PROTOCOL DATE: 2015-JUL-22
CCTG TRIAL: HE.1

AMENDMENT #1: 2018-JUL-31

ADMINISTRATIVE UPDATE #1: 2018-NOV-07

CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE III STUDY OF PALLIATIVE RADIOTHERAPY FOR SYMPTOMATIC HEPATOCELLULAR CARCINOMA AND LIVER METASTASES

CCTG Protocol Number: **HE.1**

STUDY CHAIR:	Laura A. Dawson
TRIAL COMMITTEE:	Derek Jonker Jennifer Knox Camilla Zimmerman Philip Wong
SENIOR INVESTIGATOR:	Chris O'Callaghan
BIOSTATISTICIAN:	Dongsheng Tu
PHYSICIST:	Tom Purdie
RADIATION THERAPY REVIEWER:	Alysa Fairchild
SYMPTOM CONTROL COMMITTEE COORDINATOR:	Rebecca Wong
QUALITY OF LIFE COORDINATOR:	Jolie Ringash
STUDY COORDINATOR:	Paul Stos
REGULATORY SPONSOR:	CCTG

(For contact information of study personnel see Final Page.)

TABLE OF CONTENTS

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, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

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

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

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

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

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

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: CCTG HE.1

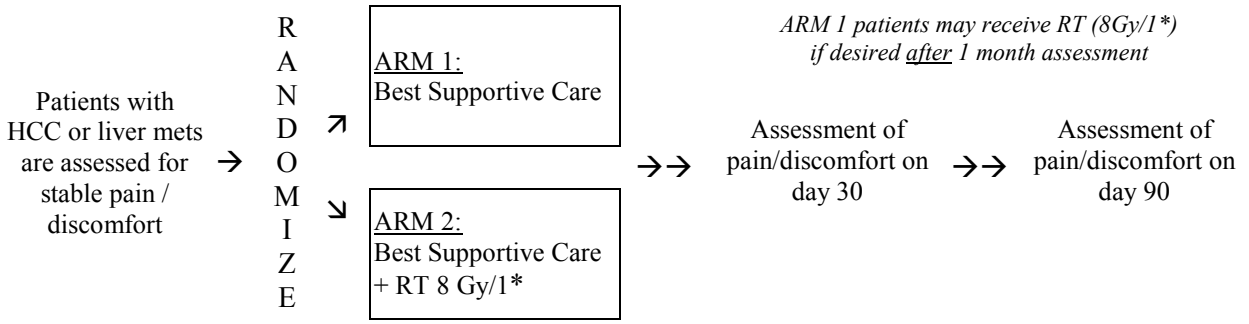
CENTRE: _____

TREATMENT SCHEMA

This is a multi-centre, randomized, phase III trial of best supportive care (BSC) with or without single fraction liver radiation therapy (8 Gy) in patients with end-stage, painful, hepatocellular carcinoma (HCC) or liver metastases.

Stratification:

- Centre
- Type of liver cancer (HCC versus liver metastases)



** Patients will also receive anti-emetic pre-medications*

Planned sample size: 45 eligible (approximately 65 randomized)

Primary Endpoint

- Proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points in pain "intensity at worst " on Brief Pain Inventory (BPI) from baseline to day 30.

Secondary Endpoints

- Proportion of patients experiencing grade ≥ 2 adverse events at day 30 and day 90.
- Proportion of patients alive at day 90.
- Proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points from baseline to day 30 and day 90 in all BPI pain scores.
- Proportion of patients reporting clinically significant improvement in QoL from baseline to day 30 and day 90 as defined by a ≥ 5 point change in the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Subscale (FACT-HBS) and Trial Outcome Index (FACT-TOI).
- Proportion of patients achieving a 25% reduction in opioid use at 30 days (employing daily morphine equivalence scale).
- Proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points in pain "intensity at worst " AND with no increase in opioid use (employing daily morphine equivalence scale) on BPI from baseline to 30 days.

1.0 OBJECTIVES

1.1 Primary Objective

To determine if patients with symptomatic liver tumours (either HCC or liver metastases) who undergo best supportive care (BSC) plus a single 8 Gy fraction of radiation therapy to the liver experience a significant improvement in symptoms (defined as a ≥ 2 point decrease in their pain "intensity at worst" score on the Brief Pain Inventory (BPI)) from baseline to 30 days as compared to patients receiving BSC alone.

1.2 Secondary Objectives

To compare the two treatment arms with respect to:

- Proportion of patients experiencing grade ≥ 2 adverse events at 30 days and 90 days.
- Proportion of patients alive at 90 days.
- Proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points from baseline to day 30 and day 90 in all BPI pain scores.
- Proportion of patients reporting clinically significant improvement in QoL from baseline to day 30 and day 90 as defined by a ≥ 5 point change in the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Subscale (FACT-HBS) and Trial Outcome Index (FACT-TOI).
- Proportion of patients achieving a 25% reduction in opioid use at 30 days (employing daily morphine equivalence).

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Liver Cancer

Hepatocellular carcinoma (HCC) is a top cause of cancer-related death globally and the most rapidly increasing cause of cancer death in Canada. In 2013, in Canada, there were over 2000 new HCCs and 1000 deaths due to HCC *[2013 Canadian Cancer Society Statistics]*. HCC is often diagnosed at an advanced stage, and symptoms of pain, anorexia and fatigue are common, especially in patients unsuitable for or refractory to standard local, regional and systemic therapies *[Zhu 2003]*.

The liver is a common site for metastases from a variety of gastrointestinal malignancies (e.g. colorectal and pancreatic cancer), as well as non-gastrointestinal malignancies, including, melanoma, breast and gynecological cancers. It is estimated that approximately 25,000 Canadian patients die with liver metastases each year *[2013 Canadian Cancer Society Statistics]*. Surgery and other local therapies are treatment options for the minority of patients with 'oligo' or few hepatic confined metastases; however the majority of patients are not suitable for local therapies due to insufficient hepatic reserve and/or a high risk of extra-hepatic disease.

2.2 Symptoms from End-Stage Liver Cancer

The majority of HCC patients experience liver pain or discomfort at some point during their disease course. Pain is likely under-reported in these patients and sometimes dismissed as "discomfort", despite the significant negative impact on patients' lives *[Kaiser 2014]*. It has been suggested that there is a need for routine pain assessment as an integral component of advanced HCC patient care *[Kaiser 2014]*. While pain related to liver metastases is not as common as in HCC patients, in later stages, diffuse and/or large hepatic metastases may invade into or stretch the liver capsule causing substantial discomfort. For HCC and liver metastases, the majority of patients become refractory to all therapy for a period of time prior to death and a substantial proportion of these patients suffer from hepatic pain. Effective palliation of hepatic pain can be challenging for these patients and there is a need for improved palliative treatments.

Opioids are commonly used for the palliation of cancer bone pain or other cancer pain outside the liver. However, in patients with impairment of liver function from underlying liver disease, which is common in patients with liver cancer, there is often reduced hepatic blood flow, limiting first pass metabolism, and phase I metabolism (P450 system) and phase II metabolism (glucuronidation) do not work as well. Thus, the parent drug or its metabolites can accumulate, which may precipitate encephalopathy or excessive sedation causing difficulty with compliance and/or in attaining analgesia without toxic side effects. The therapeutic index for opioid-induced pain relief is narrowed in many patients with hepatic pain from liver cancer. Alternate and additional strategies for hepatic pain from end-stage HCC or liver metastases are warranted to reduce pain and improve quality of life (QoL) in these patients.

The natural history of patients with symptomatic liver cancer has not been well researched and there are only a few studies of patient-reported QoL or symptom trials in patients with symptomatic liver cancer. In one study of patients treated with chemotherapy for asymptomatic liver metastases from colorectal carcinoma, there was no improvement in QoL (assessed using EORTC QLQ-C30 and QLQ-LMC21) and more problems with taste, sore mouth, and neuropathy 3 months after chemotherapy *[Blazeby 2009]*. Although these results are not directly comparable with the HE.1 study cohort who are selected as being unfit for or refractory to systemic agents, it seems unlikely that QoL in patients with more advanced liver metastases or HCC may improve with no interventions or with best supportive care (BSC) alone. There is a paucity of studies that have evaluated the impact of BSC or other treatments on symptoms in patients with end-stage primary or metastatic liver cancer and there is a strong need for prospective evaluation of patient-reported outcomes in such patients treated with novel interventions, such as radiation therapy (RT) or BSC alone.

2.3 Radiation Therapy in Liver Cancer

In selected patients with focal HCC or liver metastases unsuitable for surgery, high dose, conformal RT or stereotactic body radiation RT (SBRT) are being increasingly used. Phase I and II studies have demonstrated tumour control at 1 and 2 years in the majority of patients *[Bujold 2013; Herfarth 2003(b); Hoyer 2006; Lee 2009; Mendez 2006; Pan 2010; Seong 2000]*. However, due to the extent of liver involvement with cancer (e.g. diffuse metastases), poor underlying liver function, and/or presence of extra-hepatic metastases, the majority of patients with primary or metastatic liver cancer are not candidates for conformal RT or SBRT. The tolerance of the whole liver to radiation therapy is low, and radiation-induced liver toxicity can result if the whole liver is treated with more than approximately 30 Gy in 2 Gy per fraction (a dose too low to lead to tumour ablation).

There have been few studies of low-dose liver RT to palliate symptoms from liver cancer and most have not included patient-reported outcomes *[Borgelt 1981; Bydder 2003; Ingold 1965; Prasad 1977; Sherman 1978; Turek-Maischeider 1975; Wharton 1973]*. The largest of these studies delivered 21 Gy in 7 fractions to the whole liver and randomized patients to misonidazole; there was an 80% response rate of abdominal pain, with a median duration of response of 13 weeks *[Leibel 1987]*. A Trans-Tasman Radiation Oncology Group study observed a physician-reported symptom response of 54% at 2 weeks following 10 Gy in 2 fractions to the whole liver to palliate symptoms from liver metastases with two grade 3 toxicities *[Bydder 2003]*.

2.4 Rationale for a Phase III Study in Symptomatic Liver Cancer Patients

A phase II study of 8 Gy in one fraction to the whole (or near-whole) liver for the palliation of symptoms from liver cancer was conducted at the Princess Margaret Cancer Center by Dr. Dawson and colleagues *[Soliman 2013]*. The rationale for the use of a single fraction of RT was multi-fold. Using the shortest effective fractionation (ideally over one day) is more convenient for patients with a limited life expectancy, such as those in the HE.1 study. Eight Gy in one fraction is the lowest dose that has been used successfully to palliate cancer pain in other body parts, including bone metastases, even in the absence of objective radiological responses *[Lutz 2014; Salazar 2001]*. RT-induced liver toxicity can result if the whole liver is treated with doses higher than 30 Gy in 15 fractions *[Pan 2010]*, and 8 Gy in one fraction is a much lower biologic dose than 30 Gy in 15 fractions. Also, 8 Gy in one fraction has been shown to be safely used in the setting of hemi-body irradiation of patients with bony metastases in which the liver was included in the irradiated volume; although grade 3-4 toxicity was seen in 12% of patients treated with hemibody RT, it was primarily hematologic *[Salazar 2001]*.

The Princess Margaret Cancer Centre study investigated 41 patients with diffuse HCC (21) or liver metastases (20, 50% from a gastrointestinal primary site) who had pain (27), discomfort (6) or other (5) symptoms *[Soliman 2013]*. The use of 8 Gy in one fraction to the whole (or near whole) liver, with an anti-emetic to prevent nausea, resulted in a clinically meaningful improvement in average index symptom intensity assessed using the BPI in 48% (95% CI: 28-68%) of patients one month following RT with no differences between patients with HCC and liver metastases. In patients with pain or abdominal discomfort as their index symptom, pain relief tended to occur within a few days and was sustained with a clinically significant improvement at one month in 55% (95% CI: 32-76%) of patients when evaluating "average" pain/discomfort, and in 59% (95% CI: 36-79%) when evaluating "worst" pain/discomfort in the past 24 hours. The pathophysiology of pain relief is not clearly understood; however objective tumour shrinkage is not required for effective pain relief. There was no reduction in symptoms in patients who had nausea or fatigue as their index symptom. RT treatment was well tolerated. Grade 1 or 2 fatigue, often present at baseline, was common; grade 1 or 2 nausea was seen in 3 patients, and grade 2 gastritis was seen in 1 patient. One patient, who declined anti-emetics prior to RT, developed grade 3 vomiting. There was no other reported toxicity. From a QoL perspective, the benefits were less. Twenty-nine percent (95% CI: 8 – 45%) of patients treated with RT had a significant improvement in FACT-HBS at 30 days and 25% (95% CI: 10- 47%) of patients had significant improvement in FACT- TOI at 30 days. Based on the results of this pilot study, the next logical step is to test, in a multi-institutional randomized study, that RT may lead to a clinically significant hepatic pain reduction and QoL improvement in a greater proportion of patients compared to BSC alone *[Hoyer 2012]*.

2.5 Rationale for Patient-Reported Instruments

Patient-reported symptoms will be recorded using the Brief Pain Inventory (BPI), which consists of 4 pain intensity and 7 pain interference 11-point Likert-scale questions (range 0-10) *[Cleeland 1994].* BPI is easy to administer, imposing minimum burden to patients. It also has been translated and validated into many different languages. Patients who report liver discomfort (as opposed to liver "pain"), will still complete the "pain" questions. Although the BPI has not been validated for measuring 'discomfort', it has face validity for this use, and its 0-10 scale is also used in the Edmonton Symptom Assessment Scale (ESAS) *[Bruera 1991]* and the MD Anderson Symptom Inventory *[Cleeland 2000]*, which are both validated and include a wide variety of symptoms. This was shown to be feasible in the study by Soliman and colleagues *[Soliman 2013]*. A reduction by ≥ 2 from baseline score is considered clinically significant *[Chow 2002]*. The primary outcome measure for the present study will be the proportion of patients experiencing improvement by ≥ 2 points from baseline to 30 days on "worst pain" in past 24 hours on BPI. Worst pain and average pain in the past 24 hours were the most sensitive metrics to detect change in symptoms in the study by Soliman and colleagues *[Soliman 2013].* Worst pain was chosen as the primary endpoint since it (a) has the highest short term reliability (0.93) of all the BPI pain intensity scales *[Cleeland 1994, BPI user guide 2009]*, (b) is recommended as the primary pain endpoint in trials assessing response to palliative radiation therapy for bone metastases, and (c) has higher correlations with functional interference scores and is felt to be most important to patients, compared with other BPI scores *[Harris 2007].*

Patient-reported QoL will be recorded using the Functional Assessment of Cancer Therapy Hepatobiliary (FACT-Hep) questionnaire, a 45-item instrument consisting of the 27-item cancer specific FACT-General (FACT-G), and a site-specific 18-item hepatobiliary subscale (HBS) *(Heffernan 2002).* The FACT-G consists of four subscales: 1) physical well-being (PWB); 2) social and family well-being; 3) emotional wellbeing; and 4) functional well-being (FWB). The Trial Outcome Index (TOI) is the sum of the PWB, FWB and HBS subscales *[Cella 1993]*. The total FACT-TOI score, FACT-Hep score, FACT-G score and individual scores for each subscale will be scored. FACT was chosen for measuring QoL in these patients since, in the Phase II study, patient compliance was better with FACT versus EORTC *[Soliman 2013],* and FACT was more sensitive to demonstrating benefits in patients than EORTC. FACT QoL has been validated in the use of bone metastases response to radiation therapy and is available in different languages. Changes in QoL are secondary endpoints of this study. The FACT HBS and TOI QoL endpoints are expected to be most likely to discriminate between differences in QoL in the two treatment arms. A change in scores of the FACT-G, FACT-HBS, FACT-TOI and FACT-Hep total score by ≥ 6, ≥ 5, ≥ 7 and ≥ 8 respectively are considered clinically significant *[Heffernan 2002]*.

