local excision, the surgeon will photodocument the lesion and abandon the procedure.

The surgical specimen will be pinned to a cork board to prevent distortion of the orientation and photographed. The specimen will be reviewed by pathology for ypstaging.

7.4 Concomitant Therapy

7.4.1 *Permitted*

Use of G-CSF (Gastrofil, Neulasta or Neupogen) is at the discretion of treating physicians but is not usually necessary.

7.4.2 *Not Permitted*

Erythropoietin stimulating agents should not be administered at any point during this protocol.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Organ Preservation Rate*

All patients treated with FOLFOX or CAPOX and TEMS or TAMIS will be included in the organ preservation rate analysis as primary endpoint of this study.

Organ preservation rate will additionally be calculated for all patients that have received protocol chemotherapy.

8.1.2 *Evaluable for Rectal Cancer Control*

All patients treated with FOLFOX or CAPOX and TEMS or TAMIS will be evaluated for locoregional and distant relapse rate.

Rectal cancer control will additionally be calculated for all patients that have received protocol chemotherapy.

8.1.3 *Evaluable for Disease Free Survival*

All patients treated with FOLFOX or CAPOX and TEMS or TAMIS will be evaluable for assessment of disease free survival.

Disease Free Survival will additionally be calculated for all patients that have received protocol chemotherapy.

8.1.4 *Evaluable for Post-Operative Complications*

All patients treated with FOLFOX or CAPOX and tumour excision/surgery will be evaluable for post-operative complications.

8.1.5 *Evaluable For Adverse Events*

All patients who have received at least one dose of protocol chemotherapy will be included in the safety analysis.

8.1.6 *Evaluable for Quality of Life Assessment*

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

8.2 Evidence of Disease Progression/No Response After Chemotherapy

8.2.1 *Progression*

The diagnosis of progressive disease will be made by treating surgeon after review of the pre-excision (post-chemotherapy) MRI and endoscopy.

8.2.2 *No Response*

No response to chemotherapy will be defined as meeting at least one of the criteria below:

A. Pre-excision MRI reporting at least one of these findings:
- cT3[ab] stage
- node positive disease
- not clear circumferential radial margin (CRM)

OR

B. Excision specimen reporting at least one of these findings:
- node positive disease
- ypT2
- ypT1 tumours with:
  - poorly differentiated histology, and/or
  - lymphovascular invasion, and/or
  - positive margin within <1mm.

8.3 Organ Preservation Rate

Organ preservation rate is defined as the proportion of patients who avoid TME.

8.4 Locoregional Relapse

Locoregional relapse is defined as reappearance of a tumour within the rectum or pelvis.

Evidence of Local Disease Recurrence:

- Suspicious: Suspicious imaging requiring further confirmation.
- Definite: Confirmation by cytology or histology OR Definitive imaging documenting local recurrence.

Elevated CEA only or physical examination only are not sufficient as evidence of suspicious or definite local disease recurrence.

Locoregional relapse is dated by the day of first evidence (clinical, radiological or pathological) of locoregional disease after complete tumour surgical excision date (with pathology results negative for malignant disease within 1 mm of surgical margins). It is strongly encouraged that suspicious or unequivocal evidence of first local relapse be confirmed definitively by either biopsy (preferred) or by repeat/confirmatory imaging. Where imaging evidence of first local relapse is, in the opinion of the investigator and radiologist, absolutely unequivocal and not requiring subsequent confirmation by either biopsy or follow-up imaging, this must be clearly indicated in supporting documentation.

8.5 Distant Disease

Distant disease is defined as evidence of rectal cancer disease at sites remote from the rectum.

Evidence of Distant Disease Recurrence:

- Suspicious: Suspicious imaging requiring further confirmation.
- Definite: Confirmation by cytology or histology OR Definitive imaging documenting distant recurrence.

8.6 Dating of First Recurrence

The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first suspicious record, even when the specific imaging abnormality requires subsequent confirmation by biopsy (required for confirmation of new primary malignancy) or is otherwise determined in retrospect (e.g. bone metastases that will never be biopsied but are definitively confirmed with subsequent imaging procedures).

Initial dates of first recurrence should be made as they occur by those who are responsible for the care of the patient. Dates that are based on suspicion alone will be reviewed by the CCTG coordinating office in order to establish accuracy through subsequent clinical course.

