The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

The impact of re-irradiation of painful osseous metastases on quality of life and function: A secondary analysis of the NCIC CTG SC.20 randomized trial

Chow, et al

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NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A PHASE III INTERNATIONAL RANDOMIZED TRIAL OF SINGLE VERSUS MULTIPLE FRACTIONS FOR RE-IRRADIATION OF PAINFUL BONE METASTASES

NCIC CTG Protocol Number: SC.20

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TREATMENT SCHEMA

Study Population:

Patients with painful bone metastases after previous palliative radiotherapy to the diseased bone will be included in this study. The initial radiation dose to the extremities/ribs can be a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions. The initial radiation dose to metastases in the spine and pelvis can be a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions or 20 Gy in 5 fractions. Patients given an initial dose of 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions to the spine or any part of the pelvis encompassing small or large bowel and/or the rectum are not eligible for the study. Initial doses of 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions to the acetabulum/hip and proximal femur are eligible as long as the medial field border of the initial treatment did not cross midline (pubic symphysis).

Stratification:

1. Response to initial radiation (response versus no response)
2. Initial fractionation (single versus multiple)
3. Centre

<table>
<tr><td>ARM 1 - 8Gy
(single)</td><td>→</td><td>1 fraction</td></tr>
<tr><td rowspan="2">ARM 2 - 20 Gy
(multiple)</td><td>↗</td><td>5 fractions</td></tr>
<tr><td>↘</td><td>8 fractions (for spine and/or whole pelvis only if previous treatment to this area was given in multiple fractions)</td></tr>
<tr><td colspan="3">Planned Sample Size: 850 Patients</td></tr>
</table>

Primary Endpoint:

- Overall response rates at 2 months from the start of treatment.

Secondary Endpoints:

- Incidence of acute radiation related side effects.
- Reduction in functional interference by $\geq$ 2/10 following re-irradiation
- Freedom from progression
- In-field pathological fractures and spinal cord compression
- EORTC QLQ-C30

AMEND #1: 2004-MAY-20; #2: 2005-MAR-01; #4: 2006-MAR-24; ADMIN UPDATE #1: 2006-SEP-20

1.0 OBJECTIVES

Patients with painful bone metastases after previous palliative radiotherapy to the diseased bone will be included in this study. The initial radiation dose to the extremities/ribs can be a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions. The initial radiation dose to the metastases in the spine and pelvis can be a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions or 20 Gy in 5 fractions. Patients given an initial dose of 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions to the spine or any part of the pelvis encompassing small or large bowel and/or the rectum are not eligible for the study. Initial doses of 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions to the acetabulum/hip and proximal femur are eligible as long as the medial field border of the initial treatment did not cross midline (pubic symphysis).

1.1 Primary Objective

- To compare pain relief after re-irradiation of symptomatic bone metastases with 8 Gy or 20 Gy

1.2 Secondary Objectives

- To determine the overall incidence of pain relief in patients undergoing re-irradiation for symptomatic bone metastases;
- To determine the time to pain progression after re-irradiation;
- To assess the relationship between response to initial radiation and pain relief with re-irradiation;
- To determine the changes in functional interference following re-irradiation using the Brief Pain Inventory (and QoL using EORTC QLQ C30 in Canada, France and the Netherlands and for patients registered through RTOG);
- To determine the characteristics of the group of non-responders (to both the initial and re-irradiation);
- To monitor the incidence of acute severe radiation related side effects;
- To monitor the incidence of in-field pathological fractures and spinal cord compression.

2.0 BACKGROUND INFORMATION AND RATIONALE

Bone metastases are a common manifestation of distant relapse from many types of malignant tumours, especially from cancers of the breast, prostate and lung. Radiotherapy is a well-recognized effective modality in the palliative treatment of painful bone metastases. Palliation of bone metastases with radiotherapy represents a significant workload in the radiation oncology department. Various fractionation schedules are employed by radiation oncologists ranging from a single 6-8 Gy fraction to multiple fractions such as 40 Gy in 20 fractions over 4 weeks *[Bone Bain Trial Working Party 1999, Gaze 1997, Jeremic 1998, Nielsen 1998, Niewald 1996, Price 1986, Rasmusson 1995, Steenland 1999, Tong 1982, Cole 1989, Madsen 1983, Okawa 1988, Koswig 1999, Hirokawa 1988]*. Randomized trials addressing the optimal radiotherapy dose fractionation schedule for palliation of uncomplicated painful bone metastases have not suggested convincingly that any one fractionation is superior to another in terms of pain control. The acute radiation related side effects are acceptable when weighted against the benefits of palliative radiotherapy. The incidences of reported pathological fractures and spinal cord compressions are usually low (Table 1).

Table-1:
Percentage of patients experiencing adverse effects associated with radiotherapy for painful bone metastases.

Study	Percent with Vomiting		Percent with Pathologic Fractures		Percent with Cord Compression	
	Low #	High #	Low #	High #	Low #	High #
Trials comparing single fraction against multi-fraction RT						
Bone Pain Trial Working Party *[Bone Pain Trial Working Party 1999]*	30%*	32%*	2.0%	0.5%	1.7%	1.1%
Steenland *et al.* *[Steenland 1999]*	no significant difference		4%	2%	2%	2%
			$p < 0.05$			
Nielsen *et al.* *[Nielsen 1998]*	no significant difference		5%	5%	--	--
Cole *[Cole 1989]*	8%	11%	--	--	--	--
Price *et al.* *[Price 1986]*	no significant difference		0	1.3%	2.6%	1.3%
Trials comparing single fractions at different doses (4Gy vs 8Gy)						
Jeremic *et al.* *[Jeremic 1998]*	19%**	22%**	6%	7%	7%	6%
Trials comparing different multi-fraction regimens						
Madsen *[Madsen 1983]*	7%	0	--	--	--	--
Tong *et al.* *[Tong 1982]* (RTOG 7402) - Solitary met	--	--	4%	18%	--	--
- Multiple mets	--	--	5%	8%	--	--

Low#: lower number of fractions for trials of single vs multiple fractions, lower dose for trials comparing different doses;

High#: higher number of fractions for trials of single vs multiple fractions, higher dose for trials comparing different doses

* percentage of patients experiencing vomiting on days 1-14; subgroup of N = 133, recruited into secondary nausea/vomiting study

** RTOG/EORTC grade 1 & 2 nausea/vomiting.

As effective systemic treatment and better supportive care result in improved survival, certain subsets of patients with bone metastases have longer life expectancies than before. An increasing number of patients outlive the duration of the benefits of initial palliative radiotherapy for symptomatic bone metastases, requiring re-irradiation of the previously treated sites. Additionally, some patients fail to respond initially but may benefit from re-irradiation.

Among the radiation trials comparing single versus multiple fractionation schemes, re-irradiation rates varied from 11 – 42% following single fraction and 0 – 24% following multiple-fraction regimes (Table 2). However, re-irradiation to the previously radiated sites was done at the discretion of the treating radiation oncologists who were not blinded to the initial treatment, and there was no guideline to when, why and what dose of re-irradiation should be given.

Table 2: Re-irradiation rates reported in randomized trials of dose-fractionation schedules

Randomized Study	Re-irradiation Rate	
	Low #	High #
Trials comparing single fraction against multi-fraction RT		
Bone Pain Trial Working Party *[Bone Pain Trial Working Party1999]*	23%	10%
Steenland *et al.* *[Steenland 1999]*	25%	7%
Nielsen *et al.* *[Nielsen 1999]*	20%	12%
Cole *[Cole 1989]*	25%	0%
Price *et al.* *[Price 1986]*	11%	3%
Trials comparing single fractions at different doses (4Gy vs 8Gy)		
Jeremic *et al.* *[Jeremic 1998]*	42%	38%
Hoskin *et al.* *[Hoskin 1992]*	20%	9%
Trials comparing different multi-fraction regimens		
Niewald *et al.* *[Niewald 1996]*	2%	2%
Tong *et al.* *[Tong 1982, Gillick 1981]* (RTOG 7402) - Solitary met	24%	11%
- Multiple mets	23%	12%

Many patients with relapsed pain or poor response to initial radiation may be lost to follow up or may not be referred back to radiation oncologists for consideration of re-irradiation. Limited clinical data on the efficacy of re-irradiation does support its role and further studies are necessary.

Since the reported response rates in some of the randomized bone metastases trials included response to re-irradiation, it is difficult to estimate the response rate from re-irradiation alone from those trials.

Moreover, there are at least three scenarios of "failure" where re-irradiation may be considered. Response to re-irradiation may be different for each of these scenarios:

1. no pain relief or pain progression after initial radiotherapy;
2. partial response with initial radiotherapy and the hope to achieve further pain reduction with more radiotherapy, and
3. partial or complete response with initial radiotherapy but subsequent recurrence of pain.

2.1 Studies Reporting Results of Re-Irradiation Following Initial Radiotherapy for Bone Metastases

A few single-fraction radiotherapy studies reported on sporadic re-treatments with either single or multiple fractionation regimens.

Price et al reported on 7 patients who, after failure to respond to the initial single 4 Gy fraction, were given repeat radiotherapy within 8 weeks. Four of them received a single 8 Gy and the other three a fractionated course. No significant pain relief was achieved by the second radiotherapy treatment in these seven patients *[Price 1988]*.

Cole reported in another study that re-treatment of patients after initial single or multi-fraction treatment was not successful in all patients, and 50% of the 42 patients requiring re-treatment needed supplementary stronger analgesics *[Cole 1989]*.

Hoskin et al in their study randomized patients to either 4 or 8 Gy single dose RT in the treatment of metastatic bone pain. During the 12-week study period, 28 patients randomized to 4 Gy were retreated with radiotherapy to the same site compared to 12 randomized to 8 Gy. 12/17 (71%) evaluable patients responded to re-treatment in the 4 Gy arm and 4/9 (44%) responded in the 8 Gy arm *[Hoskin 1992]*.

Uppelschoten et al reported that after long intervals from previous single 6 Gy of radiation, re-irradiation with another 6 Gy was able to reduce pain in 13 out of 18 patients. *[Uppelschoten 1995]*

Mithal et al reported a retrospective analysis of 105 consecutive patients treated with palliative radiotherapy for painful bone metastases. A total of 280 individual treatment sites were identified, of which 57 were retreated once and 8 were retreated twice. The overall response rate to initial treatment was 84% for pain relief, and at first re-treatment this was 87%. 7/8 (88%) patients retreated a second time also achieved pain relief. A total of 17/23 (74%) patients responded (complete response and partial response) to second radiation that used a number of single fraction regimens, which was not significantly inferior to 31/34 (91%) obtained with more protracted regimens. No relation to radiation dose, primary tumour type, or site was seen *[Mithal 1994].*

Jeremic et al investigated the effectiveness of a single fraction of 4 Gy given for re-treatment of bone metastasis after previous single fraction radiotherapy. Of 135 patients retreated, 109 patients were retreated because of pain relapsing while 26 patients were re-irradiated after initial non-response. Of the 109 patients that were re-irradiated for pain relapse, 80 (74%) patients responded (complete response (CR) = 31%; partial response (PR) = 42%). Among the 26 patients that initially did not respond, there were 12 (46%) responses. The authors concluded that the lack of response to initially single fraction radiotherapy should not deter repeat irradiation. Toxicity in their series was low and only gastrointestinal. Grade 1 or 2 diarrhea (RTOG acute toxicity criteria) was observed in 25/135 (19%) patients. No acute toxicity $\geq$ grade 3 was reported. Pathological fractures were reported in 3/135 (2%) patients and spinal cord compression in 3/135 (2%) patients in their series *[Jeremic 1999]*.

The same group recently reported the efficacy of the second single 4 Gy re-irradiation for painful bone metastases following the previous two single fractions. The overall response rate of the 25 patients (19 responders and 6 non-responders to the 2 prior single fractions) was 80%, with both complete response and partial response being 40%. No acute or late high-grade toxicity ($\geq$ 3) was observed in their study. No pathological fractures or spinal cord compression were seen in any of these patients during the follow up *[Jeremic 2002]*.

In RTOG studies that involved wide-field or hemibody radiotherapy, patients who did relapse after wide-field irradiation were reported to tolerate local irradiation within that field with success *[Quasim 1981, Salazar 1986]*.

In summary, available data supports the re-irradiation of sites of metastatic bone pain following initial irradiation, particularly where this follows an initial period of response. There is also limited evidence that a proportion of non-responders would respond to a re-irradiation. However, there remains a small group of patients who appear to be non-responsive to any amount of palliative radiotherapy.

Although the data does support the clinical practice of re-irradiation, the preferred dose-fractionation at time of re-irradiation is unknown. Small patient number in retrospective and prospective studies, and prevailing reservation attitudes of radiation oncologists in re-irradiation clearly emphasize the need for more information on re-irradiation.