2.6 Correlative Studies

The mechanism of liver-related cancer pain and how radiation therapy may reduce pain is not well understood. Hepatic pain may be caused by direct tumour invasion or stretch of the hepatic capsule, by infiltration of adjacent organs (such as diaphragm or chest wall), or from a large burden of cancer causing mass effect in the abdomen and/or releasing chemicals that may increase the pain response to otherwise non-painful stimuli. Furthermore, hepatic visceral pain can be diffuse and difficult for patients to describe. The rapid benefit to patients following low dose radiation therapy seen in the Soliman study *[Soliman, 2013]* (at 1 week and 1 month post radiation therapy) suggests that reduction in pain is not due to objective tumour responses that would be unexpected following such low dose radiation therapy (8 Gy in one fraction). Radiation has been postulated to reduce bone pain from metastases from a direct tumour effect on tumours stimulating them to reduce their production of pain "promoting" cytokines *[Goblirsch 2005]*. This may be mediated by an inflammatory pathway. Pro-inflammatory cytokines been associated with pain and changes in serum cytokines (including C-reactive protein, TGFβ, interleukin-1 (IL-1) and IL-6) have has been observed following radiation therapy *[Menard 2006, Bower 2009]*. Changes in IL-6 have been correlated with radiation associated fatigue.

It is hypothesized that larger changes in the inflammatory cytokines post radiation therapy will be more highly correlated with patient reported reduction of pain. In the present study, by collecting serum at the time of planned blood draws (baseline, 30 days and 90 days post randomization), changes in cytokines or other proteins can be measured. If there are patterns of change in inflammatory cytokines highly correlated with the strongest responders post radiation therapy, this may provide some insight to the mechanism of pain relief from radiation therapy, which may help in future research to try to exploit the palliative benefit of radiation therapy.

3.0 BACKGROUND THERAPEUTIC INFORMATION

There are no therapeutic agents involved in this study.

4.0 TRIAL DESIGN

Please see Appendix VI for a schematic overview of the trial.

4.1 Stratification

Patients will be stratified by:

- Centre
- Type of liver cancer (HCC versus liver metastases)

4.2 Randomization

Patients will be randomized 1:1 to receive best supportive care alone or best supportive care plus radiation therapy (8 Gy in 1 fraction), to a planned sample size of approximately 65 patients (45 eligible).

Arm	Agent(s)	Dose	Volume	Duration
1	Best Supportive Care*	---	---	90 days
2	Best Supportive Care*	---	---	90 days
	Palliative Radiation Therapy **	8 Gy in 1 fraction	Whole liver or near whole liver	---

* Including analgesics, palliative care and/or pain specialist assessment as needed.

** Including anti-emetic pre-medications.

4.3 Inclusion of Women and Minorities

There are no exclusions based on race or ethnicity in this trial.

To date, there is no evidence of superiority of one form of treatment over another according to racial or ethnic group. The appropriate racial/ethnic mix will be recruited to this study based on the epidemiology of cancer in the participating centres.

5.0 STUDY POPULATION

This study will recruit patients with hepatic pain or discomfort from HCC or liver metastases. In the 7 days prior to randomization, patients must have no significant change (range of 3 points is allowable) in pain score as measured over 2 days. All patients will receive best supportive care, and it is recommended that this include a palliative care or pain specialist assessment prior to randomization, when available.

5.1 Eligibility Criteria

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

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

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

5.1.1 A diagnosis of cancer by at least one criterion listed below:

- Pathologically or cytologically proven carcinoma from primary site or site of metastases;
- Pathologically or cytologically proven HCC;
- HCC diagnosed by standard imaging criteria: arterial enhancement and delayed washout on multiphasic computerized tomography (CT) or magnetic resonance imaging (MRI) in the setting of cirrhosis or chronic hepatitis B or C without cirrhosis.

5.1.2 Largest burden of cancer in the liver is confirmed with CT scan or MRI corresponding to the clinically painful area done within 120 days prior to randomization.

5.1.3 Diffuse (infiltrative involving > 50% of the liver), multifocal (> 10 lesions) or locally advanced cancer (at least one lesion > 10cm, vascular invasion, or multiple lesions with at least one > 6cm) involving the liver.

5.1.4 In the investigator's opinion, patient is unsuitable for or refractory to standard local and regional therapies. For example:

- HCC unsuitable for resection, radiofrequency ablation (RFA), transarterial chemo embolization (TACE) or radical intent, ablative dose stereotactic body radiation therapy (SBRT);
- Colorectal carcinoma metastases unsuitable for resection, RFA or radical intent, ablative dose SBRT (e.g. SBRT, > 30 Gy in 5 fractions, may be an option for up to 3 metastases < 5cm each, or up to 5 metastases < 3 cm each).

5.1.5 Unsuitable for, high risk for, or refractory to, standard systemic chemotherapy or targeted therapy (e.g. sorafenib).

5.1.6 Patient reports moderate or severe pain/discomfort prior to the baseline evaluation and this pain is considered "stable" over a period of up to 7 days prior to randomization (see Appendix III for full details);

Definition of moderate pain:

Patient reports level of 4-6 (on a BPI scale from 0 to 10) pain or discomfort "at its worst in the past 24 hours", occurring in the right upper quadrant of the abdomen, the upper abdomen and/or referred to the right shoulder, attributable to liver cancer.

Definition of severe pain:

Patient reports level of 7-10 (on a BPI scale from 0 to 10) pain or discomfort "at its worst in the past 24 hours", occurring in the right upper quadrant of the abdomen, the upper abdomen and/or referred to the right shoulder, attributable to liver cancer.

Definition of "stable" pain:

Patient must show moderate or severe "stable" pain by reporting a score of 4 or greater (on 2 separate days within the 7 day period prior to randomization) with the difference of these scores being 0, 1, 2 or 3.

5.1.7 Patient reports moderate or severe pain (i.e. pain score is 4 or higher). This baseline score must also be stable compared to the most recent pre-baseline pain score with the difference between these scores being 0, 1, 2, or 3 (see Appendix III for full details).

5.1.8 Blood work obtained within 14 days prior to randomization as follows:

- Hemoglobin > 70 g/L;
- Platelets > 25 x 10^9/L;
- Absolute neutrophil count (ANC) > 1.0 x 10^9/L;
- INR < 3;
- Bilirubin < 2.5 UNL (except for subjects with Gilbert's Disease who are eligible despite elevated serum bilirubin level);
- AST or ALT < 10 x ULN.

5.1.9 Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-3 within 14 days of Randomization (see Appendix II).

5.1.10 Life expectancy of > 3 months.

5.1.11 18 years of age or older at the time of randomization.

5.1.12 Patient is willing to complete the Pre-Baseline Pain/Discomfort Questionnaire and the Pain/Discomfort and Medication Questionnaire in English, French or other validated language (please contact the HE.1 Study Coordinator). The baseline assessment must be completed within required timelines prior to randomization. Unwillingness to complete the Pre-Baseline Pain/Discomfort Questionnaire and Pain/Discomfort and Medication Questionnaire will make the patient ineligible for the study.

5.1.13 Patient is able (i.e. sufficiently fluent) and willing to complete the QoL questionnaires in English, French or other languages in which the FACT-Hep is available (please contact the HE.1 Study Coordinator). The baseline assessment must be completed within required timelines prior to randomization.

Inability (illiteracy in languages listed above, 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 QoL questionnaires will make the patient ineligible for QoL assessment.

5.1.14 Patient is not pregnant, planning on becoming pregnant or planning on fathering a child in the next 90 days.

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

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Appendix I); 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.

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

5.1.16 Patients must be accessible for treatment and follow-up. Investigators must ensure the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.17 In accordance with CCTG policy, protocol treatment is to begin within 5 working days of patient randomization (earlier is preferred).

5.2 Ineligibility Criteria

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

5.2.1 Prior radiotherapy to the upper abdomen that would result in substantial overlap of the irradiated volume (e.g. > 50% of liver receiving > 24 Gy in 2 Gy equivalent dose).

5.2.2 Prior selective internal radiotherapy directed to the liver or hepatic arterial yttrium therapy, at any time.

5.2.3 Cholangitis or acute bacterial infection requiring intravenous antibiotics within 28 days prior to study entry.

5.2.4 Radiographic evidence of intrabiliary cancer within the common or main branches of the biliary system, < 4 months prior to randomization.

5.2.5 Child-Pugh score greater than C10 (a score of C10 is allowed).

5.2.6 Chemotherapy or TACE administered within the past 4 weeks.

5.2.7 Targeted therapy (e.g. Sorafenib) received within the past 2 weeks.

5.2.8 Plans for chemotherapy, targeted therapy or TACE in the next 4 weeks.

6.0 PRE-RANDOMIZATION EVALUATION
(See Appendix I)

In order to avoid enrolling patients with rapidly escalating or diminishing pain/discomfort, patients will be asked to demonstrate that they have moderate or severe, stable pain/discomfort. In addition, it is strongly recommended that the patient's use of analgesia is "stable" in the opinion of the investigator. Thus, all patients will need to assess their pain/discomfort over the previous 24 hours on 2 separate days during the week prior to study randomization. It is envisioned that this assessment will be after the patient signs the informed consent document and will involve completion of Pre-Baseline Pain/Discomfort Questionnaires, however, where a patient-reported pain score was obtained using the BPI pain questionnaire as part of routine clinical care and has been recorded in the patient medical record (i.e. as verifiable source documentation) prior to the patient consenting to participation on the trial, this score may be used as a "Pre-Baseline" value to demonstrate the patient has met the eligibility criteria concerning adequate and stable pain. All Pain scores must be collected and reported using the trial specific Pre-Baseline BPI pain questionnaire.

Patients will be given several copies of the Pre-Baseline Pain/Discomfort Questionnaire that they are to complete on two separate days within one week. The questionnaire will contain the "pain at worst in the past 24 hours" intensity question from the BPI.

Sites will use this information to determine if the patient has stable pain/discomfort (as described in Appendix III, with a range in scores of 0, 1, 2, or 3). The questionnaires may be completed at home by the patient and the site staff will phone the patient to help serve as a reminder.

If patients have changing pain/discomfort, (as described in Appendix III, with a range in scores of 4 or more) then they are not suitable for randomization. They may have their analgesia optimized and/or may repeat the 2 day assessment until they have stable pain/discomfort (with range in scores of 3 or less) over a 7 day time period, at which point they may be considered for the study. It is expected that it may take more than 2 days for some patients to reach a "steady state" pain score, and patients with high variability in their pain scores at first attempt are encouraged to be re-considered for participation in the study at any time, if they develop stable pain.

After stable pain is determined, the patient will be asked to complete the baseline Pain/Discomfort and Medication Questionnaire. If the baseline "worst" pain score is 4 or greater and if it is within 3 points of the most recent pre-baseline pain score, the patient is considered eligible. The patient will complete the baseline QoL Questionnaire and will undergo an adverse event evaluation by the investigator. These assessments will provide the necessary baseline data for analysis of the trial endpoints.

Please see Appendix III for guidance in determining "stable" pain/discomfort during the pre-baseline screening period and for examples of different scenarios that might occur.

It is recommended that BSC practices be initiated for all patients prior to randomization. BSC for this population may include an assessment by a palliative care or a pain specialist team (per local policy). This should help to avoid confounding effects from palliative care/pain specialist assessment if the first such visit was post randomization but prior to the day 30 primary endpoint assessment.

Investigations		Timing
History and Physical Exam including:	• ECOG PS (see Appendix II) • weight • assessment of ascites and encephalopathy (Child Pugh score – see Appendix IV)	≤ 14 days prior to randomization
Hematology	• hemoglobin • platelets • INR • neutrophils	≤ 14 days prior to randomization
Biochemistry	• albumin • bilirubin • AST and/or ALT • ALP • creatinine • alpha-fetoprotein (for HCC patients only)	≤ 14 days prior to randomization
Radiology	• CT or MRI scan of abdomen which establishes liver metastases or HCC per eligibility criteria	≤ 120 days prior to randomization
Pre-Baseline Stable Pain/Discomfort Assessment	• Pre-Baseline Pain/Discomfort Questionnaire x2 days within a one week period prior to randomization (range in BPI pain/discomfort scores up to 3 permitted)	≤ 7 days prior to randomization
Baseline Pain/Discomfort Assessment	• Pain/Discomfort and Medication Questionnaire	Following the completion of the last Pre-Baseline Pain/Discomfort Questionnaire that defined stability and on or prior to the date of randomization
Baseline Analgesia Assessment	• Pain/Discomfort and Medication Questionnaire	Following the completion of the last Pre-Baseline Pain/Discomfort Questionnaire that defined stability and on or prior to the date of randomization
Adverse Events*	• Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	Following the completion of the last Pre-Baseline Pain/Discomfort Questionnaire that defined stability and on or prior to the date of randomization
Quality of Life	• FACT-Hep	Following the completion of the last Pre-Baseline Pain/Discomfort Questionnaire that defined stability and on or prior to the date of randomization
Other Assessments	• Pregnancy test which may include an ultrasound to rule out pregnancy (for women of child bearing potential only)	≤ 14 days prior to randomization
Correlative Studies	• Blood draw for correlative studies (for consenting patients only)	≤ 14 days prior to randomization

* Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix VII). Only AEs deemed grade ≥ 2 are required to be reported.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations 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 randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the HE.1 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk (link in EDC) or the HE.1 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 at the time of randomization:

- trial code (CCTG HE.1)
- investigator CCTG user ID
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- optional consent version date
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- stratification factors

7.2 Stratification

Subjects will be stratified by:

- Centre
- Type of liver cancer (HCC versus liver metastases)

7.3 Randomization

Randomization 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 randomization.