8.7 Disease Free Survival

Disease-Free Survival (DFS) is defined as the interval from complete tumour surgical excision date (with pathology results negative for malignant disease within 1 mm of surgical margins) to date of first occurrence of the events in the table below.

Patients not meeting the criteria for failure by the analysis data cutoff date will be censored at their last disease assessment date.

First Event	Disease Free Survival
None	Censored
Locoregional relapse	Failure
Distant disease	Failure
Non-protocol radiotherapy, chemotherapy or biologic therapy without documentation of the site of failure	Failure
Death due to any other reason	Failure

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

Only the first event experienced will determine a patient's failure status for DFS analysis. 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 locoregional relapse, 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 disease free survival. Similarly, if a patient is first found to have distant metastasis, then a work-up for locoregional relapse should be performed at the same time. If the locoregional work-up does not reveal relapse at the same time, then this patient is considered to only have distant disease failure.

8.8 Management Following Relapse

Management following relapse is at the discretion of the investigator. Survival and protocol chemotherapy or surgery related adverse events data should continue to be capture after first relapse.

9.0 SERIOUS ADVERSE EVENT REPORTING

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

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

9.1 Definition of a Reportable Serious Adverse Event

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

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

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the CO.28 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.
Within 7 days:	Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

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

FAX paper SAE Report to:

CO.28 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533 2941

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

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

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the CO.28 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

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

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.15. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.3.2 *Pregnancy Reporting*

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

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

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

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

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

9.3.3 *Exposure Reporting (Non-study Participants)*

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

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

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

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

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

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

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

9.5 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) single reports or line listings) from other clinical trials that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial CO.28 web-based safety monitoring utility. Investigators must review and document in the trial files proof of review of these events as per ICH GCP.

Investigators must notify their Research Ethics Boards (REBs) of events, which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes and any other event required by their REB. Safety reports that are not mandated by CCTG to be submitted to the REB are marked as 'NR' (not required) in the safety report monitoring utility. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial CO.28 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

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

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Tumour progression as defined in Section 8.2.
- Request by the patient.
- Completion of therapy as outlined in Section 7.0.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment

Supportive care therapy is recommended as per local standards.

10.3 Follow-up Off Protocol Treatment

All patients will be seen 30 days after excision and then at months 6, 12, 18, 24, 30, 36, 48 and from the excision date (please refer to section 5.0 for more details). Phone contacts at months 48 and 60 after excision will be acceptable.

11.0 CENTRAL REVIEW PROCEDURES

11.1 Retrospective ypstaging Central Pathology Review

There will be central pathology review for this study. Expert retrospective pathology review will be done for all patients to confirm ypstaging after excision. At least one disease site specialty pathologist with recognized diagnostic expertise for the tumour type will review the specimens and pathology report of each case. Another expert pathologist will be consulted to resolve significant diagnostic discordance if it arises. Results of the central pathology review will not be provided to the originating institution, the patient or patient record. Please consult CO.28 Correlative Studies Manual for additional details and timelines.

11.2 Central Surgery Review

Surgeons performing TEMS/TAMIS in this trial should have performed these procedures in at least 20 previous rectal cancer cases *[Stevenson, 2015; Bonjer, 2015; Fleschman, 2015]*.

Each surgeon should submit an unedited video of a TEMS/TAMIS procedure with sutured defect closure for central review. A video of the 1st patient enrolled in CO.28 is acceptable.

Please contact CO.28 CCTG Study Coordinator for additional details about video characteristics and its submission for central review.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the CO.28 trial specific website, which will include details regarding sample preparation, handling and shipping.

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

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

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

12.1 Protocol-Mandated Correlative Studies

Tumour Tissue Collection

Consenting to submit representative tumour tissue of the diagnostic tumour tissue from a biopsy done prior to enrollment AND from the protocol excision that removes the primary tumour is mandatory for participation in this trial.

One formalin fixed paraffin embedded (FFPE) block and one adjacent normal tissue block are requested from both the diagnostic tumour tissue from a biopsy done prior to enrollment AND from the protocol excision that removes the primary tumour. Where local centre regulations prohibit submission of tissue blocks, sites should request approval from the CCTG prior to local site activation to permit cores (2 x 2 mm cores of tumour) and slides (20 X 5 micron thick unstained slides from the block) to be submitted as an alternative to a block of tumour tissue. If, at any time, the submitting hospital requires the block or slides to be returned for medical or legal concerns, it will be returned by courier on request.