To date, there has been no prospective randomized study investigating the efficacy of re-irradiation. Whether there is a dose-response phenomenon for re-irradiation is unknown. Although there is no convincing evidence that a dose-response phenomenon exists for the initial radiotherapy for bone metastases *[Bone Bain Trial Working Party 1999, Gaze 1997, Jeremic 1998, Nielsen 1998, Niewald 1996, Price 1986, Rasmusson 1995, Steenland 1999, Tong 1982, Cole 1989, Madsen 1983, Okawa 1988, Koswig 1999, Hirokawa 1988]*, patients failing initial palliative radiotherapy may exhibit a different tumor biology that necessitates a higher radiation dose for clinical response. A large prospective randomized study of re-irradiation with commonly used dose-fractionation schedules will help address these practical questions facing radiation oncologists when providing palliative radiation services.

2.2 Rationale for Choice of Re-Irradiation Dose

Since there is no guideline on the optimal re-irradiation dose fractionation, commonly employed radiation schedules (e.g. 8 Gy in one fraction; 20 Gy in five fractions) for bone pain are first considered. The choice of dose fractionation is also limited by potential toxicity of cumulative radiation doses. Total biological equivalent doses for acute effect ($\alpha/\beta = 10$) and late effect ($\alpha/\beta = 2$ for spinal cord) at various dose fractionations are tabulated below for reference (Table-3).

Table-3: Total biological equivalent doses of various fractionation schemes

	BEDα/β	8 Gy/1#	20 Gy/8#	20 Gy/5#	24 Gy/6#	30 Gy/10#
Acute Effects	BED_{10}	14.4	25	28	33.6	39
Late Effects	BED_2	40	45	60	72	75

After an initial single dose of 6, 7 or 8 Gy, it is within spinal cord tolerance (conservatively estimated at $BED_{10} = 100$) to deliver another single dose of 8 Gy or 20 Gy in 5 fractions with an interval of 4 weeks.

When initial treatment is 18 Gy in 4 fractions or 20 Gy in 5 fractions, the cord and small bowel are expected to tolerate another single dose of 8 Gy or 20 Gy in 8 fractions.

However, after the initial dose of 24 Gy in 6 fractions, 27 Gy in 8 fractions, 30 Gy in 10 daily fractions, the risk of radiation myelitis and severe enteritis may increase with a further single 8 Gy or multiple radiotherapy treatments and therefore re-irradiation is not advised to spinal and pelvic bone metastases in this situation *[Wong 1994]*.

With regards to the acute effects, the BED with α/β of 10 for 20 Gy in 8 fractions is more in keeping with that of 20 Gy in 5 fractions, hence the choice of 20 Gy in 8 fractions as an alternative multi-fraction dose to 20 Gy in 5 fractions for pelvic and spinal bone metastases.

2.3 Rationale for Patient-Assessed Instruments

Brief Pain Inventory (BPI) and the EORTC QLQ-C30 will be employed as the measurement tools. They measure patient-based assessments and have been validated. BPI is easy to administer, hence imposing minimum burden to the patients. Moreover, it has been translated and validated into many different languages.

3.0 TRIAL DESIGN

This is a multicentre randomized trial of the NCIC Clinical Trials Group. Canadian, UK, Dutch, French, TROG and RTOG centres will participate.

3.1 Stratification

Patients will be stratified by:

- Their response to initial radiation as per physician's interpretation of patient history at the time of randomization into responders versus non-responders (i.e. patients who did or did not gain pain improvement after initial radiation);
- Initial fractionation, i.e. single fraction (6, 7 or 8 Gy) versus multiple fractions (18 Gy in 4 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions);
- Centre.

3.2 Randomization

Patients will be randomized to a planned sample size of 850 patients according to the following schema:

Arm	Dose	Number of fractions
One *(single fractionation)*	8 Gy	One
Two *(multiple fractionation)*	20 Gy	Five
		Eight *(for spine and/or whole pelvis only if previous treatment to this area was given in multiple fractions)*

AMENDMENT #1: 2004-MAY-20; #2: 2005-MAR-01; AMENDMENT #4: 2006-MAR-24

4.0 STUDY POPULATION

Patients with painful bone metastases after previous palliative radiotherapy to the diseased bone will be included in this study. The initial radiation dose to the extremities/ribs can be a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions. The initial radiation dose to metastases in the spine and pelvis can be a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions or 20 Gy in 5 fractions. Concerns over re-irradiation to the spine or pelvis encompassing small or large bowel and/or the rectum previously treated with 24 Gy in 6 fractions, 27 Gy in 8 fractions and 30 Gy in 10 fractions preclude these groups of patients from this study. Initial doses of 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions to the acetabulum/hip and proximal femur are eligible as long as the medial field border of the initial treatment did not cross midline (pubic symphysis).

Re-irradiation may be offered for the following indications:

- Relapse of pain, after complete or partial response to previous (initial) palliative radiotherapy
- Further reduction of pain is desired in partial responders
- No response or progression of pain (without any response) since initial treatment

4.1 Eligibility Criteria

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

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

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

4.1.1 Patient must be 18 years of age or older at the time of randomization.

4.1.2 Patient must have histologically or cytologically proven malignancy. Histological diagnosis may be established from needle biopsy, bone marrow biopsy, cytology, or a surgical biopsy or resection. All malignant histologies/cytologies are eligible.

4.1.3 Plain radiographs, radionuclide bone scans, CT scans and/or magnetic resonance imaging confirm the presence of bone metastases corresponding to clinically painful area.

4.1.4 Patient has a worst pain score of $\geq$ 2/10 as reported using the baseline Brief Pain Inventory completed by the patient prior to randomization.

4.1.5 There is no plan to make an immediate change in the analgesic regimen on the day of randomization.

4.1.6 Karnofsky Performance Status $\geq$ 50 within one week prior to randomization.

4.1.7 The interval between the last fraction of the initial radiation and the date of randomization in this study is $\geq$ 4 weeks.

4.1.8 Initial radiation treatment field is reproducible for re-irradiation.

4.1.9 Pain is arising from the previously irradiated metastasis(es) and not from progressive disease in the adjoining or remote areas.

4.1.10 Site of pain considered for palliative radiotherapy must be encompassed by the *same or smaller* treatment field/portal as initial treatment.

4.1.11 *Canadian, Dutch, French and RTOG centres only*: Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaire in English, French, Spanish or Dutch. The baseline assessment must already have been completed. Inability (illiteracy in English, French, Spanish or Dutch, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

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

For patients not randomized through NCIC CTG: Patient consent and centre regulatory compliance must be obtained according to the policies mandated by the responsible cooperative or coordinating group and/or national regulations. Patients must sign the consent form prior to randomization.

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

4.1.14 In accordance with NCIC CTG policy, treatment must begin within 4 weeks of randomization.

4.1.15 If the site followed for this study is in the ribs or extremities, the initial radiation was given in a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions. If the site followed for this study is the acetabulum/hip and/or the proximal femur without the medial field border crossing midline (pubic symphysis), the initial radiation was given in a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions. If the site followed for this study is the spine or another area of the pelvis that is not excluded from the study (see 4.2.11), the initial radiation was given as a single fraction of 6, 7 or 8 Gy, 18 Gy in 4 fractions or 20 Gy in 5 fractions.

4.2 Ineligibility Criteria

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

4.2.1 Clinical or radiological evidence of spinal cord compression at the time of assessment for this study.

4.2.2 Clinical or radiological evidence of pathological fractures of extremities in the area to be re-irradiated.

4.2.3 Radiological evidence of high-risk lesions for pathological fractures in the extremities (lytic lesions > 3 cm or > 50% cortical erosion of bone diameter) *and* candidate for surgical intervention. Patients who are NOT surgical candidates are eligible for this study.

4.2.4 The treatment area has received prior palliative surgery.

4.2.5 There is planned surgical intervention on the treated bone.

4.2.6 Treatment field of initial radiation volume has to be enlarged/modified to accommodate symptomatic disease not previously irradiated, or to provide adequate treatment margin.

4.2.7 Systemic radiotherapy (Sr-89) has been received within 30 days prior to randomization.

4.2.8 Patient has received half body irradiation including the current re-irradiation field within 30 days prior to randomization.

4.2.9 Current site has already had 2 or more courses of radiation.

4.2.10 The patient has been previously admitted to the study.

4.2.11 The patient has been previously treated to the spine or any part of the pelvis encompassing small or large bowel and/or the rectum with 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions.

4.2.12 Patient is a pregnant or nursing woman.

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5.0 PRE-TREATMENT EVALUATION

(See Appendix I)

Investigations		Timing	Location
History and Physical Exam including	Karnofsky Performance Status Baseline Symptoms/toxicity	within 7 days prior to randomization	Clinic
Radiology	Report documenting painful metastases corresponding to painful area	No limit	Clinic
Other Investigations	• Baseline Brief Pain Inventory (see Appendix V for scale and method of administration)* • List of current analgesics	Within 7 days prior to randomization and day of first fraction if interval from randomization to re-irradiation is greater than 7 days or if a new analgesic regimen has been started since randomization	Clinic
Quality of Life	EORTC QLQ-C30 (for Canadian, Dutch, French and RTOG centres). See Appendix VI for scale and method of administration	Within 7 days prior to day of randomization and day of first fraction if interval from randomization to re-irradiation is greater than 7 days.	Clinic

* Worst pain score used to determine eligibility must be taken from this questionnaire completed prior to randomization.

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6.0 ENTRY/RANDOMIZATION PROCEDURES

6.1 Entry Procedures

All eligible patients enrolled on the study by a participating treatment centre will be entered into a patient registration log provided by the NCIC CTG. This will automatically provide a serial number for that patient which should be used on all documentation and correspondence with the NCIC CTG.

The following information will be required in all cases:

- trial code (NCIC CTG SC.20)
- treatment centre and investigator name
- date of REB approval* for study at participating centre
- patient's initials, hospital number and date of birth
- confirmation of the requirements listed in section 4.0, including dates of essential tests
- completed eligibility checklist
- stratification parameters

* Initial approval of all studies must be Full Board.

Canadian centres
All randomizations will be done centrally by the NCIC CTG and will be obtained by calling the NCIC CTG Clinical Trials Assistant at (613) 533-6430 or by faxing the eligibility checklist to (613) 533-2941. At the time of randomization, a copy of the completed eligibility checklist must be available.

UK centres
All randomizations will be done centrally by the Cancer Research UK and UCL Cancer Trials Centre trial coordinator for SC.20 at 0207 679 8036/8005 who will review the eligibility with the caller and will obtain the study allocation using a web-based system provided by NCIC CTG.

Dutch centres
All randomizations will be done centrally by the data management of the Radiotherapy Institute Friesland (RIF) and will be obtained by calling Karin van den Elsaker or Yvette van der Linden at 058-2866667 or by faxing the eligibility checklist to 058-2887750. Karin van den Elsaker will review the eligibility with the caller and will obtain the study allocation using a web-based system provided by NCIC CTG.

TROG centres *(see Appendix IX for additional details)*
All randomizations will be done centrally by TROG and will be obtained by calling the Radiation Oncology Data Manager at 61(0)8 8222 5024 or by faxing the eligibility checklist to 61(0)8 8222 2016. The Radiation Oncology Data Manager will review the eligibility with the caller and will obtain the study allocation using a web-based system provided by NCIC CTG.

AMENDMENT #2: 2005-MAR-01; ADMIN UPDATE #1: 2006-SEP-20; AMENDMENT #5: 2009-AUG-07
RTOG Centres *(see Appendix X for additional details)*
All randomizations will be done centrally by RTOG Headquarters. RTOG institutions will fax the NCIC CTG Form 1 to RTOG Headquarters (215-574-0300; 8:30 AM to 4:00 PM Eastern Time, Monday through Friday). **U.S. sites** also must fax regulatory documentation to the CTSU Regulatory Office (215-579-0206). **Canadian sites** must fax regulatory documentation to RTOG Headquarters (215-574-0300). When RTOG Headquarters receives the NCIC CTG Form 1 from the RTOG institution, Headquarters will confirm patient eligibility and regulatory compliance before the patient will be registered to this study. Upon confirmation of eligibility and regulatory compliance, RTOG Headquarters will register the patient on the NCIC CTG web site and then will call the RTOG institution to confirm registration.

French centre (*see Appendix XII for additional details*)
All randomizations will be done centrally by the Radiotherapy Service of Henri Mondor Hospital (Prof. Lagrange and Dr. Diana), after review of the eligibility criteria using a web-based system provided by NCIC CTG.

6.2 Stratification

- Response to initial radiation
- Initial fractionation
- Centre

6.3 Randomization

Randomization will be given by telephone for Canadian centres and through the NCIC CTG website for cooperative groups, and confirmed by email.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, except on disclosure of initial ineligibility.