All randomized patients are to be followed for 90 days after randomization. Data submission for ineligible participants should be followed according to the protocol to allow for pain/discomfort and adverse event assessment.

8.0 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 randomization (earlier is preferred).

8.1 Best Supportive Care (Arms 1 and 2)

Patients on both treatment arms will receive BSC, with analgesia as needed and palliative care/ pain specialist involvement in their care (per local policy). The treating team will determine the most appropriate interventions for individual patients. In general, analgesia strategies that may be considered include:

- Opioids: Short-acting hydromorphone q 2-4 hours prn is the opioid of choice with the dose individualized and titrated to maximize pain relief effect and minimize side effects. A longer interval between dosing may be needed for patients with more impaired liver function. Long acting hydromorphone may also be used if around-the-clock pain relief is required. The pharmacokinetics of fentanyl and methadone are not significantly affected by hepatic impairment, so they are alternatives in the setting of liver failure *[Smith 2009]*. Other opioids are also permitted;
- Steroids: Dexamethasone is sometimes useful in these patients. If patients are on dexamethasone, it is recommended that they stay on the same dose for at least 3 days before entering the trial with no plans for altering the dose during the first month of the study, if clinically suitable. Note that even if patients are taking regular steroids, anti-emetics one hour prior to RT delivery, including a steroid, should be delivered (see section 8.3.1); and,
- Acetaminophen: 325 mg to 1 g q 4 hours, up to 3 g per day.

It is recommended that patients bring their pain medication pill bottles to each follow-up appointment and that the study nurse or CRA review the medication table completed by the patient (in Part Two of the Pain/Discomfort and Medication Questionnaire). All changes in pain medication, including steroid and over the counter analgesia, should be recorded.

8.2 Arm 1: Best Supportive Care Alone

8.2.1 *Premedication (Arm 1)*

Not applicable.

8.2.2 *Patient Monitoring (Arm 1)*

Patients will be seen at 30 and 90 days post randomization.

8.2.3 *Dose Adjustments (Arm 1)*

Not applicable.

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

The major adverse effects are expected to be related to underlying disease (cancer and/or liver disease such as cirrhosis) and from analgesia use. The most likely toxicities from analgesia use and/or underlying cancer and/or liver disease are confusion, fatigue, nausea, vomiting, constipation, encephalopathy, insomnia, and decline in liver function.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix VII).

8.2.5 *Duration of Therapy (Arm 1)*

Patients will be followed for 90 days post-randomization.

8.2.6 *Patient Compliance (Arm 1)*

Pain/Discomfort and Medication Questionnaire and FACT-Hep QoL compliance will be measured at baseline, 30 days and 90 days.

In addition, the Pain/Discomfort and Medication Questionnaire will record analgesia use from the past 24 hours at baseline, 30 days and 90 days.

8.2.7 *Patient Cross-Over (Arm 1)*

Following completion of the day 30 assessment, patients on Arm 1 who continue to be bothered by pain/discomfort may choose to receive palliative radiation therapy as described below for Arm 2 patients, including completion of appropriate quality assurance (see protocol sections 8.4.12 and 8.4.13). These patients must still return for the 90 day post-randomization visit and undergo the required assessments. Change in pain BPI scores from 30 days to 90 days will be evaluated in Arm 1 patients who receive radiation therapy.

8.3 Arm 2: Radiation Therapy plus Best Supportive Care

A single fraction of 8 Gy in 1 fraction to the liver will be delivered, with dexamethasone 4 mg and granisetron 1 mg (ondansetron 8 mg substitution permitted) given one hour (+/- 1 hour allowable) prior to RT to prevent nausea and vomiting.

8.3.1 *Premedication (Arm 2)*

All Arm 2 patients will be pre-medicated with:

Agent(s)	Dose	Route	Duration	Schedule
Dexamethasone	4 mg	po	60 min pre RT	once
Granisetron *	1 mg	po	60 min pre RT	once
*Substitution with Ondansetron permitted	*8 mg	*po	*60 min pre RT	*once

8.3.2 *Patient Monitoring (Arm 2)*

Patients will be seen at 30 and 90 days post-randomization.

8.3.3 *Dose Adjustments (Arm 2)*

Not applicable.

8.3.4 *Non-hematologic Adverse Events (Arm 2)*

The major adverse effects are expected to be related to underlying disease and from analgesia use. The most likely toxicities from analgesia use and/or underlying cancer and/or liver disease are confusion, fatigue, nausea, vomiting, constipation, encephalopathy, insomnia, and decline in liver function.

In addition to the above toxicities, radiation related toxicities may occur such as anorexia, nausea, vomiting, diarrhea, fatigue, gastritis, esophagitis or duodenitis. It is possible that a pain flare and worsening of liver function may occur within the first 2-3 days post RT.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix VII).

8.3.5 *Duration of Therapy (Arm 2)*

Patients will be followed for 90 days post-randomization.

8.3.6 *Patient Compliance (Arm 2)*

Pain/Discomfort and Medication Questionnaire and FACT-Hep QoL compliance will be measured at baseline, 30 days and 90 days.

In addition, the Pain/Discomfort and Medication Questionnaire will record analgesia use from the past 24 hours at baseline, 30 days and 90 days.

8.4 Radiation Treatment Plan

The radiation therapy plan is designed to deliver 8 Gy in one fraction to the symptomatic liver cancer. This will require whole (or near whole) liver irradiation, generally using simple techniques such as an oblique or anterior-posterior parallel pair beam arrangement (see Appendix VIII).

8.4.1 *Patient Evaluation*

Patients must be able to lie supine for the duration of treatment (e.g. 30 minutes).

8.4.2 *Equipment and Treatment Delivery*

8.4.2.1 *Equipment*

Treatment is to be delivered using 4-18 MV photons.

8.4.2.2 *Treatment Delivery*

3D conformal radiation or IMRT, with multi-leaf collimators, blocks or wedges is permitted.

8.4.3 *Positioning, Immobilization and Localization/Simulation*

8.4.3.1 *Positioning*

Patients will be positioned supine with arms above their head. If not possible, one or both arms at the sides is permitted, although this will require care to avoid irradiation through the arms.

8.4.3.2 *Immobilization*

Use of chest board or vacuum lock bag is recommended, in combination with calf and knee supports. For anterior-posterior beam arrangements, no such devices are required.

8.4.3.3 *Localization Imaging/Simulation*

Unenhanced computed tomography (CT) scan is recommended for simulation. The CT scanner should be 8-slice at minimum, ideally 16-slice or higher, with a slice thickness of 5 mm or less. The scan volume must include the whole liver and both kidneys plus a margin superiorly and inferiorly of at least 2 cm.

CT scanning may be done during a voluntary breath hold (exhale preferred) or during free breathing. 4D CT or use of inspiration and expiration scans on a fast CT scanner are permitted, but not required.

Fusion of the diagnostic CT or MRI delineating the GTV is recommended if anything other than the whole liver is to be treated.

8.4.3.4 *Motion Management*

Motion management is not mandatory, as these patients are unwell and the treatment intent is palliative using large treatment volumes.

Imaging studies to measure and/or estimate liver motion, including kV fluoroscopy (to assess diaphragm caudal-cranial motion), 4D CT and inspiration and expiration scans on a fast CT scanner may be used.

Active or passive breath hold for liver immobilization during treatment delivery is not recommended. Gating, tracking and abdominal compression are not permitted.

8.4.4 *Volume Definitions*

8.4.4.1 *Gross Tumour Volume (GTV)*

The GTV includes all hepatic tumour(s) causing pain, based on a contrast enhanced diagnostic CT or MRI. However, GTV(s) do not need to be contoured.

8.4.4.2 *Clinical Target Volume (CTV)*

Delineation of a CTV is required. The minimum margin around the GTV to form the CTV is 0 mm. Most commonly, the CTV will consist of the whole liver. In situations where one lobe is spared from cancer, the spared portion of the liver may be excluded from the CTV.

8.4.4.3 *Internal Margin (IM)*

An IM is not mandatory. If individual patient liver motion is measured, an IM can be used.

8.4.4.4 *Set up Margin (SM)*

If an IM is used, the SM to be added to the IM should be between 5 and 10 mm (10 mm is preferred).

8.4.4.5 *Planning Target Volume (PTV)*

The **minimum PTV margins** to be used (regardless of use of IM) are 15 mm in superior and inferior directions and 10 mm in other directions.

The **maximum PTV margins** are 30 mm inferiorly, 20 mm superiorly, anteriorly and posteriorly, and 15 mm in the right and left directions.

A modification of the PTV (modPTV) must be used for dose reporting for PTVs that are close to (< 5 mm from) skin. The modPTV is created by contracting the PTVs by 5mm from the surface of the skin.

8.4.4.6 *Organs at Risk (OAR)*

The dose limiting OARs which must contoured in all patients include:

Spinal canal
Liver (no need to edit out the GTV)
Right kidney
Left kidney
Bilateral kidneys

If the maximal point dose in the plan is 9.5 Gy or higher, then the following OARs must be contoured in axial slices in the region of the PTV:

Stomach
Duodenum
Small bowel*
Large bowel*

* *Alternatively, instead of small bowel and large bowel, the peritoneal cavity in the axial contours of the PTV may be contoured.*

It is highly recommended that the RTOG upper abdominal OAR contouring atlas be consulted *[Jabbour 2013]*.

8.4.4.7 *Nomenclature*

If multiple CTVs are contoured, they may be labelled as CTV1, CTV2, CTV3 etc., which then should be combined within one PTV. Alternatively, all CTVs may be included within one contour labelled CTV.

'R' or 'L' should be used to represent the right or left kidney as follows: Kidney_R and Kidney_L.

Please refer to Santanam and colleagues *[Santanam 2012]* for standard OAR nomenclature.

8.4.5 *Dose Specification*

8.4.5.1 *Target*

The goal is that 95% of the modPTV receives 8 Gy in one fraction.

8.4.5.2 *OAR*

Critical OARs dose limits are:

Maximum permitted dose to spinal canal < 10 Gy
Maximal permitted mean liver (including GTV) dose < 9 Gy

Non-critical OAR dose limits are:

Maximal permitted dose to stomach < 9.5 Gy
Maximal permitted dose to duodenum < 9.5 Gy
Maximal permitted dose to small bowel < 9.5 Gy
Maximal permitted dose to large bowel < 10 Gy.
Maximal permitted dose to peritoneal cavity < 9.5Gy
The kidneys: One kidney is recommended to be spared from radiation if possible. If the mean dose to one kidney is > 6 Gy, then the mean dose to the other kidney should be < 3 Gy. The mean dose to bilateral kidneys should not exceed 4.5 Gy.

8.4.5.3 *Fractionation*

Radiation will be delivered in one fraction.

8.4.5.4 *Corrections for Interruptions*

Not applicable.

8.4.6 *Treatment Planning*

8.4.6.1 *Beam Energy*

4 – 18 MV beam energies are permitted.

8.4.6.2 *Beam Arrangement*

In order to deliver whole (or near whole) liver irradiation, simple beam arrangements are recommended. The most common technique is an oblique parallel opposed pair with shaped apertures to reduce the dose to surrounding stomach and bowel. An alternative technique is an anterior-posterior parallel opposed pair which is best suited for right sided liver cancer (away from majority of the stomach). Appendix VIII demonstrates examples of these two beam arrangements.

Modulation of beams may be needed for some patients, and wedges, virtual wedges and IMRT are permitted. The minimum permitted number of beam angles is 2. It is recommended that no more than 5 beam angles and no more than 10 segments be used.

8.4.6.3 *Beam Modifiers*

Multi-leaf collimators are recommended for field shaping. Field-in-field IMRT may be used to improve dose homogeneity and reduce the volume receiving > 8 Gy. The maximum number of segments recommended is 10.

Blocks are permitted for field shaping. Physical wedges are permitted.

8.4.6.4 *Field Junctioning*

Not applicable.

8.4.6.5 *Planning Priorities*

The protocol priorities are: 1) critical OAR, 2) PTV coverage, 3) non-critical OAR.

8.4.6.6 *Inhomogeneity Corrections*

Inhomogeneity corrections are recommended.

8.4.6.7 *Acceptable Dose Heterogeneity*

The goal is that the modPTV receive 8 Gy in one fraction +/- 10%; however, a greater degree of heterogeneity is often seen and is acceptable.

The minimum dose to 0.5 cc of the modPTV should be 6.4 Gy.

The maximum dose to the modPTV should be no higher than 11.5 Gy.

8.4.6.8 *Planning technique*

Forward planning is recommended. Inverse planning is permitted for IMRT plans.

The dose calculation grid should include the PTV, the liver and bilateral kidneys with at least a 1 cm margin.

8.4.6.9 *Treatment Delivery Constraints*

When a IMRT technique is used, up to 10 segments are permitted.

8.4.7 *Verification*

8.4.7.1 *Position Verification/Correction*

Verification of positioning before treatment is recommended, using MV or kV portal imaging or volumetric imaging such as kV CBCT. Alignment based on bone or liver may be used. Maximal dose per portal image/image guidance technique should not exceed 20 MU.

8.4.7.2 *Dose Verification*

An independent monitor unit check or automated dose check is required. No measurements such as irradiation of a phantom, portal dosimetry or diode arrays are required.

8.4.8 *Concurrent Therapy*

Chemotherapy or biologic systemic therapy is not permitted to be delivered within 4 weeks of randomization or prior to completion of the 30 day post randomization Pain/Discomfort and Medication Questionnaire.

8.4.9 *Patient Specific Documentation Requirements*

8.4.9.1 *Volumes*

The volume of the GTV(s) (if contoured), the sum of all CTVs, PTV, modPTV and the liver (without editing out the GTV/CTV) are to be documented.

The CTV(s) and PTV, along with the GTV(s) if contoured, should be displayed on the planning CT.