Whole blood (for ctDNA), Whole Blood, Serum and Plasma Collection

The submission of whole blood (for ctDNA), whole blood, serum and plasma is mandatory for participation in this trial.

The CCTG is interested in exploring the use of surrogate tissues such as serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodymanic effects. Whole blood, serum and plasma will be collected from all patients for planned studies for this trial.

Planned priority assay:

- Circulating tumour DNA

Detailed instructions for whole blood (for ctDNA), whole blood, serum and plasma sample acquisition, preparation, and shipping are found in the CO.28 Correlative Studies Manual.

12.2 Optional Banking of Samples

Banking of Tumour Tissue

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

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

Banking of Whole Blood, Serum and Plasma

Mandatory submission of whole blood, serum and plasma has been described above. The subsequent banking of any remaining blood samples collected is not mandatory for participation in the study. Blood samples will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

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

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is a single-arm two-stage trial with the primary objective to determine the organ preservation rate in patients with early (cT1-3a,bN0) rectal cancer treated with neoadjuvant FOLFOX or CAPOX and TEMS or TEMIS. Secondary objectives include estimation of 3 year locoregional relapse rate, distant relapse rate, and disease free survival in patients treated with organ preservation and evaluation of toxicities and quality of life.

13.2 Endpoints and Analysis

The primary endpoint of this study is the protocol specified organ preservation rate, defined as the proportion of patients with tumour downstaging to ypT0/T1^{good} N0 and who avoid radical surgery. The 95% confidence interval for the organ preservation rate will be calculated.

The 3 year locoregional relapse rate, distant relapse rate, and disease free survival will be estimated based on Kaplan-Meier method.

13.3 Sample Size and Duration of Study

Prospective phase II studies have documented an organ preservation rate of 50-68% among patients with clinical T1-3N0 rectal tumours treated with chemoradiation and minimally invasive surgery.

Based on these historic phase II data, the experimental treatment would be considered of no interest if the protocol specified organ preservation rate is 50% or lower (H0) and as promising if its avoidance rate is 65% or higher (H1). With an optimal two-stage minimax design, 22 patients would be accrued in the first stage.

The trial would be stopped at the end of the first stage if the number of patients who avoided radical surgery is 10 or less. Otherwise the trial would proceed to the second stage to accrue 28 additional patients. The experimental procedure would be considered as promising if, out of the total patients accrued, 30 or more patients avoided radical surgery. The exact type I error rate and power of this design are respectively 0.1 and 0.8. The minimum and maximum sample sizes are respectively 22 and 50 evaluable patients. Allowing for a 15% inevaluable rate, the total sample size is 58 patients.

The interim analysis at 22 patients will also determine if the trial has recruited a proportional representation of T1/2 and T3 patients. If the interim analysis shows disproportionality between the number of T1/2 and T3 patients, the eligibility criteria and reasons limiting enrollment will be reviewed and the trial team will consider extending accrual of one or the other group if it is determined to be necessary.

If the avoidance rate of the proposed procedure is 50% or lower, there is a 42% chance this study would be stopped.

Based on CCTG previous survey results, the study potentially opening at 12 centres, each centre accruing 3 patients per year, the estimated minimum accrual time for 58 patients is 19 months.

13.4 Safety Monitoring

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

13.5 Interim Analysis

Please refer to Section 13.3 for analysis after first stage (n=22).

13.6 Quality of Life Analysis

The quality of life of patients will be assessed using EORTC-QLQ C30 with EORTC QLQ-CR29 subscale. Scoring of the EORTC-QLQ C30 and CRC29 data will be completed following the procedures recommended by the EORTC Study Group on Quality of Life. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. Questionnaire compliance rates will be ascertained at each measurement time point. Mean baseline scores for each subscale and summary scores will be calculated.

Mean change scores from baseline at each assessment time and associated standard deviation will be calculated. Standard CCTG QOL Response Analysis categorizing patients as either having improved, stable, or worsened QOL will also be performed *[Osoba 2005]*. A change score of 10 points from baseline is defined a priori as clinically relevant. For functional scales and global health status, patients will be considered to have QOL improvement if reporting a score 10-points or better than baseline at any time of QOL assessment. Conversely, patients will be considered worsened if reporting a score minus 10-points or worse than baseline at any time of QOL assessment without any improvement. Patients whose scores fall between 10-point changes from baseline at every QOL assessment will be considered as stable. In contrast to functional scales, for the determination of patient's QOL response, classification of patients into improved and worsened categories will be reversed for symptom scales. QoL response rate and associated 95% confidence interval will be calculated for each domain and item.