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

All eligible patients are to be followed until death or for twelve months, whichever is sooner.

7.0 TREATMENT PLAN

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

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

7.1 Radiation Treatment Plan

If a patient requires radiation to other sites, only the re-irradiated site will be the study site.

If patient requires re-irradiation to more than one site, only one site will be chosen as the study site. The follow-up Brief Pain Inventory questionnaires will refer specifically to the study site.

7.1.1 ARM 1: 8 Gy in 1 fraction

7.1.2 ARM 2: 4 Gy x 5 daily fractions to 20 Gy total dose OR 2.5 Gy x 8 daily fractions to 20 Gy total dose if treatment area involves the spine and/or whole (bilateral) pelvis AND the previous radiation dose is 18 Gy in 4 fractions or 20 Gy in 5 fractions.

7.1.3 Treatment can be given using mega-voltage equipment with Cobalt-60, 4-20 MV photons. Orthovoltage or 5-20 MeV electrons may be used for superficial bones such as the sternum, clavicle or ribs.

7.2 Treatment volume

Re-irradiation portals must be the same as initial radiation portals, unless a smaller volume is deemed adequate, to reduce potentially confounding effect of encompassing adjacent but previously untreated bone metastases.

The treatment volume should include at least one vertebral body for single incident field *[Chow 2002]* above and below the painful vertebra(e) and a minimum of 2 cm margin on long bones. That is, initial treatment volume should have included such margins (see also Section 4.1.8). For spinal metastases, the re-treatment length should not exceed 20 cm.

7.3 Dose Prescription and Treatment Verification

For spinal bone metastases, radiation dose should be prescribed to mid-vertebral body for single incident field *[Chow 2002]*; other sites should be prescribed to D_{max} for single incident fields and mid-plane dose for opposed fields.

Simulation and verification films are required to document target localization, however these films should not be sent to the various data centres (i.e. do not send films to NCIC CTG, CRUK and UCL CTC, DBMG, TROG or RTOG).

7.4 Anti-emetic prophylaxis

For treatment fields that include the epigastrium, lumbar spine or pelvis, prophylactic antiemetic, such as ondansetron, is recommended, though not mandatory. *[Priestman 1993; Kirkbride 2000; Gralla 1999]*

7.5 Pain Flare

Patients should be informed of the possibility of "pain flare", regardless of whether the re-irradiation is given as single or multiple fractions. "Pain flare" is characterized by a transient increase in pain in the irradiated area during the first 1-2 days following single fraction re-irradiation, or during the first 3-4 days of multi-fraction re-irradiation.

Patients should be instructed to take breakthrough pain medications as required, if a pain flare is experienced. Patients should be told pain flare is a transient phenomenon that is expected to last 1-3 days. Thereafter, analgesia consumption should return to baseline.

7.6 Analgesia Adjustments following Re-Irradiation

7.6.1 Patients may be told that if pain improves following re-irradiation, the dose and/or interval of analgesia may be reduced slowly. Titration of analgesia dosing may be continued by physicians involved or by home care nurse familiar with the practice of analgesic adjustments.

7.6.2 *Second Re-Irradiation* (i.e. 3rd course of radiation to index site)
At the discretion of the oncologist, a second re-irradiation, or a 3rd course of radiation, may be offered to the same treated site no sooner than 4 weeks after re-irradiation. If 2nd re-irradiation is undertaken, the fact that 2nd re-irradiation was required will be recorded and any response to treatment will not be attributed to the 1st re-irradiation.

7.6.3 *Criteria for the Second Re-Irradiation*
Pain progression as defined in section 9.3.

Poor pain control as defined by an increase in worst pain score by ≥ 2 *without* concomitant increase in analgesic. The reasons for not increasing analgesia might be patient compliance and/or poor tolerance to analgesia.

Interval for the second re-irradiation:
The minimum interval between the first and second re-irradiation is 4 weeks.

7.6.4 *Second Re-Irradiation dose*
The dose is at the discretion of the treating physician.

AMEND #1: 2004-MAY-20; #2: 2005-MAR-01; #4: 2006-MAR-24; ADMIN UPDATE #1: 2006-SEP-20

8.0 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 III (or Appendix IX for TROG patients).

8.1 Location of Patient Evaluation

Patient-completed questionnaires are the preferred mode of data acquisition, whether the questionnaires are filled out during a follow up clinic visit or at home. In the latter situation, the research assistant will telephone the patient to remind the patient to complete and return the questionnaire by mail at the appropriate follow up intervals. If a patient has completed the questionnaire but cannot mail it to the centre, the research assistant can get the answers from the questionnaire by phone.

8.2 Minimum Data to Collect

When a patient becomes unable to complete or return a questionnaire, the worst, average and right now pain scores, and analgesic intake will be obtained by telephone interview. As the data from the 2 month follow-up is vital to the primary endpoint, research assistants should try their best to get this information by mail or in a telephone interview.

8.3 Adverse Event Scoring

All patients will be given an acute toxicity scoring questionnaire (Appendix V) along with the Brief Pain Inventory (Appendix V) to be completed at days 7 and 14. In addition, the late effects of radiation will be recorded on the Form 5 evaluations at Months 3, 4, 5, 6, 9 and 12.

8.4 Follow-Up Data Collection

Investigations		Timing	Location
Acute Toxicity	Acute Toxicity Questionnaire *(see Appendix V for scale and method of administration)*	Day 7 and Day 14 from the first fraction of radiation on either arm. (The first day of re-irradiation is Day 1.)	Clinic or Home (= return questionnaires by mail)*
Pain Levels and Analgesic Intake	Brief Pain Inventory *(see Appendix V for scale and method of administration)***	Day 7 and Day 14 from the first fraction of radiation on either arm, then months 1-6, 9, and 12 after RT. (The first day of re-irradiation is Day 1.)	Clinic or Home (= return questionnaires by mail)*
Quality of Life	EORTC QLQ-C30 for Canadian, Dutch, French and RTOG centres ONLY. *(See Appendix VI for scale and method of administration.)*	Months 1, 2, 3, 4, 5, 6.	Clinic or Home (= return questionnaires by mail)*
Patient Status Changes/Other Events	Form 5	Every month for 6 months starting one month from the first day re-irradiation, then at months 9 and 12.	Clinic or Home (phone contact)*
Late effects of radiation	Form 5	Months 3, 4, 5, 6, 9 and 12.	Clinic or Home (phone contact)*

* Clinical Research Assistant (CRA) will telephone to remind patient to complete follow up forms. CRA will also remind patient to list pain medications and their doses, and review Other Events with patient as per Form 5.

** If patient is unwilling or unable to complete the Brief Pain Inventory, the CRA shall determine the patient's worst and average pain scores and analgesic intake and record in the appropriate section of Form 5.

If patient is unable to fill in and return forms, CRA will obtain information on the following data over telephone:

- acute toxicity information on day 7 and day 14 after the first day of re-irradiation (see Appendix V)
- minimum pain and analgesic scoring (complete appropriate sections on the corresponding Form 5 if Brief Pain Inventory questionnaire cannot be completed)

Bone metastases-related events prompting hospital admission will be recorded. Investigator will determine whether bone-related events correspond to re-irradiation area.

8.5 Other Events

Each of the following events will be considered "single-occurrence"; i.e. once the event occurred, there is NO need to check again in a subsequent follow up visit/telephone call. This information is asked for on the Form 5.

- changes in chemotherapy
- changes in hormone therapy
- any surgical intervention at the re-irradiated site
- any pathological fracture at the re-irradiated site
- any spinal cord compression at the re-irradiated site
- date of death (Form 6)

8.6 Study Duration

The on-study period is from randomization to 12 months after re-irradiation or death, whichever occurs sooner. Data will be collected only during the 12-month study period.

8.7 Withdrawals or Dropouts

Patients may be withdrawn from the study by the investigator at any time should it be detrimental for the patient to continue. Patients may choose to be withdrawn from the study at any time without prejudice to their subsequent treatment.

If the patient is withdrawn before completing their protocol treatment, the time and reason for withdrawal must be recorded in section 6 of the Form 4. Every effort must be made to complete all study assessments on patients who withdraw.

All "withdrawn" patients will be included in the study arm to which they were assigned.

9.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

9.1 Evaluability

9.1.1 *Evaluable for adverse events*: All patients will be evaluable for adverse events from the time of their first fraction of radiation.

9.1.2 *Evaluable for response*: All patients who have received at least one fraction of radiation and have completed the Brief Pain Inventory at baseline and follow-up will be considered evaluable for response at month 2.

9.1.3 *Evaluable for quality of life assessment*: All patients who have completed the quality of life questionnaire (EORTC QLQ-C30) and one follow-up questionnaire are evaluable for quality of life.

9.2 Response

Complete Response is defined as a *worst pain score* of zero at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalents).

Partial Response is defined as any of the following:

- *Worst pain score* reduction of 2 or more at the treated site without analgesic increase.
- Opioid analgesic reduction of 25% or more from baseline without an increase in worst pain score.

9.3 Progression

Pain progression is defined as any of the following:

- An increase in worst pain score of 2 or more points above baseline at the treated site without reduction of analgesic use on any assessment.
- An increase of 25% or more in daily oral morphine equivalent compared with baseline, without reduction in baseline worst pain score.

9.4 Endpoints

All endpoints will be determined on intention-to-treat basis.

Primary endpoint: overall response rates (complete response and partial response) at 2 months from the start of treatment.

Secondary endpoints:
- Incidence of acute radiation related side effects.
- Reduction in functional interference by $\geq$ 2/10 following re-irradiation
- Freedom from progression as defined in section 9.3 above
- In-field pathological fractures and spinal cord compression
- EORTC QLQ-C30

10.0 SERIOUS ADVERSE EVENT REPORTING

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

TROG centres should refer to Appendix IX for additional information.

RTOG centres should refer to Appendix X for additional information.

The participating centre in France must refer to Appendix XII as additional reporting requirements apply.

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

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

10.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 10.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the literature for palliative radiotherapy.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

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

10.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported as follows:

Within 24 hours:	FAX preliminary Serious Adverse Event Form to: Dr. Ralph Meyer or Carolyn Wilson NCIC Clinical Trials Group Fax: 613-533-2941
Within 10 days:	Mail NCIC CTG Serious Adverse Event form (signed by the investigator and updated as much as possible) *Please use the NCIC CTG standard SAE Report*

10.3 Reporting Malignancies or Myeloid Dysplasia

Malignancies or myeloid dysplasia that are unexpected AND related to protocol treatment in the opinion of the investigator must be reported as Serious Adverse Events as described in Section 10.0 and 10.2, within 15 working days of when diagnosis is known to investigator. Other malignancies occurring or recurring during the trial, which are considered unrelated or expected, need not be reported.

10.4 Reporting Serious Adverse Events to Local Research Ethics Boards

NCIC CTG will notify all Investigators of all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol therapy from this trial. Investigators must notify their Research Ethics Boards (REBs) and file the report in their study files. The date of REB Submission for SAEs will need to be entered into the NCIC CTG trial SC.20 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:

- this letter must be either printed on institutional letterhead or contain the centre identification/REB name;
- the date of REB submission must be provided;
- this form must be signed by one of the approved participants (according to the Participants List) for this trial

The submission of these events to your ethics board should be done as soon as possible (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.

11.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

11.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity.
- Pain progression as defined in section 9.3.
- Request by the patient.
- Completion of therapy.

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

11.2 Therapy After Protocol Treatment is Stopped

Other treatment is to be given at the discretion of the treating physician.

12.0 CENTRAL REVIEW PROCEDURES

There will be no central review of radiotherapy fields.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Study Design

The primary objective is to compare the efficacy of pain relief after re-irradiation of symptomatic bone metastases with 8 Gy single fraction and with 20 Gy in 5 (or 8) fractions. The secondary objectives include determining the overall incidence of pain relief, time to pain progression, studying the relationship between pain relief after re-irradiation and the response to previous irradiation, determining the characteristics of group that does not respond to irradiation, monitoring the acute severe radiation related adverse effects, monitoring in-field pathological fractures and spinal cord compression and quality of life.

The study is designed as a non-inferiority equivalence study. Patients will be randomized with equal probability to each of the two arms (8 Gy in 1 fraction and 20 Gy in 5 or 8 fractions). The null hypothesis is there is a significant difference in primary endpoint between the two arms. The patients will be stratified according to single or multiple initial radiation dose, response to previous therapy and centre.

13.2 Primary Endpoint and Analysis

The overall response rate at two months after the first fraction of re-irradiation is the primary endpoint of this study. The overall response rate is defined as the sum of the complete response (CR) and partial response (PR) rates as assessed by the patient worst pain score and records of analgesic intake (see protocol section 9.2). The analysis will be on the intention-to-treat principle.