8.4.9.2 *Dose Summary Statistics*

The volume, minimum dose, mean dose and maximum dose must be reported for the sum of all GTVs (if contoured), the sum of all CTVs, the modPTV (or PTV if there is no modPTV) and for the following OARs –spinal canal, liver (including GTVs/CTVs), the right and left kidney, and bilateral kidneys. The global maximum point dose must be reported. If it is < 9.5 Gy, stomach, duodenum, small and large bowel (or peritoneal cavity) dose metrics do not need to be reported. If it is 9.5Gy or higher, maximum doses to these OARs must be reported.

The dose delivered to 95% of modPTV (or PTV if no modPTV) must be reported

8.4.9.3 *Dose Distributions*

Dosimetry through orthogonal planes at the isocenter are required, with the 11 Gy, 10 Gy, 9 Gy, 8 Gy, 7 Gy, 6.4 Gy, 6 Gy and 4 Gy isodoses displayed.

8.4.9.4 *Dose Volume Histogram (DVHs)*

Graphical cumulative DVHs (with percent volume) of all CTVs, PTVs and contoured OARs, including the liver, along with GTV(s) if contoured, must be reported.

8.4.10 *Quality Assurance Review Criteria*

Treatment-related deviations outside protocol guidelines will be reported as minor or major. In general, minor protocol deviations will be reported but will not preclude patient treatment, while major protocol deviations will require re-planning prior to patient treatment. Please see Radiotherapy Quality Assurance Manual for more details.

8.4.11 *Credentialing Requirements*

All centres participating in the study will require credentialing prior to local activation. This credentialing will consist of completion of a Facility Questionnaire, submission of a beam output audit (see below), and demonstration of the ability to comply with protocol specifications using anonymized archival data provided by CTG (dummy run with delineation exercise).

In addition, for sites planning to deliver IMRT, evidence of previous successful IMRT credentialing must be provided.

Institutions must be participating in IROC TLD Remote Monitoring Program and provide the most recent TLD/OSL irradiation report.

All credentialing documents must be uploaded to a secure website and CCTG OwnCloud created to facilitate radiotherapy QA review for this trial.

Please review the Radiotherapy Quality Assurance Manual for more details.

8.4.12 *Prospective Centre Based Individual Pre- Treatment Case Review*

Radiation treatment plans will be reviewed for every patient treated on study, prior to the commencement of radiotherapy, by another investigator designated for this purpose and identified as “local QA reviewer”.

The following will be reviewed: contoured volumes, dose summary statistics, dose distributions, and DVHs. Sites must also submit for review the “Delivery Technique, Motion Management and Verification Imaging" form for each patient, available on the RTQA website.

The local reviewer will verify that there are no major deviations as defined in the Radiotherapy Quality Assurance Manual prior to approving the delivery of the radiotherapy and submit a Radiotherapy Reviewer form to central office reflecting this approval through the RTQA website. Once this is obtained, the patient may proceed with radiotherapy. Specifications for the review are included in the Radiotherapy Quality Assurance Manual.

8.4.13 *Retrospective Individual External Post-Treatment Case Review*

An external post-treatment review will be performed for all patients completing radiotherapy.

Sites must upload the required documentation to the RTQA website within 4 weeks of the completion of radiotherapy. The Central QA Reviewer will document the Post-Treatment Review within 4 weeks of data submission.

Anonymized radiotherapy treatment documentation as well as site credentialing documentation will also be submitted online to the CCTG OwnCloud platform for additional RTQA review. This additional RTQA central review will be conducted by using software from Princess Margaret Hospital in Toronto, Ontario, Canada, and from a company called MIM Software in Cleveland, Ohio, USA.

Specifications for the review are included in the Radiotherapy Quality Assurance Manual.

8.5 Concomitant Therapy

8.5.1 *Permitted*

Analgesia and medications used for best supportive care should continue to be delivered with no alteration. However, dramatic changes in analgesia are not recommended prior to the 30 day post-randomization study visit, unless clinically required.

Pre-radiation anti-emetics should be delivered to all patients receiving radiation therapy, even those who are already on regular steroids.

Bisphosphonates, herceptin, tamoxifen, aromatase inhibitors and other hormonal therapies are permitted to be continued if thought to be in the patient's best interest by the treating oncologist.

8.5.2 *Not Permitted*

Chemotherapy, including oral chemotherapy, immunotherapy and targeted agents such as sorafenib, avastin, sunitinib, iressa or cetuximab, are not permitted to be delivered concurrently with radiation therapy and are not permitted to be used prior to the 30 day post-randomization study visit.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

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

Patients will be assessed with a history and physical and for toxicity (CTCAE v4.0) at baseline and again on day 30 and day 90. Bloodwork, including albumin, bilirubin, CBC and liver enzymes will be collected at baseline, day 30 and day 90.

In both arms, patients will complete the Pain/Discomfort and Medication Questionnaire (containing the validated patient-reported symptom assessment (BPI)) at baseline and on day 30 and day 90 from randomization. **This questionnaire must be completed correctly and in full for the patient to data to be included in the endpoint analyses.** The Pain/Discomfort and Medication Questionnaire is a patient reported outcome; however, the study nurse/CRA can help the patient to complete this questionnaire during the clinic visit. If the patient is too unwell to be seen in clinic, the study nurse/CRA can phone the patient and complete the questionnaire on the patient's behalf.

In both arms, patients will also complete the FACT-Hep QoL questionnaire at baseline, on day 30 and on day 90 from randomization. This is also a patient reported outcome but in this case the patient must complete the questionnaire on their own. It is not acceptable for the study nurse/CRA to complete the QoL questionnaire on the patient's behalf via a telephone call and the use of a translator is not allowed. For more information, please refer to Appendix IX.

9.1 Compliance

Patient compliance with Pain/Discomfort and Medication Questionnaire and FACT-Hep QoL will be measured at baseline, on day 30 and on day 90. The same Pain/Discomfort and Medication Questionnaire will be used to record analgesia use in the past 24 hours at these same time points.

9.2 Adverse Events

Adverse events will be monitored by CCTG Central Office using CTCAE and their frequencies reported annually at investigator meetings. Standard CCTG auditing and monitoring will occur (10% of data from 10% of forms for 10% of patients randomly selected) with sites visited at least once during the trial.

9.3 Evaluation During/After Protocol Treatment

Investigations		Timing
History and Physical Exam including:	• ECOG PS (see Appendix II) • weight • assessment of ascites and encephalopathy (Child Pugh score – see Appendix IV)	On day 30 and day 90 post randomization
Hematology	• platelets • INR • hemoglobin	On day 30 and day 90 post randomization
Biochemistry	• albumin • bilirubin • AST and/or ALT • ALP • creatinine • alpha-fetoprotein (for HCC patients only)	On day 30 and day 90 post randomization
Pain/discomfort Assessment	• Pain/Discomfort and Medication Questionnaire*	On day 30 and day 90 post randomization
Analgesia Assessment	• Pain/Discomfort and Medication Questionnaire*	On day 30 and day 90 post randomization
Adverse Events	• Adverse events (grade ≥ 2) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix VII)*	On day 30 and day 90 post randomization
Quality of Life	• FACT-Hep	On day 30 and day 90 post randomization
Correlative Studies	• Blood draw for correlative studies (for consenting patients only)	On day 30 and day 90 post randomization
* **If the patient is too unwell to be seen in the clinic for the day 30 and day 90 follow-up visits, the Pain/Discomfort and Medication Questionnaire and adverse events assessment may be done over the telephone. It is critical to the study endpoints that the Pain/Discomfort and Medication Questionnaire be completed in full at the required time points.**		

9.4 Evaluation After Protocol Treatment

There will be no further follow-up after the 90 day post-randomization visit.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of randomization.

10.1.2 Evaluable for BPI response. All patients who have completed a baseline and 30 days follow-up BPI will be considered evaluable for the primary endpoint. Patients who complete a baseline and a day 90 follow-up BPI will be considered evaluable for secondary BPI endpoints. Patients from Arm 1 who cross over to Arm 2 after their day 30 assessment are evaluable for BPI response from day 30 to day 90, if they have completed their day 30 and day 90 BPI.

10.1.3 Evaluable for quality of life assessment. All patients who have completed the quality of life questionnaire at baseline and on days 30 and 90 are evaluable for the quality of life endpoint.

10.1.4 Evaluable for change in opioid analysis. All patients who have completed Pain/Discomfort and Medication Questionnaires at baseline and within 24 hours of the 30 day visit are eligible for assessment. Only analgesic use in the past 24 hours will be recorded to increase compliance. If the patient is too unwell to visit the clinic, the Pain/Discomfort and Medication Questionnaire can be completed by the study nurse following a telephone call to the patient. Note: large fluctuations in opioid use are unlikely to occur due to intolerability of medications for many patients.

10.2 Measurement Tools

10.2.1 *Brief Pain Inventory (BPI)*

The BPI consists of 4 pain/discomfort intensity and 7 pain/discomfort interference 11-point Likert-scale questions (range 0-10) *[Cleeland 1994]*.

Patients who identify their index symptom as abdominal discomfort are still to complete the Pain/Discomfort and Medication Questionnaire even though the questions refer to “pain”.

10.2.2 Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)

The FACT-Hep questionnaire is a 45-item instrument consisting of the 27-item cancer-specific QoL instrument FACT-G, and a site-specific 18-item hepatobiliary subscale (HBS) *[Heffernan 2002]*. The FACT-G consists of four subscales: (1) physical well-being (PWB); (2) social and family well-being (SFWB); (3) emotional well-being (EWB); and functional well-being (FWB). The total FACT-Hep score, FACT-G score, individual scores for each subscale, and the trial outcome index (TOI) will be scored according to the paper by Cella et al *[Cella 1993]*.

11.0 SERIOUS ADVERSE EVENT REPORTING

This protocol does not contain investigational agent(s), and adverse events occurring as a result of the radiation therapy and/or the anti-emetic pre-medications should be reported to CCTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix VII). All appropriate treatment areas should have access to a copy of the CTCAE which 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.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment (radiation therapy) must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after the date of RT) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the sample consent form.
- Adverse events considered related to protocol treatment (radiation therapy) are those for which a relationship to the protocol treatment 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.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported via the 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 HE.1 section of the CCTG website (www.ctg.queensu.ca).

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

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

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

FAX paper SAE Report to:

HE.1 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 HE.1 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).

11.3 Other Protocol Reportable Events – Pregnancy Reporting

11.3.1 *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 5.1.15. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

11.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants.

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.

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.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada
(Office of Clinical Trials and Marketed Health Products Directorate (MHPD))

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials and to Marketed Health Products Directorate (MHPD)) 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).

11.5 Reporting Serious Adverse Events to Investigators

CCTG will notify Investigators of all serious adverse events from this trial that are reportable to regulatory authorities in Canada as reported to CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial HE.1 web-based safety monitoring utility.

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. The date of REB Submission for these SAEs will need to be entered into the CCTG trial HE.1 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.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Therapy After Protocol Treatment is Stopped

No systemic therapy is permitted prior to the 30 days post randomization assessment. It is expected that the majority of patients will be not candidates for further line systemic therapy, but if they develop progressive disease and are recommended for systemic therapy, they may be treated following completion of the 30 day Pain/Discomfort and Medication Questionnaire and FACT-Hep assessment. Patients who receive systemic therapy prior to the day 90 post-randomization visit will be inevaluable for the secondary endpoints.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

Not applicable.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Radiotherapy Quality Assurance (RTQA)

All sites will be credentialed for RT prior to site activation. All patients who receive radiation therapy on study will undergo prospective Centre Based Individual Pre-Treatment Case Review prior to receiving radiation therapy, as well as an external, retrospective Individual External Post-Treatment Case Review. Please see Section 8.4 and the RTQA Manual for complete details.

13.4 Blood Collection

The collection of blood is an important part of this trial. This is not mandatory for entry in the study, but the participation of all centres is strongly encouraged. Blood will be carefully banked as part of the CCTG tissue bank at Queen's University in Kingston, Ontario.

The blood may be used by researchers now or in the future to better understand the nature of palliative radiation therapy and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the blood will take place and any successful proposals will also undergo ethics review and approval. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial and 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 for whom a blood sample is collected will be aware of this retrieval and will have given their consent.

Blood, plasma and serum samples will be collected at baseline and at day 30 and day 90 post-randomization.

There will be no specimen collection kits provided for this study; however, pre-printed labels will be sent to each centre at the time of local activation. For complete details regarding the procedures for optional blood collection, please refer to the HE.1 Correlative Studies Lab Manual which has been posted to the HE.1 trial website.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this multi-centre, randomized, phase III trial is to determine whether a single 8 Gy dose of RT with best supportive care (BSC) would show an improvement of ≥ 2 points in pain "intensity at worst" on the Brief Pain Inventory (BPI) from baseline to day 30 relative to BSC alone in patients with painful liver tumours (either HCC or liver metastases).

Patients will be randomized to receive either a single 8 Gy dose of RT with BSC or BSC alone in a 1:1 ratio using a minimization method after stratification by centre and type of liver cancer (HCC versus liver). Secondary objectives include comparison of proportion of patients experiencing adverse events at day 30 and day 90; proportion of patients alive at day 90; proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points in pain "intensity at worst" on Brief Pain Inventory (BPI) from baseline to day 30; proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points from baseline to day 30 and day 90 in other BPI pain scores; proportion of patients reporting clinically significant improvement in QoL from baseline to day 30 and day 90 as defined by a ≥ 5 point change in the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Subscale (FACT-HBS) and Trial Outcome Index (FACT-TOI), proportion of patients achieving a 25% reduction in opioid use (employing daily morphine equivalence scale) at 30 days and proportion of patients achieving improvement of liver cancer pain/discomfort by ≥ 2 points in pain “intensity at worst” AND with no increase in opioid use (employing daily morphine equivalence scale) on BPI from baseline to 30 days.

14.2 Endpoints and Analysis

A stratified Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factor (HCC versus liver metastases) will be used to compare between two treatment arms for binary endpoints, such as proportion of patients with symptomatic HCC or liver metastases who report an improvement in pain/discomfort “intensity at worst” on BPI from baseline to day 30, proportion of patients with a clinically significant favourable change from baseline to day 30 and day 90 in other BPI scores, QoL on FACT-HBP, TOI and FACT-Hep and subscales, and proportion of patients with a 25% reduction in opioid use at 30 days. Primary analysis will include all patients who are assessed at both baseline and follow-up time of interest. Sensitivity analysis will also be performed by including those without assessment at specific follow-up time in the “no improvement” group. As cross-over of control patients to the RT Arm is permitted after day 30, after the primary endpoint (change in BPI on average) is assessed, the proportion of crossover patients who have RT at day 30 who have a subsequent clinically significant improvement in BPI at day 90 will be reported. The stratified logrank test will be used for time-to-event outcomes such as survival. A subgroup analysis will be performed based on the location of the metastases (HCC versus liver).