13.7 Economic Analysis

The purpose of the economic evaluation is to measure health utilities starting from baseline over time for patients who are treated with the protocol neoadjuvant chemotherapy. The health states of patients will be collected using the EQ-5D-5L questionnaire *[Herdman 2011]* and the health utilities of the health states will be obtained using the Canadian value sets *[Xie 2016]*.

The prospective collection of health utilities directly from CO28 patients will enable the development of a model-based cost-effectiveness analysis to compare protocol treatment with the current standard treatment. Current standard therapy for T1-3 tumours includes radical surgery with Total Mesorectal Excision (TME), and preoperative chemoradiation for patients with T3 tumours or N1 tumours.

A state-transition model will be constructed to conduct a cost-utility analysis of the neoadjuvant chemotherapy approach based on this protocol vs. the current standard approach from a government payer's perspective, over a lifetime horizon with a 5% discounting for cost and effectiveness. The input of the model will be obtained by prospectively collecting efficacy data and health utilities in CO.28. Other efficacy data, utility data, resource utilization data and unit costs will be obtained from existing literature or retrospective chart reviews as needed.

The primary endpoint of the economic analysis will be incremental cost-utility ratio, which is the ratio of the incremental of cost between the two approaches to the incremental quality-adjusted life year gained between the two approaches. The incremental cost-effectiveness ratio will also be calculated, which is the ratio of the incremental cost between the two approaches to the incremental life-years gained between the two approaches. One way sensitivity analyses and probabilities sensitivity analysis will be conducted to assess for the robustness of the results and to examine the drivers of cost and effectiveness.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

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

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

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

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

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

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

14.3 Submission of Material for Presentation or Publication

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

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

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

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

15.2 Inclusivity in Research

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

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

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

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

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

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

15.3 Obtaining Informed Consent

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

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

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

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

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

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

15.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

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

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

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

Obtaining Consent for Research on Children

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

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

15.4 Discontinuation of the Trial

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

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

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

15.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

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

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

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

15.6 Centre Performance Monitoring

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

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

15.7 On-Site Monitoring/Auditing

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

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

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

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

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

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

APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

All CO.28 chemotherapy drugs are commercially available and will not be supplied for this study.

APPENDIX III - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of enrollment and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 9.0 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the CO.28 area of the CCTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial are:

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool*
BASELINE REPORT	Due within 2 weeks of patient enrollment.	Copies of signature pages of main and optional consent forms; relevant pathology & radiology reports.
CHEMOTHERAPY REPORT	To be completed after each chemotherapy cycle. Due within 2 weeks of end of cycle. This report documents treatment, adverse events and investigations for each chemotherapy cycle.	Relevant radiology reports.
PRE-EXCISION VISIT REPORT	To be complete within 2 weeks after pre-excision visit.	Relevant radiology reports.
END OF TREATMENT REPORT	To be complete within 4 weeks after final tumour excision	
SURGERY REPORT	To be complete within 4 weeks after surgery (either TME or TEMS/TAMIS)	Relevant pathology and surgery reports.
CORRELATIVE STUDIES	See Section 12 in this protocol.	Relevant pathology reports.
FOLLOW-UP REPORT	Continued follow-up after chemotherapy, radiotherapy and/or protocol tumour excision(s) completed. Due within 2 weeks after contact with patient.	Relevant pathology, radiology and surgery reports.
RELAPSE REPORT	To be completed at the time of disease relapse or failure. Due within 2 weeks after contact with patient.	Relevant pathology, radiology and surgery reports.
SHORT FOLLOW REPORT	To be completed after disease relapse or failure and for patients that have no protocol tumour excision.	
DEATH REPORT**	Required for all patients while study is open. Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT (SAE) REPORT	All reportable serious adverse events must be reported as described in Section 9.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.	All relevant test reports, admission, discharge summaries/notes.

* Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically. All supporting documents must have personal identifiers redacted.

** It is the investigator's responsibility to investigate & report the date/cause of death of any patient who dies during this period. Any death that occurs during this protocol therapy or within 30 days after last dose that is considered as unexpected an related to protocol treatment must also be reported as a Serious Adverse Event as described in Section 9.0.