Analyses are scheduled at 1, 2 and 3 months after the first fraction of re-irradiation, however the result at 2 months will be considered the primary endpoint. A Chi-square analysis will be applied to the response rates between the two arms and the upper 95% confidence limit of the rate difference between the two arms will be calculated. If the rate difference is less than 10%, then the two treatment arms are considered of equal efficacy. The method of Mantel-Hanzeal Chi-square will be used for the stratified analysis.

13.3 Secondary Endpoints and Analysis

The overall incidence of pain relief after re-irradiation will be displayed as a proportion and confidence limits calculated.

Logistic regression will be used to assess the relationship between response to initial and re-irradiation and to determine which factors are related to the non-response.

Data from the functional index on Quality of Life will be analyzed according to the standard NCIC CTG approach. Patients will be classified as ‘improved’, ‘stable’ and ‘worsened’. Data from the functional index of the Brief pain Inventory will be used to classify patients as ‘responders’ or ‘non-responders’. These results will be analyzed as categorical data with Chi-square method.

The incidence of acute severe adverse effects for each arm will be calculated with its 95% confidence interval and compared by means of Chi-square analysis.

13.4 Sample Size and Duration of Study

The sample size was determined based on the non-inferiority design. Assuming response rate on the multiple fraction arm is 70%, 260 patients would be required in each treatment arm to have 80% power to exclude, with a one sided alpha of 0.05, a response rate of 60% or less in the single fraction radiation group. With an inevaluability rate estimate of 20%, it was determined that 650 patients (325 for each treatment arm) would be randomized to the study. If at the time of the interim analysis, the overall response rate is obviously different from the pre-estimated 70%, an adjustment of sample size may be necessary. Estimated study duration was 3 years.

When the planned interim analysis was performed (see section 13.6), the overall two-month response rate was significantly different from the projected rate of 70% and the inevaluability and attrition rate was determined to be 32.4%. Accordingly, the sample size was revised to 850 patients to accommodate these differences. This sample size provides 80% power to exclude that the response rate in the single fraction arm is 10% or less than the multiple fraction arm.

As it is possible that the inevaluability and attrition rate may decrease as the trial progresses, an attempt will be made to avoid accruing more patients than required to determine the results of the study. As such, the inevaluability and attrition rate will be evaluated for all patients when 650 patients (the original study sample size) have been evaluated for the primary endpoint (two months after study radiation treatment). If data permit, a request will be made to the Data Safety Monitoring Committee to advise the trial committee whether there remains a need to continue accrual beyond the number reached at the time the results of this additional analysis become available.

With a sample size of 850 patients, it is estimated that the trial will complete accrual approximately 8 years after central activation.

13.5 Safety Monitoring

The incidence of acute severe adverse events will be summarized by treatment arms and presented every six months to the NCIC CTG Data Safety Monitoring Committee and the frequency of adverse events will also be reported annually at the investigator meetings.

13.6 Interim Analysis

An interim analysis is planned for the study to ensure that the single fraction arm is not inferior. The interim analysis will be applied when 260 patients can be assessed for the primary endpoint, i.e., response at 2 months. The stopping boundary for the interim analysis will be 0.005, which will allow the final analysis to be conducted at an alpha level of 0.048, using the O'Brien-Fleming type boundaries. *[Armitage 1994, O'Brien 1979, Jones 1996]*

13.7 Quality of Life Analysis

The standard NCIC CTG QOL data analysis will be conducted, that is, the change of QOL scores will be summarized in categories and an improvement rate generated. We assume that approximately one half of the patients will participate in the QOL analysis. If the rate in improvement in QOL in the reference group is 0.6, with a sample size of 400, we will be able to exclude a 12.2% lower rate of improvement in the test group at an alpha of 0.05 and 80% power.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc

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

- The first author will generally be the chair of the study.
- Members of the trial committee will also generally be co-authors.
- A limited number of the members of the NCIC Clinical Trials Group central office 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.

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

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

14.2 Responsibility for Publication

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

14.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the NCIC CTG physician coordinator, senior biostatistician and 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.

AMENDMENT #2: 2005-MAR-01; ADMIN UPDATE #1: 2006-SEP-20; AMENDMENT #5: 2009-AUG-07

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

TROG centres should refer to Appendix IX for additional information.
RTOG centres should refer to Appendix X for additional information.

The participating centre in France should refer to Appendix XII for additional information.

15.1 Institution Eligibility for Participation

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

15.2 Investigator Qualifications

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

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

For investigators participating through other cooperative or coordinating groups, all applicable regulations pertaining to investigator qualifications must be adhered to.

15.3 REB (Research Ethics Board) Approval for Protocols

This section applies to Canadian centres participating through NCIC CTG only. All other centres, including those participating through other cooperative or coordinating groups must adhere to the appropriate regulations established by those groups and/or the appropriate national regulations.

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

Initial Approval

Member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB. A completed NCIC CTG Confirmation of Initial Ethical Approval form must be submitted to document the REB was properly constituted and there were no conflicts of interest in the REB approval process.

Annual Re-Approvals

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

AMENDMENT #2: 2005-MAR-01; ADMIN UPDATE #1: 2006-SEP-20; AMENDMENT #5: 2009-AUG-07

Amendments/Revisions

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

REB Refusals

If an REB refuses to approve this protocol (or an amendment/administrative update to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s) for the refusal.

Serious Adverse Events and Safety Updates

During the course of the study serious adverse events or safety updates may be sent to you for reporting to your REB. The date of REB submission for these documents will need to be entered into the NCIC CTG trial SC.20 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

15.4 Informed Consent

This section applies to Canadian centres participating through NCIC CTG only. All other centres including those participating through other cooperative or coordinating groups must adhere to the appropriate regulations established by those groups and/or the appropriate national regulations.

Informed Consent Document

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

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

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

Consent Process/Patient Eligibility

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

AMENDMENT #2: 2005-MAR-01; ADMIN UPDATE #1: 2006-SEP-20; AMENDMENT #5: 2009-AUG-07

15.5 Retention of Patient Records and Study Files

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

NCIC CTG will notify all the trial investigators/institutions when trial related records no longer need to be retained.

15.6 Centre Performance Monitoring

Ineligibility and timeliness of data submission are monitored for all centres and the results are reported in the Centre Performance Index. There are minimum standards for performance.

Forms are to be submitted according to the schedule in Appendix III (Documentation for Study).

15.7 On-Site Monitoring/Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, NCIC CTG site monitoring may be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The auditors will require access to patient medical records to verify the data, as well as essential document binders, standard operating procedures (including electronic information) and ethics documentation.

15.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, can be found in Appendix III (or Appendix IX for TROG patients).

15.9 Source Document Requirements for Telephone Calls

If the CRA telephones the patient to obtain information that is required by the study, a note including the date, caller, and summary of the conversation should be prepared and filed in the patient's medical records.

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AMEND #2: 2005-MAR-01 ; #4: 2006-MAR-24; ADMIN UPDATE #1: 2006-SEP-20

APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Prior to randomization	Day 1 of RT	Day 7	Day 14	Every month for 6 months	9 mths	12 mths
Physical							
Baseline Characteristics	X						
Karnofsky Performance Status	X						
Radiology							
Radiological evidence of bone metastases	X						
Other Investigations							
Baseline Brief Pain Inventory♦	X	X**					
Follow-up Brief Pain Inventory			X	X	X	X	X
Other Events (Form 5)					X	X	X
Toxicity							
Acute toxicity questionnaire			X	X			
Late effects of radiation (Form 5)					Months 3, 4, 5 and 6	X	X
Quality of Life*							
EORTC QLQ-C30	X	X***			X		

* Canadian, Dutch, French and RTOG centres only.
** Only if more than 7 days since randomization or if a new analgesic regimen has been started since randomization.
*** Only if more than 7 days since randomization.
♦ Worst pain score used to determine eligibility must come from the baseline Brief Pain Inventory completed prior to randomization.

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.

AMEND #1: 2004-MAY-20; #2: 2005-MAR-01 ; #4: 2006-MAR-24; ADMIN UPDATE #1: 2006-SEP-20

APPENDIX III - DOCUMENTATION FOR STUDY

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

Form	To be Completed	Due in Central Office	Supporting Documentation Required
Form 1 Eligibility Checklist/ Initial Evaluation	prior to randomization	within 6 weeks of randomization	patient consent form (Canadian patients only)
Form 4 Radiotherapy Report	at the end of radiotherapy	within 6 weeks of the completion of treatment	none
Form 5 Follow-up Report	every month for 6 months after RT, then at 9 and 12 months post RT	within 8 weeks of the date the patient was seen at the clinic, or telephone contact was made with the patient	none
Form 6 Final Report	at the time of the patient's death	within 8 weeks of the patient's death	autopsy report if done
Serious Adverse Event Report Form*	at time of the event	within 10 working days of the event	documentation of the event
Quality of Life**	prior to randomization, day 1 of RT (only if > 7 days since rand.), and months 1-6 after RT	submit with Form 1, Form 4 or Form 5, as appropriate	none
Brief Pain Inventory Baseline Questionnaire***	prior to randomization, day 1 of RT (only if > 7 days since rand. or new analgesic regimen started)	submit with Form 1 or Form 4, as appropriate	none
Brief Pain Inventory Follow-Up Questionnaire	day 7, 14, months 1 - 6, 9 and 12	submit with Form 5	none
Acute Toxicity Questionnaire	at day 7 and day 14 after RT	submit with Form 5	none

* See section 10.0 Serious Adverse Event Reporting for details.
** Canadian, Dutch, French and RTOG patients only .
*** Worst pain score used to determine eligibility must come from the baseline Brief Pain Inventory completed prior to randomization.

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS, VERSION 3.0

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

APPENDIX V - BRIEF PAIN INVENTORY, ACUTE TOXICITIES

On the following pages are three questionnaires:

1. BASELINE Brief Pain Inventory

   To be completed prior to randomization. The worst pain score used to determine eligibility must come from this questionnaire. An additional baseline BPI will be completed on day of first fraction (Day 1 of RT) if the interval from randomization to re-irradiation is greater than 7 days or if a new analgesic regimen is started between randomization and re-irradiation.

2. FOLLOW-UP Brief Pain Inventory

   To be completed on Day 7, Day 14 after the first fraction of radiation, Months 1, 2, 3, 4, 5, 6, 9 and 12 after the first fraction.

3. Acute Toxicities

   To be completed on Day 7 and Day 14 after the first fraction of radiation. (Day 1 = day of first fraction of radiation on either arm).

NCIC CTG Trial: SC.20

This page to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _____ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Intergroup Patient Serial No: _____ *(if applicable)* Intergroup Centre Code: _____ *(if applicable)*

Institution: _____ Investigator: _____

Scheduled time to obtain brief pain inventory: please check (✓)

☐ Prior to randomization ☐ Day 1 of RT if randomization > 7days or new analgesic regimen started

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

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

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

Comments: _____

_____

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

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

NCIC CTG use only – Log as BPI

Logged: _____	Study Coord: _____	RA: _____	Phy:	Data Ent'd:	Verified:
_____ - ___ - ___	_____ - ___ - ___	_____ - ___ - ___	_____	_____	_____

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

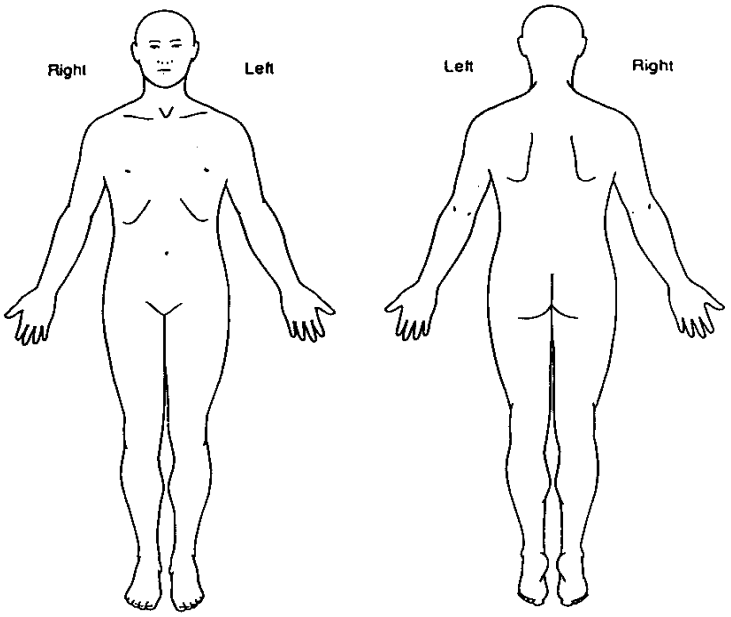
AMENDMENT #2: 2005-MAR-01

BRIEF PAIN INVENTORY - BASELINE QUESTIONNAIRE

Patient Initials _____ Date _____

- Please take a moment to complete this questionnaire designed to find out how much pain you are having and how the pain is affecting you.
- Please check to make sure that you have answered all questions.
- If you need assistance, please request it from the medical staff or if someone other than the medical staff helps you to complete the questions, please note who helped you and the reason, e.g. poor eyesight, etc.