14.3 Sample Size and Duration of Study

Forty-five eligible patients with BPI at baseline and at day 30 are required to detect a change in proportion of patients with a significant improvement in BPI from 5% (no radiation) to 45% (with radiation therapy) with 80% power and $\alpha = 0.05$. Sixty patients are to be accrued allowing for 25% drop out (which was seen in the pilot study *[Soliman 2013]* and is consistent with other end-of-life studies). The final analysis will be performed after when 45 evaluable patients are available (approximately 65 randomized patients).

RT quality assurance criteria, educational RT case examples and accrual initiatives will be developed in the first 3-6 months. Based on a national survey and accrual from the Princess Margaret Cancer Centre study, the estimated time for trial accrual is 24 months at an accrual rate of 2-3 cases/month, excluding a 6-month 'ramp-up' in accrual as sites locally activate the trial. There will be 3-months follow-up from the last accrued patient and 3 additional months required for data collection, cleaning and collation for the final analysis and trial closure, for a total duration of 36 months.

14.4 Safety Monitoring

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

14.5 Interim Analysis

There are no planned interim analyses for this trial.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

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

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian CancerTrials 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.

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

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

15.2 Responsibility for Publication

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

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).

15.3 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.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

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

16.2 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 enrolment 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.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an 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.

16.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant) 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.

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy.

16.4 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.

16.5 Retention of Patient Records and Study Files

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.

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

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

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

16.6 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.

16.7 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).

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, is to be found in Appendix V.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except the Pre-Baseline Pain/Discomfort Questionnaire, the Pain/Discomfort and Medication Questionnaire and the QoL questionnaire. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the HE.1 area of the CCTG web-site (www.ctg.queensu.ca).

17.0 REFERENCES

Blazeby JM, Fayers P, Conroy T, et al. Validation of the European Organization for Reasearch and Treatment of Cancer QLQ-LMC21 questionnaire for assessment of patient-reported outcomes during treatment of colorectal liver metastases. Br J surgery 2009; 96: 291-298.9.

Borgelt BB, Gelber R, Brady LW, et al. The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. Int J Radiat Oncol Biol Phys. 1981; 7:587-591.

Bower JE, Ganz PA, Tao ML, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clinical Cancer Research. 2009; 15(17): 5534-5540.

BPI user guide in 2009 - http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/bpi_userguide.pdf

Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991; 7:6-9.

Bujold A, Massey CA, Kim JJ, et al. Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma. J Clin Oncol. 2013; 31(13):1631-9.

Bydder S, Spry NA, Christie DR et al. A prospective trial of short-fractionation radiotherapy for the palliation of liver metastases. Australas.Radiol. 2003; 47:284-288.

Canadian Cancer Statistics 2013 at http://www.cancer.ca.

Cella,DF, Tulsky,DS, Gray,G et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993; 11:570-579.

Chow E, Wu JS, Hoskin P, et al. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Radiother.Oncol. 2002; 64:275-280.

Cleeland CS, Mendoza TR, Wang XS et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000; 89:1634-1646.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994; 23:129-138.

Goblirsch M, Lynch C, Matthews W, et al. Radiation treatment decreases bone cancer pain through direct effect on tumor cells. Radiation research. 2005; 164: 400-408.

Harris K, Li K, Flynn C, et al. Worst, Average or Current Pain in the Brief Pain Inventory: Which Should be Used to calculate the Response to Palliative Radiotherapy in Patients with Bone Metastases? Clin Oncol 2007; 19:523-7.

Heffernan N, Cella D, Webster K et al. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. J Clin Oncol. 2002; 20:2229-2239.

Herfarth KK, Hof H, Bahner ML et al. Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. Int J Radiat Oncol Biol Phys. 2003; 57:444-451.

Hoskin PJ. Radiation may lead to a direct reduction of the tumors production of pain promoting chemicals. Radiotherapy. In: Sykes N, Bennett MI & Yuan C-S. Clinical pain management: Cancer pain. 2nd ed. London: Hodder Arnold; 2008. ISBN 978-0-340-94007-5. p. 251–55.

Hoyer M, Roed H, Traberg HA et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol. 2006; 45:823-830.

Hoyer M, Swaminath A, Bydder S et al. Radiotherapy for Liver Metastases: A Review of Evidence. Intl J Rad Onc Bio Phys. 2012; 82(3): 1047-1057.

Ingold JA, Reed GB, Kaplan HS, et al. Radiation Hepatitis. Am J Roentgenol Radium.Ther Nucl Med. 1965; 93:200-208.

Jabbour S, Hashem SA, Bosch W, et al. Upper abdominal Normal Organ Contouring Guidelines and Atlas: A Radiation Therapy Oncology Group Consensus. Practical Radiation Oncology. 2013; 4(2):82-89.

Kaiser K, Mallick R, Mulcahy MF, et al. Important and relevant symptoms including pain concerns in hepatocellular carcinoma (HCC): a patient interview study. Support Care Cancer. 2014; 22(4): 919-26.

Lee MT, Kim JJ, Dinniwell R et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol. 2009; 27:1585-1591.

Leibel SA, Pajak TF, Massullo V et al. A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: results of a Radiation Therapy Oncology Group randomized prospective trial. Int J Radiat Oncol Biol Phys. 1987; 13:1057-64.

Lutz ST, Jones J, Chow E. Role of Radiation Therapy in Palliative Care of the Patient with Cancer. J of Clin Oncol. 2014; 32(26): 2913-2919.

Ménard C, Johann, D, Lowenthal M, et al. Discovering clinical biomarkers of ionizing radiation exposure with serum proteomic analysis. Cancer Research (2006); 66(3): 1844-1850.

Mendez RA, Wunderink W, Hussain SM et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. Acta Oncol. 2006; 45:831-837.

Pan CC, Kavanagh BD, Dawson LA et al. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys. 2010; 76: S94-100.

Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74-108.

Prasad B, Lee M.S, Hendrickson F.R. Irradiation of hepatic metastases. Int J Radiat Oncol Biol Phys. 1977; 2:129-132.

Salazar OM, Sandhu T, da Motta NW, et al. Fractional half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomization Phase III trial of the International Atomic Energy Agency (IAEA). Int J Radiat Oncol Biol Phys. 2001; 50: 765-75.

Santanam L, Hurkmans C, Mutic S, et al. Standardizing naming conventions in radiation oncology. Int J Radiat Oncol Biol Phys. 2012; 85(4): 1344-1349.

Seong J, Park HC, Han KH et al. Local radiotherapy for unresectable hepatocellular carcinoma patients who failed with transcatheter arterial chemoembolization. Int J Radiat Oncol Biol Phys. 2000; 47:1331-1335.

Sherman DM, Weichselbaum R, Order SE, et al. Palliation of hepatic metastasis. Cancer. 1978; 41:2013-2017.

Smith HS. Opioid Metabolism. Mayo Clin Proc. 2009; 84(7): 613-624.

Soliman H, Ringash J, Jiang H, et al. Phase II Trial of Palliative Radiotherapy for Hepatocellular Carcinoma and Liver Metastases. J Clinl Onc. 2013; 31(31): 3980-3986.

Turek-Maischeider M, Kazem I. Palliative irradiation for liver metastases. JAMA. 1975; 232:625-628.

Wharton JT, Delclos L, Gallager S, Smith JP. Radiation hepatitis induced by abdominal irradiation with the cobalt 60 moving strip technique. Am J Roentgenol Radium.Ther Nucl Med. 1973; 117:73-80.

Zhu AX. Hepatocellular carcinoma: are we making progress? Cancer Invest. 2003; 21:418-428.

APPENDIX I - PATIENT EVALUATION FLOW SHEET

	Pre-Baseline	Baseline (Pre-Randomization)	Day 30 Post Randomization	Day 90 Post Randomization
Physical				
ECOG PS		X	X	X
Weight		X	X	X
Assessment of ascites and encephalopathy (Child Pugh score – see Appendix IV)		X	X	X
Hematology				
Platelets		X	X	X
INR		X	X	X
Hemoglobin		X	X	X
Neutrophils		X		
Biochemistry				
Albumin		X	X	X
Bilirubin		X	X	X
AST and/or ALT		X	X	X
ALP		X	X	X
Creatinine		X	X	X
Alpha-Fetoprotein (for patients with HCC only)		X	X	X
Radiology				
CT or MRI scan of abdomen which establishes diffuse liver metastases per eligibility criteria		X		
Other Investigations				
Two Pre-Baseline Pain / Discomfort Questionnaires	X			
Pain/Discomfort and Medication Questionnaire		X	X	X
Pregnancy test which may include an ultrasound (WOCBP only)		X		
Adverse Events				
Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms - grade ≥ 2 only)		X		
Adverse events on study (grade ≥ 2 only)			X	X
Quality of Life				
FACT-Hep		X	X	X
Correlative Studies				
Serum, plasma and whole blood collection		X	X	X

APPENDIX II - 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 III - GUIDANCE FOR DETERMINING "STABLE" PAIN PRE-RANDOMIZATION

Pre-Baseline:

The **Pre-Baseline Pain Scores** are obtained by answering the single BPI question within the Pre-Baseline Pain/Discomfort Questionnaire: *Pain at its worst in the last 24 hours.*

Stable pain is determined using pain scores taken on two separate days. These two scores must meet each of the following criteria:

- Both scores must be ≥ 4
- Both scores must be completed on different days AND BOTH must be done ≤ 7 days prior to randomization
- The DIFFERENCE between the two scores must be 0, 1, 2 or 3 (i.e. the *range* is ≤ 3)
- If more than 2 pre-baseline scores are obtained, it is the final two scores that must be used in the determination of stable pain.

If any one of these criteria is **NOT MET**, pain is **NOT** considered **STABLE** and the patient is not yet eligible to undergo baseline testing for the HE.1 study. Patients are encouraged to continue to complete additional Pre-Baseline Pain/Discomfort Questionnaires until all of the criteria for **Stable pain** have been met.

If all of the above criteria **ARE MET**, pain is considered **STABLE** and the patient can be scheduled for a Baseline visit.

Baseline Visit:

Please refer to the table in Section 6 of the protocol for a list of the required baseline evaluations.

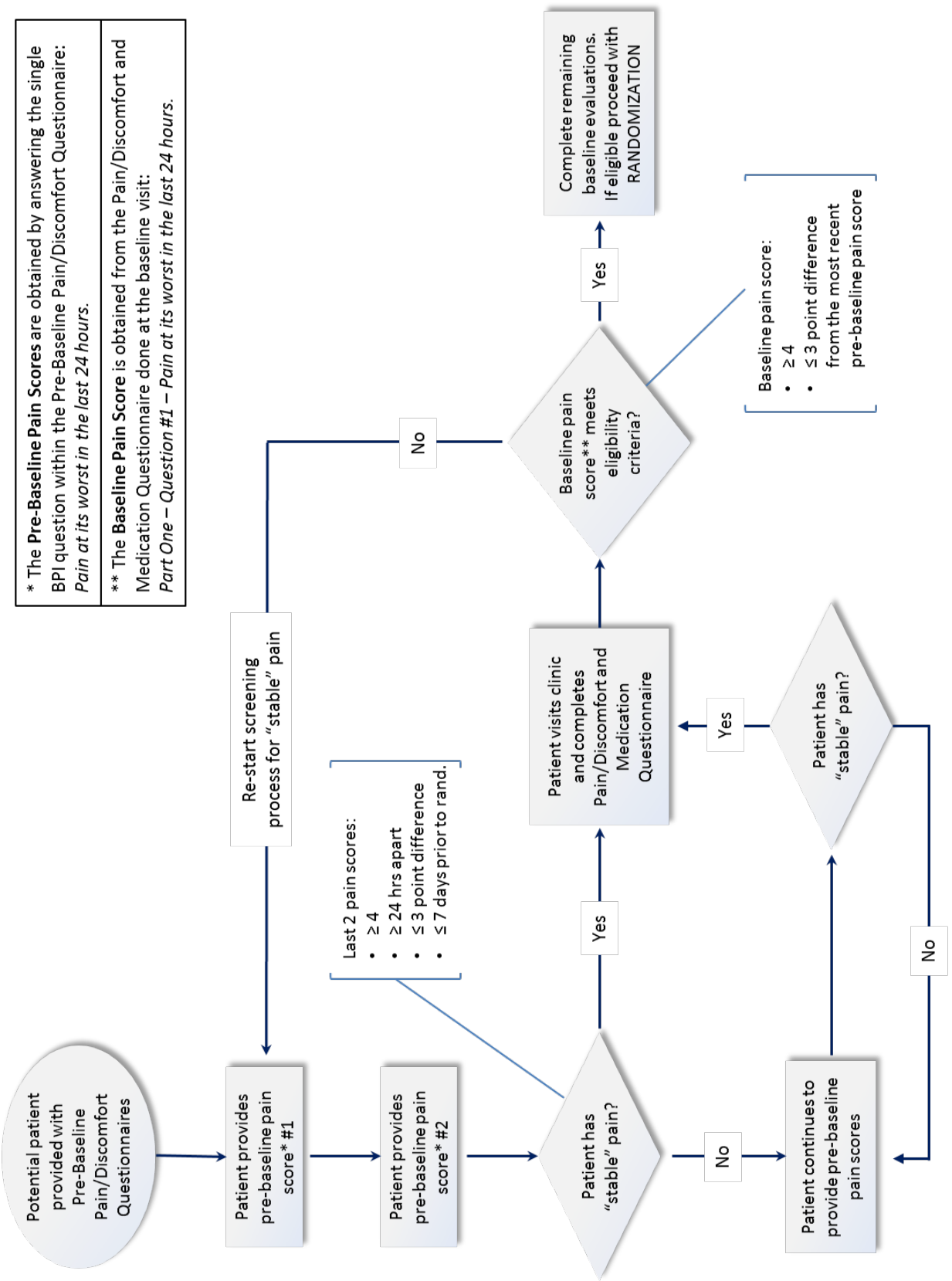
At the baseline visit, the patient completes the Pain/Discomfort and Medication Questionnaire which contains several additional BPI questions as well as information related to the pain medications that the patient has received in the past 24 hours.