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

Data	Required at	Collection /Submission	Comments
Quality of Life Questionnaire and EQ-5D Questionnaire	To be completed within 30 days prior to enrollment, at pre-excision visit, then at months 3, 6, 12, 24 and 36	Patient to complete on paper; site CRA to enter data (as required) in the EDC system within corresponding folders	Retain questionnaires at the site
Capecitabine Patient Diary	To be completed daily by the patient, if treated with Capecitabine	To be collected and reviewed for compliance each cycle. Site CRA to enter data (as required) in the EDC system within corresponding folders	Retain diary at the site

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

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

APPENDIX V - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

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-enrollment (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, et cetera.

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, as required by the schedule in the protocol.

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 cannot comprehend 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.

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **CO.28**

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

Patient Information

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

Institution: _____ Investigator: _____

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

☐ Within 30 days prior to enrollment

☐ PRE-Excision 2-4 weeks (FOLFOX) or 3-5 weeks (CAPOX) after last cycle of chemotherapy

After protocol excision. For patients who fail and go onto TME, these times are from TME date:

☐ 6 months ☐ 12 months ☐ 24 months ☐ 36 months

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

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

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

Comments: _____

_____

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

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

CCTG use only

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

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

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (CO.28)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

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

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

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

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

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

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4

Please go on to the next page

48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes	No

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4
Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

Please go on to the next page

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

During the past 4 weeks:	Not At All	A Little	Quite a Bit	Very Much
For MEN only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4
For WOMEN only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

Please go on to the next page

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

Fecal Incontinence Quality of Life Instrument

Q 1: In general, would you say your health is:

1 ☐ Excellent
2 ☐ Very Good
3 ☐ Good
4 ☐ Fair
5 ☐ Poor

Q 2: For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage.

Q2. Due to accidental bowel leakage:	**Most of the Time**	**Some of The Time**	**A Little of the Time**	**None of the Time**
a. I am afraid to go out.	1	2	3	4
b. I avoid visiting friends.	1	2	3	4
c. I avoid staying overnight away from home.	1	2	3	4
d. It is difficult for me to get out and do things like going to a movie or to church.	1	2	3	4
e. I cut down on how much I eat before I go out.	1	2	3	4
f. Whenever I am away from home, I try to stay near a restroom as much as possible.	1	2	3	4
g. It is important to plan my schedule (daily activities) around my bowel pattern.	1	2	3	4
h. I avoid traveling.	1	2	3	4
i. I worry about not being able to get to the toilet in time.	1	2	3	4
j. I feel I have no control over my bowels.	1	2	3	4
k. I can't hold my bowel movement long enough to get to the bathroom.	1	2	3	4
l. I leak stool without even knowing it.	1	2	3	4
m. I try to prevent bowel accidents by staying very near a bathroom.	1	2	3	4

Q 3: Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items.

Q3. Due to accidental bowel leakage:	Strongly Agree	Somewhat Agree	Somewhat Disagree	Strongly Disagree
a. I feel ashamed.	1	2	3	4
b. I can not do many of things I want to do.	1	2	3	4
c. I worry about bowel accidents.	1	2	3	4
d. I feel depressed.	1	2	3	4
e. I worry about others smelling stool on me.	1	2	3	4
f. I feel like I am not a healthy person.	1	2	3	4
g. I enjoy life less.	1	2	3	4
h. I have sex less often than I would like to.	1	2	3	4
i. I feel different from other people.	1	2	3	4
j. The possibility of bowel accidents is always on my mind.	1	2	3	4
k. I am afraid to have sex.	1	2	3	4
l. I avoid traveling by plane or train.	1	2	3	4
m. I avoid going out to eat.	1	2	3	4
n. Whenever I go someplace new, I specifically locate where the bathrooms are.	1	2	3	4

Q 4: During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?

1 ☐ Extremely So - To the point that I have just about given up
2 ☐ Very Much So
3 ☐ Quite a Bit
4 ☐ Some - Enough to bother me
5 ☐ A Little Bit
6 ☐ Not At All

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

Fecal Incontinence Severity Index

Q 1: For each of the following, please indicate on average how often in the past month you experienced any amount of accidental bowel leakage:

	2 or More Times a Day (1)	Once a Day (2)	2 or More Times a Week (3)	Once a Week (4)	1 to 3 Times A Month (5)	Never (6)
a. Gas	☐	☐	☐	☐	☐	☐
b. Mucus	☐	☐	☐	☐	☐	☐
c. Liquid Stool	☐	☐	☐	☐	☐	☐
d. Solid Stool	☐	☐	☐	☐	☐	☐

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

Low Anterior Resection Syndrome Score – LARS Score. English version 1.0

Bowel function questionnaire

The aim of this questionnaire is to assess your bowel function.
Please tick only one box for each question. It may be difficult to select only one answer, as we know that for some patients symptoms vary from day to day. We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into account and focus on answering questions to reflect your usual daily bowel function.