1. On the diagram, shade in the areas where you feel pain.
   Put an X on the area that hurts the most.



I was assisted by:

_____

Reason for assistance:

_____

_____

2. Please rate your pain by circling the one number that best describes your pain at its WORST in the past 3 days:

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

3. Please rate your pain by circling the one number that best describes your pain on AVERAGE in the past 3 days:

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

4. Please rate your pain by circling the one number that best describes your pain RIGHT NOW:

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

Please continue on next page

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

AMENDMENT #1: 2004-MAY-20; AMENDMENT #2: 2005-MAR-01

5. Please write ALL the regular pain medications you have been taking during the past 24 hours.
(If using a fentanyl patch, or "Duragesic", please indicate strength of each patch.)

Name of Medication	Strength (mg/pill)	Route of Administration*	Number of pills / Administrations per day	NCIC Use Only
* Possible routes: oral / intravenous / subcutaneous / rectal / patch / sublingual (under tongue) / intramuscular				

Please write ALL the breakthrough pain medications you have been taking during the past 24 hours.

Name of Medication	Strength (mg/pill)	Route of Administration*	Number of pills / Administrations per day	NCIC Use Only
* Possible routes: oral / intravenous / subcutaneous / rectal / patch / sublingual (under tongue) / intramuscular				

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

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

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

AMENDMENT #1: 2004-MAY-20

7. Circle the one number that describes how, during the past 3 days, pain has interfered with your:

A.	General Activity											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
B.	Mood											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
C.	Walking ability											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
D.	Normal Work (includes both work outside the home and housework)											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
E.	Relations with other people											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
F.	Sleeping											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
G.	Enjoyment of life											
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes

Comments: _____

_____

_____

AMENDMENT #1: 2004-MAY-20; AMENDMENT #2: 2005-MAR-01

BRIEF PAIN INVENTORY - FOLLOW-UP QUESTIONNAIRE

NCIC CTG Trial: SC.20

This page to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _____ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Intergroup Patient Serial No: _____ *(if applicable)* Intergroup Centre Code: _____ *(if applicable)*

Institution: _____ Investigator: _____

Scheduled time to obtain brief pain inventory: please check (✓)

☐ Day 7 ☐ Day 14

☐ mth 1 ☐ mth 2 ☐ mth 3 ☐ mth 4 ☐ mth 5 ☐ mth 6 ☐ mth 9 ☐ mth 12

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

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

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

Comments: _____

_____

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

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

REMINDER for CRA:
Shade in blue the area where the patient was treated by radiation, on the figures on page 1, before giving this to the patient.
If the patient was re-irradiated at more than one site, only mark the chosen study site on the diagrams.

NCIC CTG use only – Log as BPIF

Logged: _____	Study Coord: _____	RA: _____	Phy:	Data Ent'd:	Verified:
_____ - ___ - __	_____ - ___ - __	_____ - ___ - __	_____	_____	_____

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

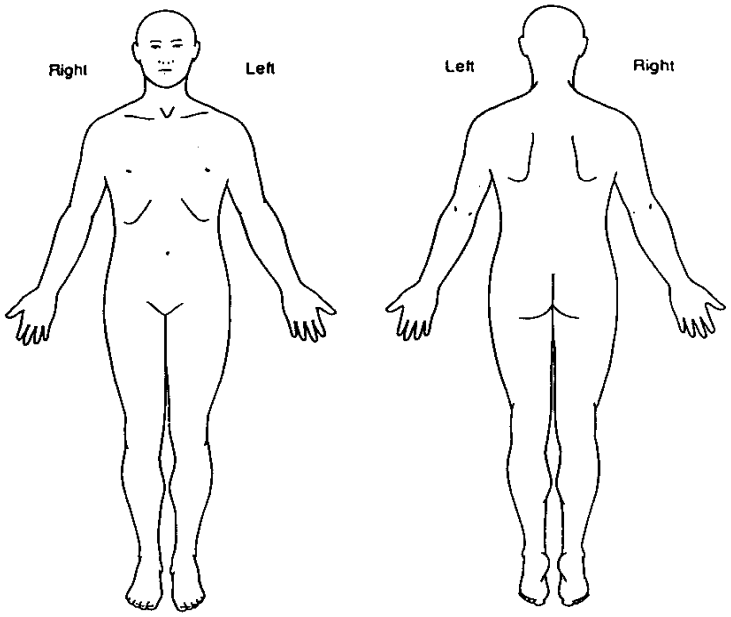
AMENDMENT #2: 2005-MAR-01

BRIEF PAIN INVENTORY - FOLLOW-UP QUESTIONNAIRE

Patient Initials _____ Date _____

- Please take a moment to complete this questionnaire designed to find out how much pain you are having and how the pain is affecting you.
- Please check to make sure that you have answered all questions.
- If you need assistance, please request it from the medical staff or if someone other than the medical staff helps you to complete the questions, please note who helped you and the reason, e.g. poor eyesight, etc.

1. The blue shaded area indicates where your pain was treated by Radiation.



I was assisted by:

_____

Reason for assistance:

_____

_____

2. Please rate your pain by circling the one number that best describes your pain at its WORST in the area treated by Radiation during the past 3 days:

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

3. Please rate your pain by circling the one number that best describes your pain on AVERAGE in the area treated by Radiation during the past 3 days:

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

4. Please rate your pain by circling the one number that best describes your pain right now in the area treated by Radiation:

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

Please continue on next page

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

AMENDMENT #1: 2004-MAY-20; AMENDMENT #2: 2005-MAR-01

5. Please write ALL the regular pain medications you have been taking during the past 24 hours.
(If using a fentanyl patch, or "Duragesic", please indicate strength of each patch.)

Name of Medication	Strength (mg/pill)	Route of Administration*	Number of pills / Administrations per day	NCIC Use Only
* Possible routes: oral / intravenous / subcutaneous / rectal / patch / sublingual (under tongue) / intramuscular				

Please write ALL the breakthrough pain medications you have been taking during the past 24 hours.

Name of Medication	Strength (mg/pill)	Route of Administration*	Number of pills / Administrations per day	NCIC Use Only
* Possible routes: oral / intravenous / subcutaneous / rectal / patch / sublingual (under tongue) / intramuscular				

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

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

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

AMENDMENT #1: 2004-MAY-20

7. Circle the one number that describes how, during the past 3 days, pain has interfered with your:

A. General Activity												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
B. Mood												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
C. Walking ability												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
D. Normal Work (includes both work outside the home and housework)												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
E. Relations with other people												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
F. Sleeping												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes
G. Enjoyment of life												
	Does not interfere	0	1	2	3	4	5	6	7	8	9	10 Completely interferes

Comments: _____

_____

_____

AMENDMENT #1: 2004-MAY-20; AMENDMENT #2: 2005-MAR-01

ACUTE TOXICITIES QUESTIONNAIRE

NCIC CTG Trial: SC.20

This page to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _____ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Intergroup Patient Serial No: _____ *(if applicable)* Intergroup Centre Code: _____ *(if applicable)*

Institution: _____ Investigator: _____

Scheduled time to obtain acute toxicities questionnaire: please check (✓)

☐ Day 7 ☐ Day 14 (after radiation)
(Day 1 = day of single radiation or 1st day of multiple fractions)

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

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

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

Comments: _____

_____

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

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

NCIC CTG use only

Logged: _____	Study Coord: _____	RA: _____	Phy:	Data Ent'd:	Verified:
_____ - ___ - ___	_____ - ___ - ___	_____ - ___ - ___	_____	_____	_____

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

AMENDMENT #2: 2005-MAR-01

ACUTE TOXICITIES QUESTIONNAIRE

Patient Initials _____ Date _____

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

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
1. Have you lacked appetite?	1	2	3	4
2. Have you felt nauseated?	1	2	3	4
3. Have you vomited?	1	2	3	4
4. Did you take any medication for nausea or vomiting?	1	2	3	4
5. Have you had diarrhea?	1	2	3	4
6. Did you take any medication for diarrhea?	1	2	3	4
7. Did you have a skin rash or reddening in the area treated with radiotherapy?	1	2	3	4

AMEND #1: 2004-MAY-20; #2: 2005-MAR-01; ADMIN UPDATE #1: 2006-SEP-20

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Quality of Life to be completed by Canadian, Dutch, French and RTOG centres only.

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 and 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 new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and toxicity data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

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

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

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

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

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

2. Pretreatment Assessment

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

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

3. Assessments During Treatment

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

4. Assessments During Follow-up

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

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

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

5. What If . . .

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

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

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

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

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

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

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

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

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

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

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

6. Waiving the Quality of Life Component

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

7. Unwillingness to Complete Quality of Life Questionnaire

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

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

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

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AMENDMENT #1: 2004-MAY-20; AMENDMENT #2: 2005-MAR-01; ADMIN UPDATE #1: 2006-SEP-20

Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: SC.20

(to be completed by Canadian, Dutch, French and RTOG patients only)

This page to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _____ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Intergroup Patient Serial No: _____ *(if applicable)* Intergroup Centre Code: _____ *(if applicable)*

Institution: _____ Investigator: _____

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

☐ Prior to randomization ☐ Day 1 of RT if randomization > 7 days

After radiation treatment:

☐ month 1 ☐ month 2 ☐ month 3 ☐ month 4 ☐ month 5 ☐ month 6

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

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

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

Comments: _____

_____

_____

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

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

NCIC CTG use only

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

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

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire SC.20

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

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not At All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

Please go on to the next page

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

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

Please go on to the next page

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

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

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

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

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

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

Thank you.

APPENDIX VII - NON-OPIOID ANALGESIA / ADJUVANT ANALGESIA

NB: Report all drug names by GENERIC names.

Record only opioid pain relief ingredients. For example, “Oxycocet 1 tablet” should be recorded as “oxycodone 5 mg”.

DRUG CLASS	GENERIC NAME	COMMON NAMES
Acetaminophen / paracetamol	Acetaminophen / paracetamol	Tylenol
Steroid	Dexamethasone	Dexasone, Decadron
	Prednisone	Prednisone
Non-Steroidal anti-inflammatory	ASA	Aspirin
	Ibuprofen	Advil, Motrin
	Naproxen	Naprosyn
	Diclofenac	Voltaren, Arthrotec
	Indomethacin	Indocid
	Sulindac	
	Piroxicam	Feldene
	Ketoprofen	Orudis, Orafin, Oruvail
	ketorolac	Toradol
	Nabumetone	Relafen
	etodolac	Ultradol
COX-2 inhibitors	Celecoxib	Celebrex
	Rofecoxib	Vioxx
	Meloxicam	Mobicox
Tricyclics Anti-depressants	Amitriptyline	Elavil, Triavil
	Desipramine	Norpramin
Anticonvulsants	Carbamazepine	Tegretol
	Gabapentin	Neurontin
	Phenytoin	Dilantin
Oral local anesthetics	Mexilitine	
	Flecainide	
Bisphosphonates	Clodronate	Bone Phos
	Pamidronate	Aredia
	Ibandronate	
	Zoledronic acid	Zometa

APPENDIX VIII - SAMPLE CONSENT FORMS

ENGLISH Sample Consent Form

Please note that this sample language does not preempt or replace local REB review and approval. Investigators are required to provide the local REB with a copy of its sample language along with the language intended for local use. Local REBs are required to weigh the unique risks, constraints, and population considerations as a condition of any approval.

A PHASE III INTERNATIONAL RANDOMIZED TRIAL OF SINGLE VERSUS MULTIPLE FRACTIONS FOR RE-IRRADIATION OF PAINFUL BONE METASTASES

NCIC CTG SC.20

Le formulaire de consentement est disponible en français sur demande.

***Note to centre*: If an REB approved French consent is not used at your institution you should remove the above statement.**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked if you would like to take part in this study because you have painful bone metastases from a previously diagnosed cancer. The usual treatment for your disease is treatment with drugs and radiation therapy. Although pain is initially reduced with radiation therapy, in a number of patients the pain returns. In some other patients, first time radiation may not improve the pain. There is some evidence that giving radiation a second time may help with both of these situations. We are interested in whether re-irradiation (radiation to the same site of previous radiation) will help with pain management.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to examine the effects of re-irradiation given in a single dose compared to re-irradiation given in multiple smaller doses on people with painful bone metastases. If you decide to take part in this study, you will only receive one of these treatments.