The **Baseline Pain Score** is obtained from the Pain/Discomfort and Medication Questionnaire done at the baseline visit: *Part One – Question #1 – Pain at its worst in the last 24 hours.*

In order to be eligible for the HE.1 study, the **Baseline Pain Score** must meet all of the following criteria:

- Score must be ≥ 4
- Score must be obtained prior to randomization - please note the BL score may be obtained on the same date (for example, later in the day) as the second pre-baseline pain score.
- The DIFFERENCE between the most recent Pre-Baseline Pain Score and the Baseline Pain Score must be 0, 1, 2, or 3 (i.e. the range between these two values must be ≤ 3).

Please refer to the Flow Diagram on the next page. A Pain/Discomfort Stability Worksheet is available on the HE.1 trial website to assist study nurses/CRAs in determining if pre-baseline/baseline scores represent stable pain.


* The **Pre-Baseline Pain Scores** are obtained by answering the single BPI question within the Pre-Baseline Pain/Discomfort Questionnaire: *Pain at its worst in the last 24 hours.*
** The **Baseline Pain Score** is obtained from the Pain/Discomfort and Medication Questionnaire done at the baseline visit: *Part One – Question #1 – Pain at its worst in the last 24 hours.*
Potential patient provided with Pre-Baseline Pain/Discomfort Questionnaires
Patient provides pre-baseline pain score* #1
Patient provides pre-baseline pain score* #2
Patient has "stable" pain?
No
Yes
Re-start screening process for "stable" pain
Last 2 pain scores:
• ≥ 4
• ≥ 24 hrs apart
• ≤ 3 point difference
• ≤ 7 days prior to rand.
Patient continues to provide pre-baseline pain scores
Patient has "stable" pain?
No
Yes
Patient visits clinic and completes Pain/Discomfort and Medication Questionnaire
Baseline pain score** meets eligibility criteria?
No
Yes
Baseline pain score:
• ≥ 4
• ≤ 3 point difference from the most recent pre-baseline pain score
Complete remaining baseline evaluations. If eligible proceed with RANDOMIZATION

APPENDIX IV - DETERMINING CHILD-PUGH SCORE

CHILD-PUGH SCORE - Patients must be **class A, B or C10** to be **eligible** for the HE.1 study.

Clinical and Biochemical Parameters	**Score**		
	1	**2**	**3**
Encephalopathy	None	Slight (stage* 1-2) *Or suppressed with medication*	Severe (stage* 3-4)
Ascites	None	Slight (grade^{+} 1)	Moderate (grade^{+} 2-3)
Albumin (g/L)	>35	28-35	<28
INR$^{\square}$	<1.7	1.7-2.3	>2.3
Bilirubin (umol/L)	<35	35-50	>50
Class A = 5-6 points Class B = 7-9 points Class C = 10-15 points		FINAL SCORE (5-15): _____ CLASS (A, B or C): _____	

* **Stages of Hepatic Encephalopathy**
Stage 1: Euphoria or depression, mild confusion, slurred speech, disordered sleep
Stage 2: Lethargy, moderate confusion
Stage 3: Marked confusion, incoherent speech, sleeping but arousable
Stage 4: Coma

$^{+}$ **Grades of ascites:**
Grade 1: mild, only visible on ultrasound and CT$^{\#}$
Grade 2: detectable with flank bulging and shifting dullness
Grade 3: directly visible, confirmed with the fluid wave/thrill test

$^{\#}$ Note that trace ascites on imaging may be counted as 'none' for this study.

$^{\square}$ INR = International Normalized Ratio for Prothrombin Time

References:

Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1-85.

Moore K P, Wong F, Gines, P et al. The management of ascites in cirrhosis: Report on the consensus conference of the international Ascites club. Hepatology, 2003; 38: 258–266.

Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9.

APPENDIX V - DOCUMENTATION FOR STUDY

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except for the Pre-Baseline Pain/Discomfort Questionnaire, Pain/Discomfort and Medication Questionnaire and Quality of Life Questionnaire which will be completed by the patient on paper. However, even in the case of these paper forms, electronic "submission" will be necessary as follows:

- The Pre-Baseline Pain/Discomfort Questionnaires and the Pain/Discomfort and Medication Questionnaires will be scanned and uploaded into the EDC system as "Supporting Documentation"
- The Quality of Life Questionnaire data will be entered by the site CRA into the EDC system within the appropriate folders

For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the HE.1 area of the CCTG web-site (www.ctg.queensu.ca).

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

Electronic Folder	Required at	To be completed electronically	Supporting Documentation Required[+]
Eligibility Checklist	Prior to randomization	At the time of randomization	Consent form* Pre-Baseline Pain/Discomfort Questionnaire ♦ Pain/Discomfort and Medication Questionnaire Pathology Report(s) CT/MRI Abdomen Report♦♦ Child Pugh Score Sheet
Baseline Report	At the time of randomization	Within 2 weeks after randomization	
Correlative Studies Report (Blood)	Continuous Running Log folder	Within 2 weeks after randomization (Baseline blood draw) *AND* within 2 weeks after 30 day visit (30 day blood draw) *AND* within 2 weeks after 90 day visit (90 day blood draw)	Consent form*
Concomitant Medications Report♦♦♦	Continuous Running Log folder	Update as/if necessary at the time of submission of the Baseline / Follow-Up Reports	-
Radiotherapy Report	At the time of radiotherapy delivery	Within 2 weeks after radiotherapy delivery	-
Follow-up Report – 30 day Visit	At the 30 day follow-up visit	Within 2 weeks after the 30 day follow-up visit	Pain/Discomfort and Medication Questionnaire
Follow-up Report – 90 day Visit	At the 90 day follow-up visit	Within 2 weeks after the 90 day follow-up visit	Pain/Discomfort and Medication Questionnaire
Death Report	At the time of patient death**	Within 2 weeks after knowledge of patient's death	Not required unless requested
SAE Report***	At the time of SAE***	Within 24 hours of the event***	Not required unless requested

[+] Scan and upload into the EDC Supporting Document Upload Tool

* Submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated.

** Deaths are only to be recorded on the CRFs if they occur within the study treatment / follow-up period (i.e. up to 90 days post-treatment). Deaths occurring after that time are outside the scope of this study and do not need to be reported.

*** See section 11.0 Serious Adverse Event Reporting for details.

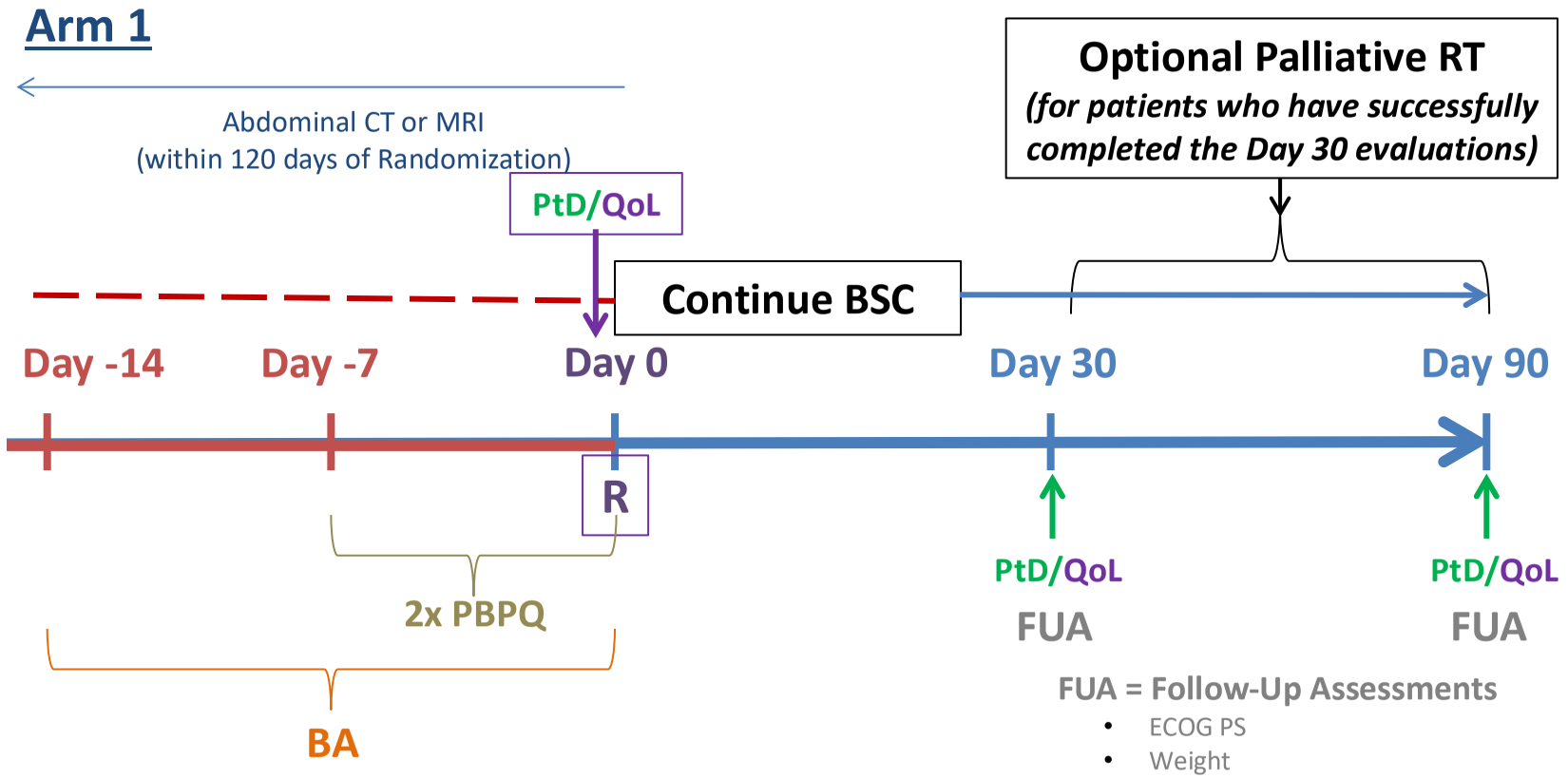
♦ Include both pre-baseline assessments.

♦♦ Report that established diffuse liver metastases per eligibility criteria (see section 5.0)

♦♦♦ Note: captures medication use that does *NOT* pertain to analgesia. Analgesic use is captured in the Pain/Discomfort and Medication Questionnaire and is meant to be entered in other relevant EDC folders.

The collection of the following information will be done on **paper**:

Paper-Based Data Collection	Required at	Submission	Comments
Pre-Baseline Pain/Discomfort Questionnaire	Prior to baseline on two separate occasions	Enter information (as required) in the EDC system within corresponding folder	Also scan and upload in the EDC Supporting Document Upload Tool
Pain/Discomfort and Medication Questionnaire	Baseline and at each follow-up visit (30 and 90 days)	Enter information (as required) in the EDC system within corresponding folder	Also scan and upload in the EDC Supporting Document Upload Tool
Quality of Life Questionnaire (FACT-Hep)	Prior to randomization and at each follow-up visit (30 and 90 days)	Enter information in the EDC system within corresponding folder	-



BA= Baseline Assessments

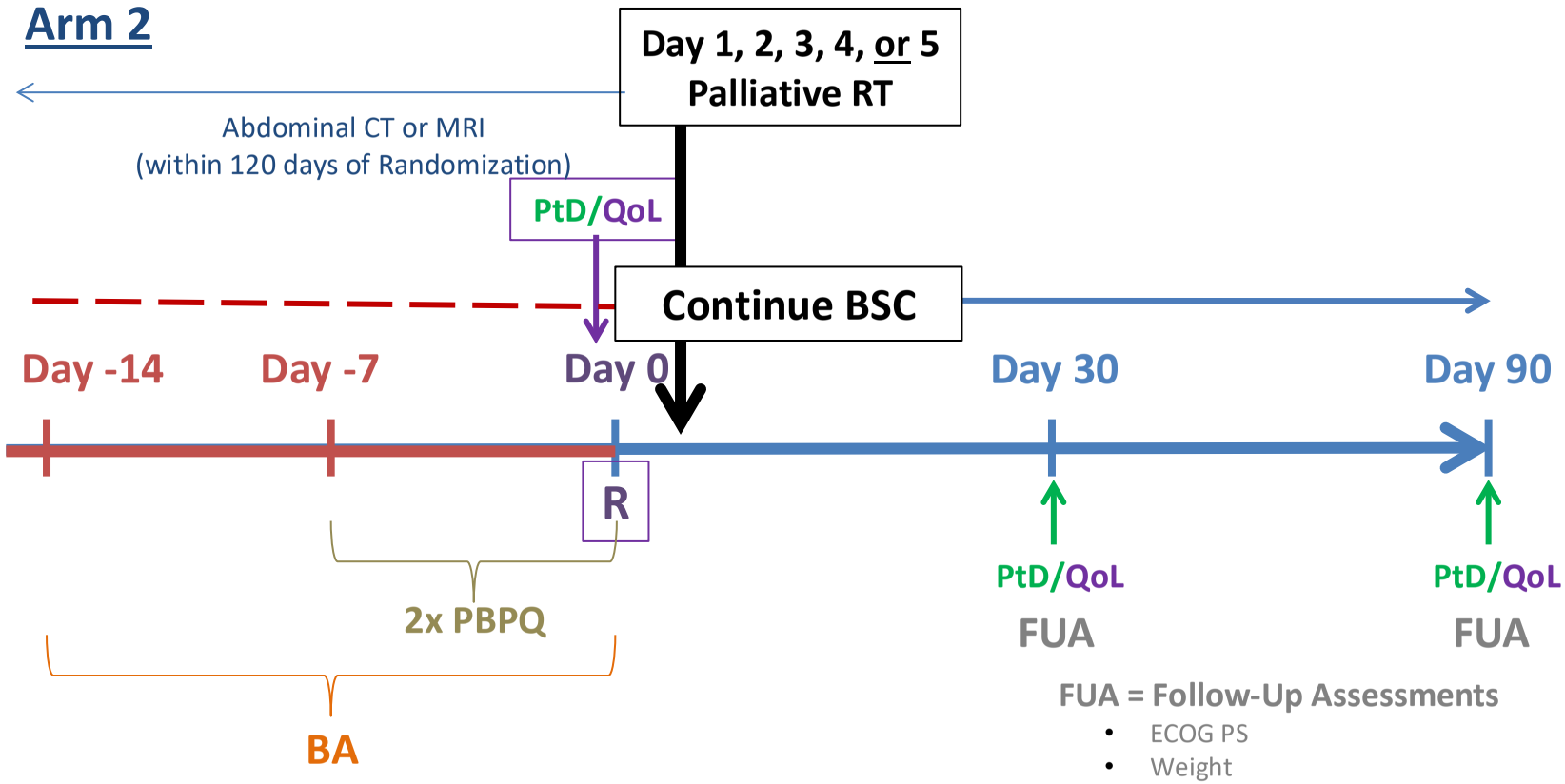
- ECOG PS
- Weight
- Assessment of ascites and encephalopathy
- AE
- Hematology
- Biochemistry
- Pregnancy Test (WOCBP only)
- Blood draw for correlative studies