Do you ever have occasions when you cannot control your flatus (wind)?
☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

Do you ever have any accidental leakage of liquid stool?
☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

How often do you open your bowels?
☐ More than 7 times per day (24 hours)
☐ 4-7 times per day (24 hours)
☐ 1-3 times per day (24 hours)
☐ Less than once per day (24 hours)

Do you ever have to open your bowels again within one hour of the last bowel opening?
☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?
☐ No, never
☐ Yes, less than once per week
☐ Yes, at least once per week

Translated March 2013 by Nick J. Battersby, Department of Colorectal Surgery, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK

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

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

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

Thank you.

APPENDIX VI - HEALTH UTILITIES ASSESSMENT

Introduction

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

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

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

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

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

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

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

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

Instructions for Administration of a Health Utilities Questionnaire

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

1. Preamble

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

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

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

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

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

2. Pre-treatment Assessment

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

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

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (not required during treatment for this trial).

4. Assessments During Follow-up

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

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

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

5. What If…

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

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if 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.

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

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after 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.

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

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D 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.

Health Utilities Questionnaire – ENGLISH

CCTG Trial: **CO.28**

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

Patient Information

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

Institution: _____ Investigator: _____

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

☐ Within 30 days prior to enrollment

☐ After 3 cycles of FOLFOX or after 2 cycles of CAPOX

☐ PRE-Excision 2-4 weeks (FOLFOX) or 3-5 weeks (CAPOX) after last cycle of chemotherapy

After protocol excision. For patients who fail and go onto TME, these times are from TME date:

☐ 30 days ☐ 6 months ☐ 12 months ☐ 24 months ☐ 36 months

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

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

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

Comments: _____

_____

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

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

CCTG use only

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

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

EQ-5D Questionnaire

CCTG: CO.28

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

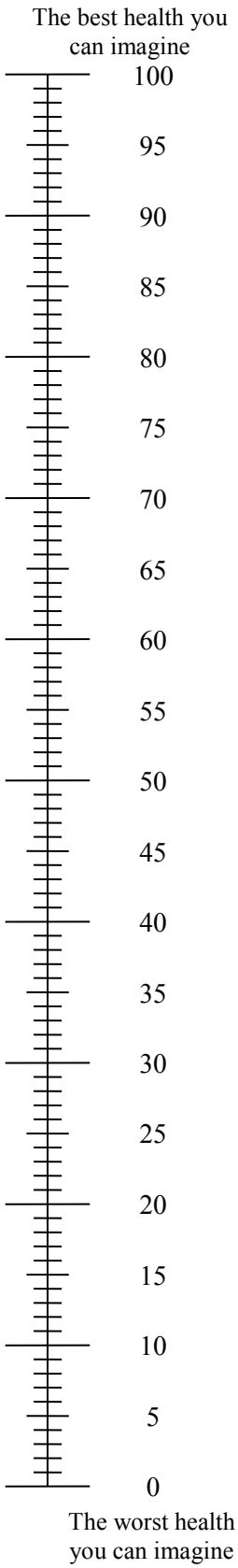
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Please check to make sure you have answered all questions.

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

Thank you.

APPENDIX VII - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

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

LIST OF CONTACTS

PATIENT ENROLLMENT

All patients must be registered with CCTG before any treatment is given.

	Contact	Tel. #	Fax #
ELECTRONIC DATA CAPTURE (EDC) AND RIPPLE (technical support)	CCTG Home Page (Toolbox): https://scooby.ctg.queensu.ca Email Support Staff at: support@ctg.queensu.ca		
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Alexander Montenegro Study Coordinator, CCTG Email: amontenegro@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CO-CHAIRS	Dr. Hagen Kennecke Study Co-Chair Email: hkennecke@bccancer.bc.ca or: Dr. Carl Brown Study Co-Chair Email: cbrown@providencehealth.bc.ca		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Alexander Montenegro Study Coordinator, CCTG Email: amontenegro@ctg.queensu.ca	613-533-6430	613-533-2941