This research is being done because we do not know which of these two commonly-used treatments is better.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 850 people from Canada, the Netherlands, the UK, the U.S., France and Australia will take part in this study. It was originally expected that 650 patients would have to enter the study over three years with an additional year of follow-up to answer the research question. The Data Safety Monitoring Committee that oversees the study reviewed a statistical examination of the data part-way through the trial (May 2009). Based on this review, it is now estimated that 850 patients need to enter the trial to answer the research question. This means that patients will need to enter the trial for another two-and-a-half years with an additional year of follow-up before the study results are known.

WHAT IS INVOLVED IN THE STUDY?

Randomization (assignment to a group):

If you decide to participate you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A central statistical office will be called which will assign one of the treatments to you. Neither you nor your doctor can choose what group you will be in. You will have an equal chance of being placed in either group.

You will be told which treatment you are to get.

Treatment:

Group 1: Single Dose of Radiotherapy

If you are randomized to Group 1 you will receive radiation in a relatively higher dose for one time only. The treatment will take several minutes.

Group 2: Multiple Smaller Doses of Radiotherapy

If you are randomized to Group 2 you will receive smaller doses of radiation given once per day for 5 days. If you need re-treatment of the spine and/or whole pelvis and your previous treatment was given in multiple fractions, the treatment will be in even smaller amounts of radiation, but for 8 days. The treatment will take several minutes per day for 5 or 8 days.

Procedures and Medical Tests:

The following tests may be done to make sure that you are eligible for this study. None of these tests are experimental. They are required to evaluate bone metastases.

- physical examination
- x-rays of your bones
- bone scan
- CT scan
- MRI

Pain Questionnaire:
You will be asked to complete this questionnaire before you are randomized into a study group, on day 7 and day 14 after the start of radiation and then at 1, 2, 3, 4, 5, 6, 9 and 12 months after your treatment is completed, to find out how much pain you are having and how the pain is affecting you. You will also be asked to fill out this questionnaire before you start your re-irradiation treatment if more than seven days pass between the day you are randomized for the study and the day you start your re-irradiation treatment. It usually takes about 10 minutes to complete this questionnaire.

Acute Toxicities Questionnaire:
Patients sometimes report that they have symptoms such as nausea or diarrhea following radiation - you will be asked to complete this questionnaire on day 7 and day 14 after the start of radiation to indicate whether or not you have experienced symptoms and to what extent. It usually takes 5-10 minutes to complete this questionnaire.

Quality of Life Questionnaire (for Canadian, Dutch, French and U.S. participants only):

You will be asked to complete a questionnaire before you are randomized into a study group. If you speak or read English, French or Spanish and you are physically able to complete the questionnaire, you must do so to be enrolled in the study. You will be asked to fill out this questionnaire again at 1, 2, 3, 4, 5 and 6 months after your treatment is completed, to understand how your treatment and illness affect your quality of life. You will also be asked to fill out this questionnaire before you start your re-irradiation treatment if more than seven days pass between the day you are randomized for the study and the day you start your re-irradiation treatment. This questionnaire asks about how you are feeling and takes about 10 minutes to complete. Some of the questions are personal; you can refuse to answer these if you wish. The information you provide is for research purposes only and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions—if you wish them to know this information please bring it to their attention.

HOW LONG WILL I BE IN THE STUDY?

If you are randomized to Group 1, your treatment with re-irradiation will be given in one day. If you are randomized to Group 2 your treatment with re-irradiation will be given over 5 days or 8 days if treatment involves the spinal cord and/or whole pelvis and your previous treatment to this area was given in multiple fractions. The researchers can take you off the study treatment early for reasons such as:

- The treatment does not work for you.
- You are unable to tolerate the study treatment.
- New information shows that the study treatment is no longer in your best interest.
- Your doctor no longer feels this is the best treatment for you.
- The sponsor decides to stop the trial.

You can choose not to take part in this study or stop taking part at any time and your doctor will continue to treat you with the best means available. If you decide to stop participating in the study, we encourage you to talk to your doctor first.

No matter which group you are randomized to, and even if you stop treatment early, we would like to keep track of your health for 12 months to look at the long-term effects of the study treatments.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects listed below. You should discuss these with your doctor. As with any experimental treatment additional unexpected and sometimes serious side effects are a possibility.

Your doctor will watch you closely to see if you have side effects. When possible other drugs will be given to you to make side effects less serious and uncomfortable. Many side effects go away shortly after radiation is stopped but in some cases side effects can be serious, long-lasting or permanent.

AMENDMENT #1: 2004-MAY-20; #2: 2005-MAR-01; #3: 2005-JUL-04; AMENDMENT #4: 2006-MAR-24

Radiation Therapy Side Effects:

Your chances of experiencing different side effects from radiation therapy depend on many different things including the area of the body being treated, the total amount of radiation that area has received, how much radiation is given each day, the type of radiation used and if you are receiving chemotherapy at the same time as your radiation therapy. Some general side effects (they may be experienced no matter which area of the body the re-irradiation is given to) as well as some side effects for different areas of the body are listed below. Your doctor will discuss with you how these side effects relate to you and your radiotherapy.

It is not known if patients in one of the treatment groups are more likely to experience side effects than patients in the other treatment group.

General side effects:

No matter which area of the body is treated, you may experience fatigue (feeling tired). This usually goes away a few weeks after the end of radiotherapy.

Another side effect that may happen is changes in the skin at the site of treatment. The skin in the area of radiation may become red or irritated or it may look tanned or you may develop a rash. It may also become very dry in this area a few weeks after radiation therapy. Skin changes usually go away a few weeks after radiotherapy stops, although in some cases the skin in the treated area may remain a slightly different colour than it was before, it may be more sensitive to sunlight or it may feel slightly thicker than before.

You may also experience “pain flare”, a temporary increase in pain in the area treated with radiation, during the first 1-2 days following single fraction treatment or during the first 3-4 days of multiple fraction treatment.

Generally, long term effects of radiation in the treatment of bone metastases include damage to organs, but the risk of developing symptoms related to these changes is very small.

Possible side effects from radiotherapy to the head and neck:

If you are receiving re-irradiation to bones in your head and/or neck area, some of that radiation may affect other body parts in this area. It could irritate the lining of your mouth and affect the glands that produce saliva. This means that you might experience redness or sores in the mouth or have a sore throat. You could also experience dry mouth, thickened saliva, changes in taste, difficulty swallowing, nausea and loss of appetite. The way things smell may also change. These side effects are often mild and usually go away after radiation treatment stops, but in some cases side effects like dry mouth may continue.

Possible side effects from radiotherapy to the chest:

If you are receiving re-irradiation to bones such as the ribs, shoulder, collarbone or certain parts of the spine, some of that radiation may affect some of the organs in your chest. The radiation may irritate the lining of your esophagus (swallowing tube), which could make it painful or difficult to swallow. You may also experience nausea, loss of appetite, vomiting or diarrhea. If the radiation affects the lungs, you may develop a slight fever, cough or shortness of breath a month or more after your re-irradiation treatment is over. If you develop these symptoms, they are usually temporary and mild, but in a few cases they may continue.

Possible side effects from radiotherapy to the abdomen and pelvis:

If you are receiving re-irradiation to bones such as the pelvis, hip, tailbone, or certain parts of the spine, you may experience loss of appetite, nausea, heartburn, cramping, vomiting or diarrhea. If you experience these symptoms, they are often mild and usually start soon after your first radiation treatment and end soon after your course of radiation is complete. If your bladder is affected, you may have difficulty urinating, need to urinate frequently, or have discomfort while urinating. This is usually temporary and may not start until a few weeks after your radiation treatment. There may be some irritation of the rectum if it is affected by your radiation treatment. These symptoms are usually mild. If you are a woman, you may stop menstruating and have other symptoms of menopause such as vaginal itching, burning or dryness.

Possible side effects from radiotherapy to the spine:

If you are re-irradiated to the spine, the radiation may affect your spinal cord. Developing symptoms related to this is uncommon. These symptoms are usually very mild and include changes in how temperature is experienced, weakness and clumsiness on one or both sides of the body; however, these symptoms may be a sign that the cancer is acting on your spinal cord. It is important that you report new symptoms such as weakness in your legs or numbness or tingling down your legs to your doctors.

Possible side effects from radiotherapy to the extremities only:

Because it is unusual for other organs to receive radiation when the arms and legs receive radiotherapy, patients usually experience few side effects, primarily skin changes. The risk of fracture associated with radiation therapy is 2 – 4 %.

Reproductive Risks:

Since radiation can harm a fetus, you should not become pregnant or father a baby while on this study. An effective method of birth control should be used while you are on study treatment. Ask about counselling and more information about preventing pregnancy. You should not nurse your baby while on this study.

Depending on your age, the site of radiation and the dose, your re-irradiation treatment may affect your ovaries or testes and impair your ability to have children. Your doctor will discuss these risks with you.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you other than the potential pain relief from re-irradiation. We hope the information learned from this study will help other patients with painful bone metastases in the future.

WHAT OTHER OPTIONS ARE THERE?

If you decide not to take part in this study you may still receive radiation treatment. Your doctor will discuss other treatment options with you. These may include:

- Pain medications
- other chemotherapy
- hormonal therapy or bisphosphonates
- surgery
- no therapy at this time

Please talk to your doctor about the known benefits and risks of these other treatment options. Your doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

WHAT ABOUT CONFIDENTIALITY?

Every effort will be made to keep your personal information confidential.

Qualified representatives of the following organizations may inspect your medical/study records for quality assurance and data analysis:

- NCIC Clinical Trials Group (NCIC CTG), the research group coordinating this study
- The research ethics committee who oversees the ethical conduct of this study in your hospital/clinic

Qualified representatives of the following organizations may receive information from your medical/study records for quality assurance and data analysis:

- NCIC Clinical Trials Group (NCIC CTG), the research group coordinating this study
- The research ethics committee who oversees the ethical conduct of this study in your hospital/clinic
- Trans-Tasman Radiation Oncology Group
- Cancer Research UK and UCL Cancer Trials Centre
- Dutch Bone Metastases Group
- Radiation Therapy Oncology Group
- Département de Recherche Clinique et du Développement, Assistance Publique Hôpitaux de Paris et Hôpital Henri Mondor, Créteil Cedex, France

This may contain information that could potentially identify you, and includes:
- test results
- reports of operations
- x-rays or other body scan reports
- reports about your treatment and side effects

The organizations listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Identifying information will be kept behind locked doors. Identifying information will never be included in a publication of the research.

The information collected during this study will be used in analyses and will be published and/or presented to the scientific community at meetings and in journals.

It is expected that the study results will be published in 2013. Your study doctor will be informed of the results of the study once they are known.

WHAT ARE THE COSTS?

The study radiation treatment will be given to you free of charge. You will not be paid for taking part in this study. Taking part in this study may result in added costs to you.

In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not waive any of your legal rights for compensation by signing this form.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Deciding not to take part or deciding to leave the study later will not result in any penalty or any loss of benefits to which you are entitled. Your doctor will discuss further treatments with you and continue to treat your cancer with the best means available.

A Data Safety Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.

We will tell you in a timely manner about new information that may affect your health, welfare, or willingness to stay in this study.

You will be given a copy of this signed and dated consent form.

CONFLICT OF INTEREST

Note to centres: Please include details of any actual or potential conflict of interest concerning this study.

This centre is receiving funds from the NCIC Clinical Trials Group to help offset the costs of conducting this research. NCIC CTG is a non-profit research group.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions about taking part in this study or if you suffer a research-related injury you can talk to your doctor. Or, you can meet with the doctor who is in charge of the study at this institution. That person is:

_____ _____

Name Telephone

If you would like advice regarding your rights as a patient or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is:

_____ _____

Name Telephone

AMENDMENT #2: 2005-MAR-01; AMENDMENT #4: 2006-MAR-24

SIGNATURES

My signature on this consent form means the following:

- The study has been fully explained to me and all of my questions have been answered,
- I understand the requirements and the risks of the study,
- I authorize access to my medical records as explained in this consent form, and
- I agree to take part in this study.

_____ _____
Signature of Patient Date

_____ _____
Signature of Investigator Date

Was the patient assisted during the consent process in one of the ways listed below?

☐ Yes ☐ No

If yes, please check the relevant box and complete the signature space below:

☐ The consent form was read to the patient, and the person signing below attests that the study was accurately explained to, and apparently understood by, the patient.

☐ The person signing below acted as a translator for the patient, during the consent process.

_____ _____
Signature of Person Assisting in the Consent Discussion Date

Please note:
More information regarding the assistance provided during the consent process should be noted in the medical record for the patient if applicable.

FRENCH Sample Consent Form

Exemple de formulaire de consentement en FRANÇAIS

Veuillez noter que cet exemple de formulation n'annule ni ne remplace l'examen par le CER local et son approbation. Les chercheurs sont tenus de communiquer au CER local une copie dans la présente langue et dans la langue locale prévue. Les CER locaux doivent évaluer les risques et les contraintes spécifiques, ainsi que des considérations démographiques, comme condition de toute approbation.