FUA = Follow-Up Assessments

- ECOG PS
- Weight
- Assessment of ascites and encephalopathy
- AE
- Hematology
- Biochemistry
- Blood draw for correlative studies

PBPQ = Pre-Baseline Pain/Discomfort Questionnaire **R = Randomization** **BSC = Best Supportive Care**

QoL = Quality of Life **PtD = Pain/Discomfort and Medication Questionnaire**



BA= Baseline Assessments

- ECOG PS
- Weight
- Assessment of ascites and encephalopathy
- AE
- Hematology
- Biochemistry
- Pregnancy Test (WOCBP only)
- Blood draw for correlative studies

FUA = Follow-Up Assessments

- ECOG PS
- Weight
- Assessment of ascites and encephalopathy
- AE
- Hematology
- Biochemistry
- Blood draw for correlative studies

PBPQ = Pre-Baseline Pain Questionnaire **R = Randomization** **BSC = Best Supportive Care**

QoL = Quality of Life **PtD = Pain/Discomfort and Medication Questionnaire**

CONFIDENTIAL

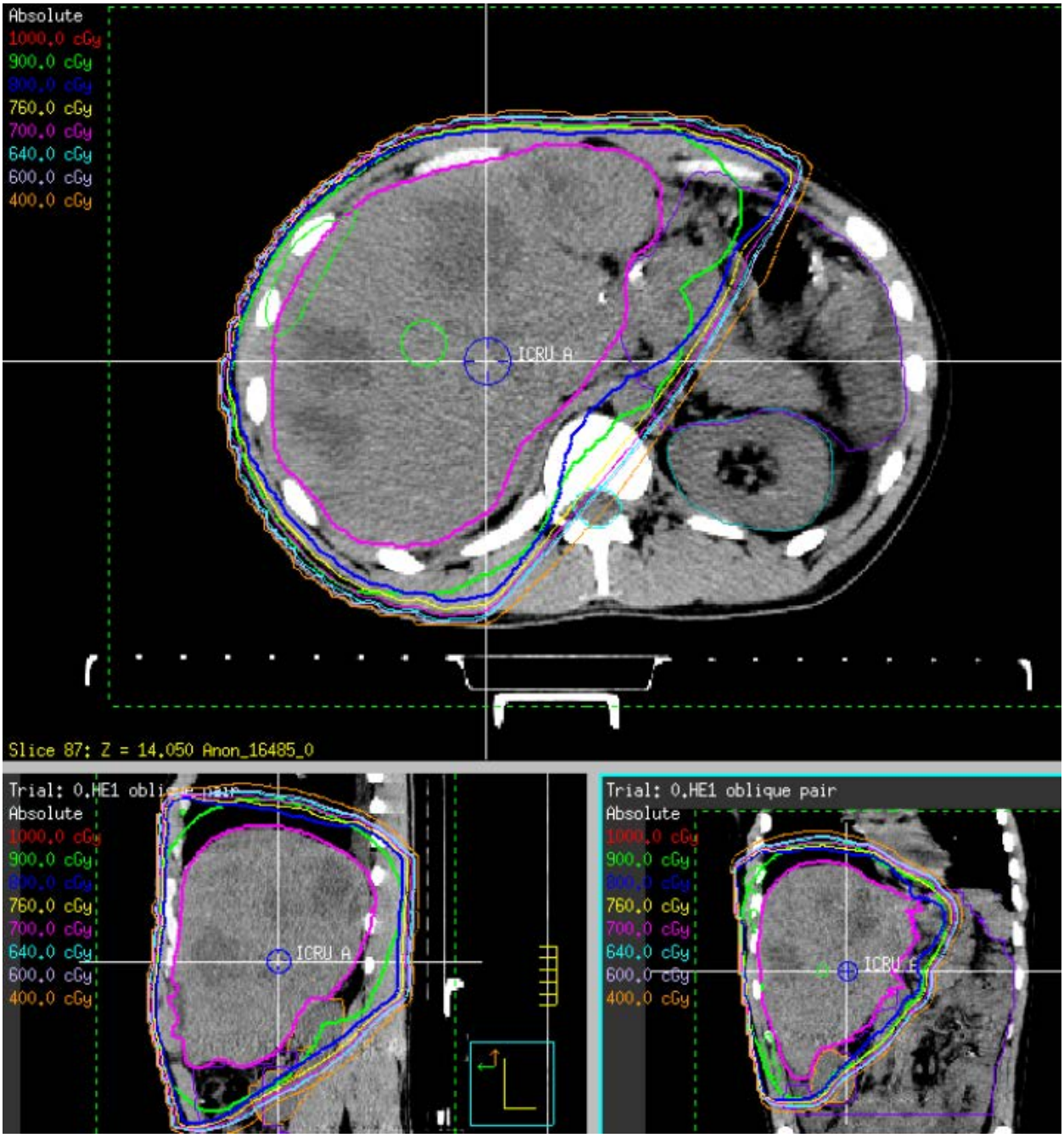
APPENDIX VII - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

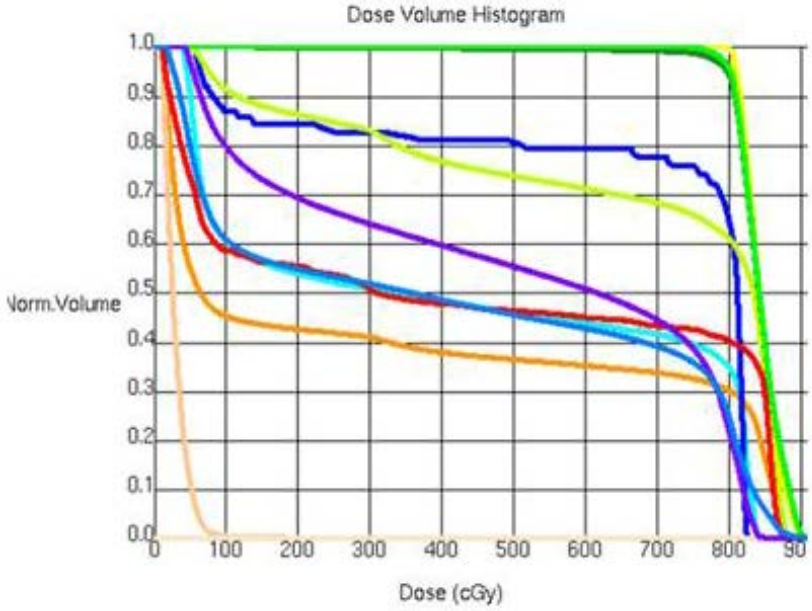
The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

APPENDIX VIII - EXAMPLES OF TYPICAL PALLIATIVE RADIOTHERAPY TO THE LIVER

Example 1: CTV (liver) in purple, and PTV in green: Oblique parallel pair fields.

The full "published plan" (HE.1 RT Protocol-1) is available on the HE.1 trial website under the heading Data Collection / Data Management.





ROI Statistics

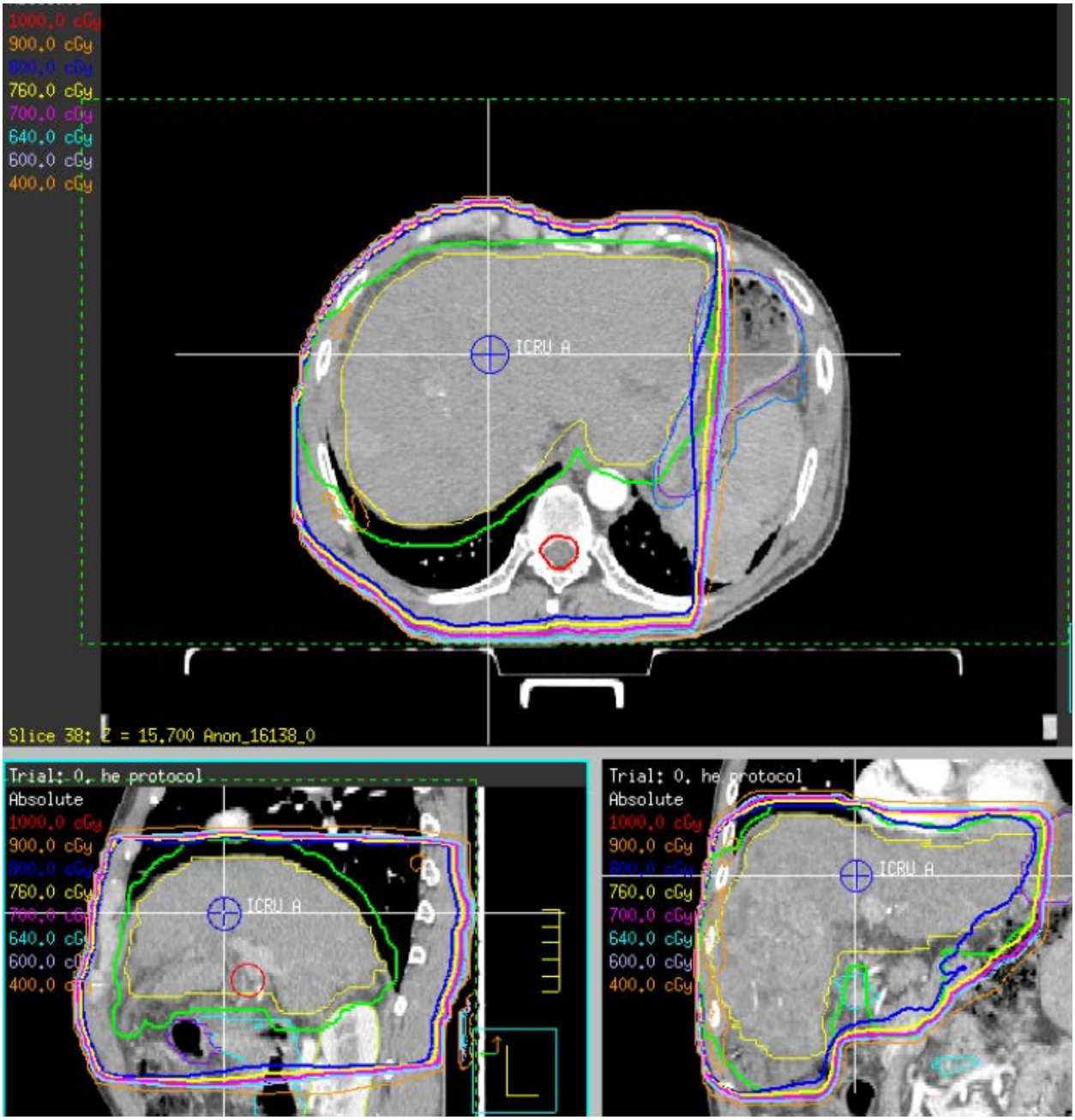
Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	Kidney_R	0. he protocol	50.7	886.7	662.3	284.7
	Large Bowel	0. he protocol	--	--	--	--
	Liver	0. he protocol	771.6	914.4	844.4	23.0
	PTV_8	0. he protocol	--	914.4	838.3	62.5
	PTV_8eval	0. he protocol	611.2	914.4	843.7	28.9
	Spinal canal	0. he protocol	10.5	879.3	422.1	380.6
	Stomach	0. he protocol	40.2	849.0	493.7	311.0
	peritoneal cavity	0. he protocol	12.7	904.7	414.8	348.6

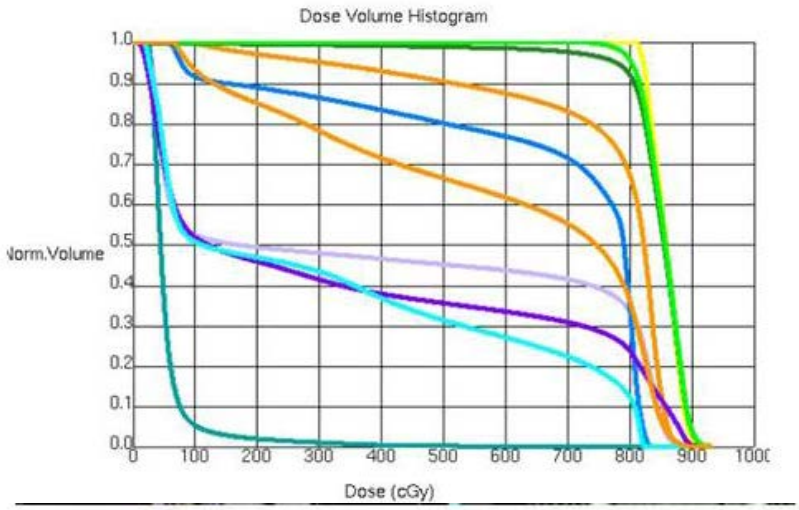
ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	Bilateral kidneys	0.HE1 oblique pair	23.5	888.6	403.1	371.4
	CTV_8	0.HE1 oblique pair	798.2	919.0	857.7	22.5
	Esophagus	0.HE1 oblique pair	57.9	835.0	660.2	242.8
	Kidney_L	0.HE1 oblique pair	23.5	524.8	54.4	41.5
	Kidney_R	0.HE1 oblique pair	83.9	888.6	754.4	170.9
	Liver	0.HE1 oblique pair	798.2	919.0	857.7	22.5
	PTV_8	0.HE1 oblique pair	--	929.5	841.8	85.7
	PTV_8eval	0.HE1 oblique pair	657.9	929.5	854.6	30.8

Example 2: CTV (liver) in yellow, and PTV in green. Anterior-posterior parallel fields.

The full "published plan" (HE.1 RT Protocol-2) is available on the HE.1 trial website under the heading Data Collection / Data Management.





ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean
	Kidney_L	0.HE1 oblique pair	23.5	524.8	54.4
	Kidney_R	0.HE1 oblique pair	83.9	888.6	754.4
	Liver	0.HE1 oblique pair	798.2	919.0	857.7
	PTV_8	0.HE1 oblique pair	--	929.5	841.8
	PTV_8eval	0.HE1 oblique pair	657.9	929.5	854.6
	Peritoneal cavity	0.HE1 oblique pair	8.0	908.2	347.5
	Spinal canal	0.HE1 oblique pair	19.3	826.5	315.6
	Stomach	0.HE1 oblique pair	60.1	893.0	593.9

ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean
	Bilateral kidneys	0. he protocol	9.2	886.7	341.4
	CTV_8	0. he protocol	771.6	914.4	844.4
	Duodenum	0. he protocol	37.0	843.0	423.6
	Esophagus	0. he protocol	56.4	827.1	668.8
	Kidney_L	0. he protocol	9.2	184.5	30.2
	Kidney_R	0. he protocol	50.7	886.7	662.3
	Large Bowel	0. he protocol	--	--	--
	Liver	0. he protocol	771.6	914.4	844.4

APPENDIX IX - 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.

   For the HE.1 study, the scheduled times to obtain the questionnaires are as follows:

   - pre-randomization (baseline)
   - Day 30
   - Day 90

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

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

2. Pre-treatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, 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 on Day 30 and Day 90

   The quality of life questionnaire should be given to the patient before being seen by the doctor. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire.

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

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

5. What If . . .

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

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

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

      Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:
      If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

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

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

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

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

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

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

6. Waiving the Quality of Life Component

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

7. Unwillingness to Complete Quality of Life Questionnaire

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

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

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

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

AMEND #1: 2018-JUL-31

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **HE.1**

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

Patient Information

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

Institution: _____ Investigator: _____

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

☐ Prior to randomization

On Study:

☐ Day 30 ☐ Day 90

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: __ __ - __ __ __ - __ __ __ __
dd mmm yyyy

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

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

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

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

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

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

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

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

CCTG Trial HE.1

A PHASE III STUDY OF PALLIATIVE RADIOTHERAPY FOR SYMPTOMATIC HEPATOCELLULAR CARCINOMA AND LIVER METASTASES

Patient Initials: _____ - _____ - _____
First *Middle* *Last*

Patient Serial #: CA__ __ __ __ __ __

Institution: _____

Investigator: _____

PRE-BASELINE PAIN/DISCOMFORT QUESTIONNAIRE

To the Patient:

If you have any questions about how or when to complete this questionnaire, please telephone the study nurse or Clinical Research Associate (CRA) listed below.

_____ _____
(Name) (Number)

Hours of Availability:

_____

INFORMATION AND INSTRUCTIONS FOR THE PATIENT

Thank you for considering participating in this research study. Before you can enrol in the study, there is a short exercise that needs to be completed to ensure that this study is the right fit for you.

This document contains one question that will ask you to record your abdominal pain/discomfort. Below are instructions to help answer this question. Please note that the question within this document will refer to "pain". Some patients describe abdominal "discomfort" rather than "pain", and if this is the case, you may still complete this questionnaire. "Pain" in the questionnaire is meant to reflect abdominal "pain" or "discomfort" from your liver cancer.

You are being asked to fill in the questionnaire on two separate days within the same week to help determine if your pain/discomfort is "stable" (i.e. not changing too much from day to day).

If you have any questions, please ask the CRA or study nurse to help you.

Your Abdominal Pain/discomfort

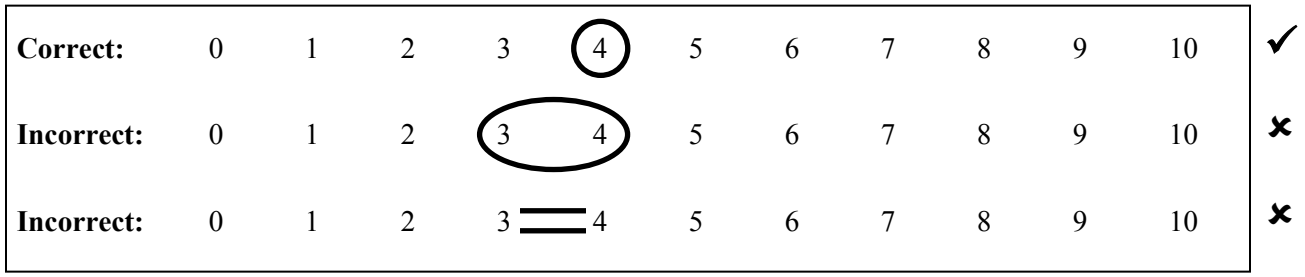
To tell us about your abdominal pain/discomfort, you will be provided with a list of numbers and asked to rate your pain/discomfort by choosing **one** number from **0 (no pain/discomfort)** to **10 (pain/discomfort as bad as you can imagine)** that best describes your pain/discomfort in the last 24 hours.

This is what that question looks like:

Please rate your abdominal pain by circling the **one** number that best describes your pain at its **WORST** in the last 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Some correct and incorrect sample answers are shown below:



Now you are ready to fill out your questionnaire.

Please go to the next page.

PATIENT QUESTIONNAIRE

Date: _____ - _____ - _____ Day of week: _____
Day *Month* *Year*

1. Please rate your abdominal pain by circling the **one** number that best describes your abdominal pain at its **WORST** in the last 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

You have now completed the questionnaire.

If this is the first questionnaire you have completed please complete a second one in the next few days.

If this is the second questionnaire you have completed, the study nurse or CRA will be phoning you in the next few days with instructions regarding what happens from here.

Please remember to bring this questionnaire back to the hospital when you return for your next study visit.

Thank you for your consideration of this research study.

AMEND #1: 2018-JUL-31

APPENDIX XI - PAIN/DISCOMFORT AND MEDICATION QUESTIONNAIRE

CCTG Trial HE.1

A PHASE III STUDY OF PALLIATIVE RADIOTHERAPY FOR SYMPTOMATIC HEPATOCELLULAR CARCINOMA AND LIVER METASTASES

Patient Initials:_____ - _____ - _____
First *Middle* *Last*

Patient Serial #:CA__ __ __ __ __ __

Institution:_____

Investigator:_____

PAIN/DISCOMFORT AND MEDICATION QUESTIONNAIRE

To the Patient:

If you have any questions about how or when to complete this questionnaire, please telephone the study nurse or CRA listed below.

_____ _____
(Name) (Number)

Hours of Availability:

_____

INFORMATION AND INSTRUCTIONS FOR THE PATIENT

Thank you for participating in this research study.

This document is a questionnaire that is split up into two parts that both relate to your abdominal pain/discomfort:

Part One will be used to record your level of abdominal pain/discomfort. Please note that the questions within this document will refer to "pain". Some patients describe abdominal "discomfort" rather than "pain", and if this is the case, you may still complete this questionnaire. "Pain" in the questionnaire is meant to reflect abdominal "pain" or "discomfort" from your liver cancer.

Part Two will record the medication you take to treat your pain/discomfort. When you receive the questionnaire, the clinical research associate (CRA) or study nurse may have already filled in the names and doses of the medications you regularly take to treat your pain.

The next pages contain instructions to help you fill in Part One of the questionnaire and the instructions for Part Two will come later on.

You are being asked to fill in the questionnaire:

- Before you enter the study,
- about 30 days after you have started the study, and
- about 90 days after you have started the study.

Each time you fill in the questionnaire, you will be asked to give us information related to:

- your abdominal pain/discomfort and its effect on your life,
- how much medication you have taken to treat your abdominal pain/discomfort, and
- any symptoms you have and any medications you have taken for reasons other than pain/discomfort control.

If you have any questions, please ask the CRA or study nurse to help you.

Please go to the next page.

INSTRUCTIONS FOR PART ONE

Your Abdominal Pain/discomfort

We will ask you about your level of pain/discomfort in this section of the questionnaire.

To tell us about your abdominal pain/discomfort, you will be provided with a list of numbers and asked to rate your pain/discomfort by choosing **one** number from **0 (no pain/discomfort)** to **10 (pain/discomfort as bad as you can imagine)** that best describes your pain/discomfort in the last 24 hours.

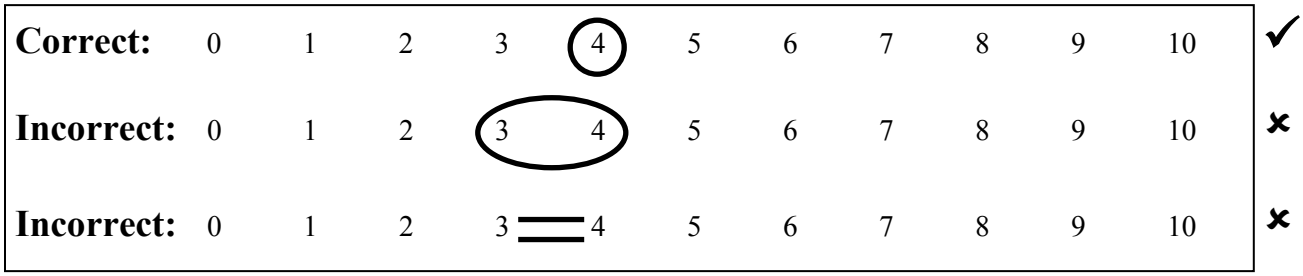
This is what that question looks like:

Please rate your abdominal pain by circling the **one** number that best describes your pain at its **WORST** in the last 24 hours:

0 1 2 3 4 5 6 7 8 9 10

No pain Pain as bad as you can imagine

Some correct and incorrect sample answers are shown below:



Now you are ready to fill out Part One of the questionnaire.

If you have any questions or need help, please contact the CRA or study nurse (contact information provided on the cover page).

Thank you for valuable contribution to this research study

Please go to the next page

PART ONE: PATIENT QUESTIONNAIRE – PATIENT TO COMPLETE

CRA / Study Nurse *to complete below,* ***in advance****:*	
Please check the timing of the questionnaire: ☐ Baseline Questionnaire ☐ 30 day Post-Randomization Questionnaire ☐ 90 day Post-Randomization Questionnaire	***NOTE:*** At the baseline visit, please ask the patient if they would describe their abdominal symptoms as "pain" or "discomfort". This information will be required at the time of randomization. Patient describes abdominal symptoms as: ☐ Pain ☐ Discomfort

Date: _____ - _____ - _____ Day of week: _____
Day *Month* *Year*

1. Please rate your abdominal pain by circling the **one** number that best describes your pain at its **WORST** in the last 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

2. Please rate your abdominal pain by circling the **one** number that best describes your pain at its **LEAST** in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

3. Please rate your abdominal pain by circling the **one** number that best describes your pain on **AVERAGE**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please go to the next page

4. Please rate your abdominal pain by circling the **one** number that tells how much pain you have **RIGHT NOW**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the **one** percentage that most shows how much how much **relief** you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

6. Circle the **one** number that describes how, during the past 24 hours, abdominal pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Please go to the next page

PART ONE: PATIENT QUESTIONNAIRE – PATIENT TO COMPLETE

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Please go to the next page

INSTRUCTIONS FOR PART TWO

Your Pain/Discomfort Medication

To tell us how much pain/discomfort medication you took in the last 24 hours, you will be asked to fill in a table. In most cases, the CRA or study nurse will have already filled in some information about the medications you usually take for pain/discomfort. For example, if you use 10 mg tablets of Medication A and 2 mg tablets of Medication B, the table will look like this:

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆
Medication A	10 mg	By mouth	
Medication B	2 mg	By mouth	

◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.
**	For example, medications can be taken by mouth, rectally, or in patch form.

Here are some examples of how to fill in the medication table:

Ex. 1: Your doctor has prescribed 10 mg tablets of Medication A for your pain/discomfort and told you to take one tablet in the morning and one at night. Your doctor has also prescribed 2 mg tablets of Medication B and told you to take one tablet as needed when you have extra pain/discomfort (also called breakthrough pain/discomfort), up to four times a day. In the last 24 hours, you took both of the 10 mg Medication A tablets and three of the 2 mg Medication B tablets.

This is the <u>correct</u> way to fill in the table:

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆	
Medication A	10 mg	By mouth	2	✓
Medication B	2 mg	By mouth	3	✓

◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.
**	For example, medications can be taken by mouth, rectally, or in patch form.

This is an <u>incorrect</u> way to fill in the table:

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆	
Medication A	10 mg	By mouth	2	✓
Medication B	2 mg	By mouth	1 as needed	✘
◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.			
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.			
**	For example, medications can be taken by mouth, rectally, or in patch form.			

This is incorrect because it does not tell us <u>exactly</u> how much of Medication B you took before filling in the table. We need to know this to be able to get complete results for the study.

Here are some examples of how to record your medication if you use formats other than tablets:

Ex. 2: You use a patch on your skin that delivers 25 mcg of Medication C every hour. You change this patch every three days.

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆	
Medication C	25 mcg / h	Patch	1 every 3 days	✓
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.			

Ex. 3: Some pain/discomfort medications are available in liquid or syrup form. Your doctor has prescribed 2 mg/mL Medication D to you. You can take 1 to 3 mL of this liquid when you have pain/discomfort, up to six times a day. Today, you took 2 mL of Medication D just before lunch, 1 mL in the middle of the afternoon, and 3 mL just before going to bed (for a total of 6 mL).

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆	
Medication D	2 mg / mL	By mouth	2 + 1 + 3 = 6	✓
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.			

Please go to the next page

PART TWO: PATIENT QUESTIONNAIRE – PATIENT TO COMPLETE

Please record all the medications you took for pain/discomfort today, including what you have already taken since getting up this morning. Please make sure you record all the medication you take for breakthrough pain/discomfort, and any medication you take for pain/discomfort that wakes you up while sleeping at night.

In the following table, the CRA or study nurse has listed all the medications you usually take to treat your ***abdominal pain/discomfort***. If you did not use any of a particular medication in the last 24 hours, please note this by writing "zero" (0) in the dose column.

If you took other medications to treat your pain/discomfort that are not included in the table, please write them in the table and fill in all the columns.

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆
◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.		
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.		
**	For example, medications can be taken by mouth, rectally, or in patch form.		

If you have any questions about how to complete this table, please ask the CRA or study nurse.

If you wish, you can write down any other medications you have taken today here:

_____

If you wish, you can write down any symptoms you are having here:

_____

You have now completed the study questionnaire.

Please remember to bring this questionnaire back to the hospital
when you return for your next study visit.

Thank you for your valuable contribution to this research study.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
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)	Paul Stos Study Coordinator CCTG Email: pstos@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Chris O'Callaghan Senior Investigator CCTG Email: cocallaghan@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Laura Dawson Study Chair Email: laura.dawson@rmp.uhn.on.ca	416-946-2125	416-946-6566
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Paul Stos Study Coordinator CCTG	613-533-6430	613-533-2941