ÉTUDE RANDOMISÉE INTERNATIONALE DE LA PHASE III PORTANT SUR L'UTILISATION DE FRACTIONS SIMPLES OU MULTIPLES POUR UNE NOUVELLE IRRADIATION DE MÉTASTASES OSSEUSES DOULOUREUSES

NCIC GEC SC.20

An English version of this consent form is available upon request.

***Note** : Si votre établissement n'utilise PAS le formulaire de consentement en français approuvé par le CER, il faut biffer cette phrase.*

Cette étude est une étude clinique (type d'étude de recherche). Les études cliniques portent seulement sur les patients qui choisissent d'y participer. Veuillez prendre le temps nécessaire pour vous décider. Discutez-en avec vos amis et les membres de votre famille.

Nous vous demandons si vous voulez participer à cette étude parce que vous avez des métastases osseuses douloureuses causées par un cancer diagnostiqué plus tôt. On traite habituellement votre maladie au moyen de médicaments et de la radiothérapie. Même si la radiothérapie atténue la douleur au début, elle réapparaît chez de nombreux patients. Chez d'autres, il se peut qu'une première irradiation n'atténue pas la douleur. Des données probantes indiquent qu'une deuxième irradiation peut aider dans ces deux cas. Nous voulons déterminer si une nouvelle irradiation (au même endroit que la précédente) aidera à gérer la douleur.

POURQUOI EFFECTUER CETTE ÉTUDE?

Cette étude vise à analyser les effets qu'une nouvelle irradiation administrée en une seule dose comparativement à ceux d'une nouvelle irradiation administrée en multiples doses plus petites a sur les personnes qui ont des métastases osseuses douloureuses. Si vous décidez de participer à l'étude, vous recevrez un seul de ces traitements.

Nous effectuons cette recherche parce que nous ne savons pas lequel de ces deux traitements d'usage courant est le meilleur.

COMBIEN DE PERSONNES PARTICIPERONT À L'ÉTUDE?

Quelque 850 personnes du Canada, des Pays-Bas, du R.-U., des É.-U., de la France et de l'Australie participeront à l'étude. On s'attendait à l'origine à ce que 650 patients doivent participer à l'étude en trois ans et à ce qu'il y ait une autre année de suivi pour répondre à une question de recherche. Le Comité de pharmacovigilance qui surveille l'étude a effectué un examen statistique des données sur une partie de l'étude (mai 2009). Compte tenu de cette étude, on estime maintenant qu'il faut inscrire 850 patients pour répondre à la question de recherche. Cela signifie qu'il faudra inscrire des patients pendant encore deux ans et demi et qu'il faudra un an de plus pour assurer le suivi avant que les résultats de l'étude soient connus.

QU'EST-CE QUE COMPREND L'ÉTUDE?

Randomisation (affectation à un groupe) :

Si vous décidez de participer à l'étude, on vous affectera « par randomisation » à un des groupes d'étude décrits ci-dessous. Randomisation veut dire affectation au hasard. C'est comme tirer à pile ou face. On fera appel à un bureau statistique central qui vous affectera à un des traitements. Ni votre médecin ni vous ne pourrez choisir le groupe dont vous ferez partie et vous aurez autant de chance que l'on vous affecte à l'un ou l'autre des deux groupes.

On vous dira quel traitement vous recevrez.

Traitement :

Groupe 1 : Dose unique de radiothérapie

Si l'on vous affecte par randomisation au Groupe 1, vous recevrez une seule dose relativement plus élevée de radiothérapie. Le traitement prendra plusieurs minutes.

Groupe 2 : Doses multiples plus faibles de radiothérapie

Si l'on vous affecte par randomisation au Groupe 2, vous recevrez des doses plus faibles de radiothérapie une fois par jour pendant cinq jours. Si vous avez besoin d'un nouveau traitement à la colonne ou au bassin au complet, et vous avez reçu un traitement à fractions multiples le traitement vous sera administré par doses encore plus faibles, mais pendant huit jours. Il prendra quelques minutes par jour pendant cinq ou huit jours.

Interventions et examens médicaux :

On pourra vous soumettre aux examens suivants afin d'assurer que vous êtes admissible à l'étude. Aucun de ces examens n'est de nature expérimentale. Ils sont nécessaires à l'évaluation des métastases osseuses.

- Examen médical;
- radiographies osseuses;
- scintigraphies osseuses;
- tomodensitométries;
- IRM.

Questionnaire sur la douleur :
On vous demandera de remplir ce questionnaire avant l'affectation par randomisation à un groupe d'étude, le jour 7 et le jour 14 après le début de la radiothérapie, et ensuite 1, 2, 3, 4, 5, 6, 9 et 12 mois après la fin du traitement, pour déterminer l'importance de la douleur que vous ressentez et l'effet qu'elle a sur vous. On vous demandera de remplir ce questionnaire avant le début de la nouvelle irradiation s'il s'écoule plus de sept jours entre celui de votre affectation par randomisation à l'étude et celui où vous commencez votre nouvelle irradiation. Il faut habituellement une dizaine de minutes pour répondre au questionnaire.

Questionnaire sur les toxicités aiguës :
Des patients signalent parfois qu'ils ont des symptômes comme des nausées ou la diarrhée après une irradiation – on vous demandera de remplir ce questionnaire le jour 7 et le jour 14 après le début de la radiothérapie pour indiquer si vous avez eu des symptômes et pour en préciser la gravité. Il faut habituellement de 5 à 10 minutes pour répondre au questionnaire.

Questionnaire sur la qualité de vie (participants du Canada, de la Hollande, de la France et des É.-U. seulement) :

On vous demandera de remplir un questionnaire avant votre affectation par randomisation à un groupe d'étude. Si vous parlez ou lisez l'anglais, le français ou l'espagnol et si vous êtes physiquement capable de remplir le questionnaire, vous devez le faire pour participer à l'étude. On vous demandera de remplir de nouveau le questionnaire mois 1, 2, 3, 4, 5 et 6 après la fin du traitement, afin de comprendre l'effet de votre traitement et de votre maladie sur votre qualité de vie. On vous demandera aussi de le remplir avant le début de la nouvelle irradiation s'il s'écoule plus de sept jours entre celui de votre affectation par randomisation à l'étude et celui où vous commencez votre nouvelle irradiation. Il faut une dizaine de minutes pour répondre à ce questionnaire, où l'on vous demande comment vous vous sentez. Certaines des questions sont personnelles et vous pouvez refuser d'y répondre. Les renseignements que vous fournirez serviront à la recherche seulement et demeureront strictement confidentiels. Les personnes (p. ex., médecins, infirmières, etc.) qui participent directement aux soins qui vous sont donnés ne verront habituellement pas vos réponses à ces questions — c'est à vous qu'il revient de leur en faire part.

PENDANT COMBIEN DE TEMPS PARTICIPERAI-JE À L'ÉTUDE?

Si l'on vous affecte par randomisation au groupe 1, vous recevrez votre nouveau traitement de radiothérapie en un seul jour. Si l'on vous affecte par randomisation au Groupe 2, votre nouvelle irradiation vous sera administrée pendant cinq ou huit jours si le traitement touche la moelle épinière ou le bassin au complet et le traitement que vous avez reçu à cet endroit vous a été administré par fractions multiples. Les chercheurs peuvent mettre fin plus tôt que prévu au traitement qui fait partie de l'étude, pour des raisons comme les suivantes :

- Le traitement ne donne pas de résultat dans votre cas.
- Vous ne pouvez tolérer le traitement prévu à l'étude.
- De nouveaux renseignements disponibles montrent que le traitement à l'étude n'est plus dans votre meilleur intérêt.
- Votre médecin ne pense plus que ce traitement est le meilleur pour vous.
- Le commanditaire décide de mettre fin à l'étude.

Vous pouvez décider de ne pas participer à l'étude ou cesser d'y participer n'importe quand et votre médecin continuera de vous traiter par les meilleurs moyens disponibles. Si vous décidez de cesser de participer à l'étude, nous vous encourageons à en parler d'abord à votre médecin.

Quel que soit le groupe auquel on vous affectera par randomisation, et même si vous arrêtez le traitement plus tôt que prévu, nous souhaitons suivre votre état de santé pendant 12 mois afin d'évaluer les effets à long terme des traitements prévus à l'étude.

QUELS SONT LES RISQUES?

Pendant l'étude, vous risquez de ressentir les effets secondaires énumérés ci-dessous. Il faut en discuter avec votre médecin. Comme dans le cas de tout traitement expérimental, d'autres effets secondaires inattendus et parfois graves peuvent faire leur apparition.

Votre médecin vous suivra de près pour déterminer si vous avez des effets secondaires. Lorsque ce sera possible, on vous administrera d'autres médicaments pour les atténuer et les rendre moins inconfortables. Beaucoup d'effets secondaires disparaissent peu après l'arrêt de la radiothérapie, mais ils peuvent dans certains cas être sérieux, durer longtemps ou être permanents.

MODIFIÉ #1: 2004-MAY-20 ; #2: 2005-MAR-01 ; #3: 2005-JUL-04 ; MODIFIÉ #4: 2006-MAR-24

Effets secondaires de la radiothérapie :

Vos chances d'avoir différents effets secondaires de la radiothérapie dépendent de nombreux facteurs, y compris la région du corps traitée, la quantité totale de rayonnements reçue dans cette région, la quantité de rayonnements administrée chaque jour, le type de rayonnements utilisé et si vous recevez une chimiothérapie en même temps que votre radiothérapie. Vous trouverez ci-dessous une liste d'effets secondaires généraux (que vous pourrez ressentir peu importe la région du corps où est administrée la nouvelle irradiation), ainsi que de certains effets secondaires dans différentes régions du corps. Votre médecin discutera avec vous du lien entre ces effets secondaires, votre radiothérapie et vous.

On ne sait pas si des patients d'un des groupes de traitement sont plus susceptibles d'avoir des effets secondaires que ceux de l'autre groupe.

Effets secondaires généraux :

Peu importe la région du corps traitée, vous pourrez ressentir de la fatigue. Cette sensation de fatigue disparaît habituellement quelques semaines après la fin de la radiothérapie.

Les changements de la peau au point de traitement constituent un autre effet secondaire possible. La peau de la région irradiée peut devenir rouge ou irritée, peut avoir l'air bronzée, ou une éruption peut y faire son apparition. Elle peut aussi devenir très sèche dans cette région quelques semaines après la radiothérapie. Les changements cutanés disparaissent habituellement quelques semaines après la fin de la radiothérapie, même si dans certains cas, la peau de la région traitée peut demeurer d'une couleur légèrement différente de ce qu'elle était auparavant, peut être plus sensible à la lumière du jour, ou vous pourrez la sentir un peu plus épaisse qu'auparavant.

Vous pourrez aussi ressentir une « flambée de douleur », soit une augmentation temporaire de la douleur dans la région irradiée au cours des deux premières journées qui suivent le traitement à fraction unique ou des trois ou quatre jours suivant un traitement à fractions multiples.

En général, les effets à long terme de l'irradiation administrée pour traiter des métastases osseuses comprennent des dommages aux organes, mais le risque d'apparition de symptômes liés à ces changements est très faible.

Effets secondaires possibles de la radiothérapie de la tête et du cou :

Si l'on vous administre une nouvelle irradiation des os de la région de la tête ou du cou, une partie de cette irradiation peut atteindre d'autres parties du corps dans cette région. Elle pourrait irriter la muqueuse de la bouche et avoir des répercussions sur les glandes salivaires. Cela signifie que vous pourriez avoir des rougeurs ou des lésions dans la bouche, ou avoir mal à la gorge. Vous pourriez aussi avoir la bouche sèche, une salive épaissie, ressentir des changements du goût, avoir de la difficulté à avaler, des nausées et perdre l'appétit. Les odeurs peuvent aussi changer. Ces effets secondaires sont souvent bénins et disparaissent habituellement après la fin de l'irradiation, mais certains comme la bouche sèche peuvent toutefois persister dans certains cas.

Effets secondaires possibles d'une radiothérapie du thorax :

Si vous recevez une nouvelle irradiation d'os comme les côtes, l'épaule, la clavicule ou certaines parties de la colonne, une partie de cette irradiation peut toucher certains des organes de la poitrine. L'irradiation peut irriter la muqueuse de l'œsophage (tube par où vous avalez), ce qui pourrait faire qu'il est douloureux ou difficile d'avaler. Vous pouvez aussi ressentir des nausées, perdre l'appétit, vomir ou avoir la diarrhée. Si l'irradiation touche les poumons, vous pourrez aussi avoir un peu de fièvre, tousser ou manquer de souffle un mois ou plus après la fin de la nouvelle irradiation. S'ils font leur apparition, ces symptômes sont habituellement temporaires et bénins, mais ils peuvent persister dans certains cas.

Effets secondaires possibles de la radiothérapie de l'abdomen et du bassin :

Si vous recevez une nouvelle irradiation d'os comme le bassin, la hanche, le coccyx ou certaines parties de la colonne, vous pourrez perdre l'appétit, avoir des nausées, des brûlements d'estomac, des crampes, vomir ou avoir la diarrhée. Si vous avez ces symptômes, ils sont souvent bénins et font habituellement leur apparition peu après le premier traitement d'irradiation et disparaissent peu après la fin du traitement. Si votre vessie est touchée, vous pourrez avoir de la difficulté à uriner, avoir besoin d'uriner souvent ou ressentir de l'inconfort pendant que vous uriner. Cet effet secondaire est habituellement temporaire et peut faire son apparition quelques semaines seulement après la fin du traitement d'irradiation. Vous pourrez avoir le rectum irrité s'il est touché par votre traitement d'irradiation. Ces symptômes sont habituellement bénins. Si vous êtes une femme, vos menstruations pourront cesser et vous pourrez avoir d'autres symptômes de la ménopause comme des démangeaisons, une sensation de brûlure ou la sécheresse vaginales.

Effets secondaires possibles d'une radiothérapie de la colonne :

Si l'on vous administre une nouvelle irradiation de la colonne, le traitement pourra avoir un effet sur votre moelle épinière. L'apparition de symptômes à cet égard n'est pas courante. Ces symptômes sont habituellement très bénins et comprennent des modifications de la façon de ressentir la température, la faiblesse et la maladresse d'un côté du corps ou des deux. Ces symptômes peuvent toutefois indiquer que le cancer a un effet sur votre moelle épinière. Il importe de signaler à vos médecins l'apparition de nouveaux symptômes comme la faiblesse, l'engourdissement ou les picotements dans les jambes.

Effets secondaires possibles d'une radiothérapie des membres seulement :

Comme il est inhabituel que d'autres organes soient irradiés lorsqu'on administre une radiothérapie aux bras et aux jambes, les patients ressentent habituellement peu d'effets secondaires, et surtout des changements de la peau. Le risque de fracture associé à une radiothérapie est de 2 à 4 %.

Risques pour la reproduction :

Comme les rayonnements peuvent nuire à un fœtus, il ne faut pas devenir enceinte ou procréer pendant que vous participez à cette étude. Il faut utiliser une méthode contraceptive efficace pendant que vous recevez le traitement prévu à l'étude. Consultez et trouvez d'autres renseignements sur la prévention de la grossesse. Il ne faut pas allaiter pendant l'étude.

Selon votre âge, le site de l'irradiation et la dose, votre nouvelle irradiation peut avoir des répercussions sur vos ovaires ou vos testicules et nuire à votre capacité d'avoir des enfants. Votre médecin discutera de ces risques avec vous.

Y A-T-IL DES AVANTAGES À PARTICIPER À L'ÉTUDE?

Si vous consentez à participer à l'étude, vous pourrez en tirer ou non des avantages directs autres que le soulagement possible de la douleur par la nouvelle radiothérapie. Nous espérons que les renseignements tirés de cette étude aideront un jour d'autres patients qui ont des métastases osseuses douloureuses.

QUELLES SONT LES AUTRES OPTIONS?

Si vous décidez de ne pas participer à l'étude, vous pourrez quand même recevoir la radiothérapie. Votre médecin discutera avec vous d'autres traitements possibles. Ces possibilités peuvent inclure les suivantes :

- médicaments contre la douleur;
- autre chimiothérapie;
- hormonothérapie ou bisphosphonates;
- chirurgie;
- aucune thérapie pour le moment.

Veuillez discuter avec votre médecin des avantages et des risques connus de ces autres traitements possibles. Votre médecin peut aussi discuter avec vous de ce qui se passera si vous décidez de ne pas entreprendre de traitement pour le moment.

ET LE CARACTÈRE CONFIDENTIEL DES RENSEIGNEMENTS?

On fera tous les efforts possibles pour que vos renseignements personnels demeurent confidentiels.

Des représentants qualifiés des organisations suivantes peuvent inspecter vos dossiers médicaux de l'étude pour des fins d'assurance qualité et d'analyse des données :

- le NCIC Groupe des essais cliniques (NCIC GEC), groupe de recherche qui coordonne l'étude;
- le comité d'éthique en recherche qui supervise la conduite éthique de cette étude dans votre hôpital/clinique;

Des représentants qualifiés des organisations suivantes peuvent recevoir des renseignements provenant de vos dossiers médicaux et d'étude pour des fins d'assurance de la qualité d'analyse des données :

- le NCIC Groupe des essais cliniques (NCIC GEC), groupe de recherche qui coordonne l'étude;
- le comité d'éthique en recherche qui supervise la conduite éthique de cette étude dans votre hôpital/clinique;
- le Trans-Tasman Radiation Oncology Group;
- le Cancer Research UK et UCL Cancer Trials Centre;
- le Dutch Bone Metastases Group.
- le Radiation Therapy Oncology Group
- Département de Recherche Clinique et du Développement, Assistance Publique Hôpitaux de Paris et Hôpital Henri Mondor, Créteil Cedex, France

Ces renseignements peuvent en contenir qui pourraient permettre de vous identifier, et notamment les suivants :
- résultats d'examen;
- rapports d'intervention;
- rapports de radiographie ou d'autres examens radiologiques;
- rapports sur votre traitement et ses effets secondaires.

Les organisations mentionnées ci-dessus maintiendront la confidentialité des renseignements qu'elles voient ou reçoivent à votre sujet, dans la mesure où les lois pertinentes le permettent. Les renseignements qui permettront de vous identifier seront gardés sous clé. Aucune publication sur la recherche ne contiendra de renseignements permettant de vous identifier.

L'information recueillie au cours de l'étude servira dans des analyses et sera publiée ou présentée aux milieux scientifiques au cours de réunions et dans des journaux.

On s'attend à ce que les résultats de l'étude soient publiés en 2013. On communiquera à votre médecin participant à l'étude les résultats de celle-ci lorsqu'ils seront connus.

QU'EST-CE QU'IL EN COÛTE?

La radiothérapie vous sera administrée gratuitement. Vous ne toucherez aucun paiement pour participer à l'étude. La participation peut entraîner des frais supplémentaires pour vous.

En cas d'effets secondaires ou de traumatismes reliés à la recherche, les soins médicaux vous seront dispensés par votre médecin, ou l'on vous enverra recevoir les soins médicaux nécessaires. Même si l'on n'a pas réservé de fonds pour vous indemniser en cas de traumatisme ou de maladie découlant du traitement donné ou des interventions pratiquées dans le cadre de l'étude, vous ne renoncez à aucun de vos droits légaux à une indemnisation en signant ce formulaire.

QUELS SONT MES DROITS EN TANT QUE PARTICIPANT(E)?

La participation à l'étude est volontaire. Vous pouvez décider de ne pas y participer, ou cesser d'y participer n'importe quand. En décidant de ne pas y participer ou de quitter l'étude par la suite, vous ne vous exposez à aucune pénalité et ne risquez nullement de perdre des avantages auxquels vous avez droit. Votre médecin discutera plus à fond des traitements avec vous et continuera de traiter votre cancer par les meilleurs moyens disponibles.

Un conseil de surveillance de la sécurité des données, groupe indépendant d'experts, examinera les données issues de cette recherche pendant toute l'étude.

Nous vous informerons, en temps et lieu, des nouveaux renseignements qui peuvent avoir un effet sur votre santé, votre mieux-être ou votre volonté de continuer de participer à l'étude.

Vous recevrez une copie de ce formulaire de consentement portant votre signature et la date.

CONFLIT D'INTÉRÊTS

Note aux centres : Veuillez inclure des détails sur tout conflit d'intérêts réel ou possible au sujet de cette étude.

Ce centre reçoit du Groupe des essais cliniques de l'INCC des fonds qui l'aident à compenser les coûts de cette recherche. Le GEC INCC est un groupe de recherche sans but lucratif.

QUI APPELER SI J'AI DES QUESTIONS OU DES PROBLÈMES?

Si vous avez des questions au sujet de votre participation à cette étude ou si vous subissez un traumatisme relié à la recherche, vous pouvez en parler avec votre médecin. Vous pouvez aussi rencontrer le médecin responsable de l'étude ici. Il s'agit de :

_____ _____

Nom Téléphone

Si vous cherchez des conseils au sujet de vos droits de patient(e) ou de questions d'éthique reliées à l'étude, vous pouvez en parler à quelqu'un qui n'a aucun lien avec l'étude. Il s'agit de :

_____ _____

Nom Téléphone

Date de la version de cette formule ou date d'approbation par le CER : _____	N^{O} série Pt GEC INCC :_____

MODIFIE #2: 2005-MAR-01 ; MODIFIÉ #4: 2006-MAR-24

SIGNATURES

Ma signature apposée sur ce formulaire de consentement signifie ce qui suit :

- L'étude m'a été expliquée au complet et l'on a répondu à toutes mes questions.
- Je comprends les exigences de l'étude et les risques qu'elle comporte.
- Je permets qu'on ait accès à mes dossiers médicaux de la façon expliquée dans ce formulaire de consentement.
- Je consens à participer à cette étude.

_____ _____
Signature du(de la) patient(e) Date

_____ _____
Signature du chercheur Date

A-t-on aidé le(la) patient(e) pendant l'obtention du consentement d'une des façons indiquées ci-dessous?

☐Oui ☐ Non

Si oui, veuillez cocher la case pertinente et remplir l'espace réservé à la signature ci-dessous :

☐ On a lu le formulaire de consentement au(à la) patient(e) et la personne qui a apposé sa signature ci-dessous atteste qu'on a expliqué précisément l'étude au(à la) patient(e), qui semble l'avoir comprise.

☐ La personne qui appose sa signature ci-dessous a fait fonction d'interprète pour le(la) patient(e) au cours du processus visant à obtenir le consentement.

_____ _____
Signature de la personne qui a participé à la discussion sur le consentement Date

Veuillez noter :
Il faut consigner dans le dossier médical du(de la) patient(e), le cas échéant, d'autres renseignements sur l'aide fournie au cours du processus visant à obtenir le consentement.

Date de la version de cette formule ou date d'approbation par le CER : _____	N^{o} série Pt GEC INCC :_____

APPENDIX IX - PROCEDURES FOR TRANS-TASMAN RADIATION ONCOLOGY GROUP [TROG] PARTICIPATING SITES (AUSTRALIA & NEW ZEALAND)

The TROG Trial Centre (TROG TC) for this study is located at the Royal Adelaide Hospital.

Institution Eligibility for Participation

Prior to the recruitment of a patient for this study, investigators must be registered members of TROG.

An investigator's agreement will be forwarded to all participating centres and should be returned with names and signatures of all investigator's who intend to participate in the trial.

Ethics Approval

Each participating centre will obtain ethics approval of both the protocol and informed consent document by the appropriate local Ethics Committee. A copy of letters documenting ethics approval as well as the finalised version of the patient information document will be forwarded to the TROG TC.

All amendments or revisions to the protocol must be submitted to local ethics committees for review and correspondence of appraisal from the committee will be forwarded to the TROG TC.

Informed Consent

The sample consent form provided by the NCIC CTG is satisfactory as a template for TROG centres and is supplied as Appendix VIII to the protocol. Please remove reference to the Quality of Life Questionnaire. The form layout or format may be changed though the content should only be altered to include details of each centre and to satisfy the centre's specific Ethics Committee requirements. Importantly, no alterations should be made that reduce the amount of information on the form.

Centre Performance Monitoring

The timeliness and quality of data submission are monitored for all centres. The results will be reported twice a year and centres must reach a minimum standard for performance. Guidelines for submission times are listed at the end of this Appendix.

On-Site Monitoring/Auditing

No on-site monitoring has been planned for TROG centres.

Case Report Forms

The CRFs will be downloaded from the NCIC CTG website by the TROG data manager and distributed to TROG centres.

Data Submission

Please adhere to the schedule provided for TROG centres listed at the end of this Appendix.

AMENDMENT #1: 2004-MAY-20 ; AMENDMENT #4: 2006-MAR-24; AMENDMENT #5: 2009-AUG-07
TROG centres will not be completing quality of life questionnaires as part of this trial.

All report forms and data must be sent to TROG TC:

Julie Butters
TROG Trial Centre Data Manager
Department of Radiation Oncology
Royal Adelaide Hospital
North Terrace
Adelaide SA 5000

Source Documenting Telephone Calls

Telephone calls in which information is exchanged that is pertinent to the trial should be recorded and filed in the source documents. The record should cite the date, caller's name and position and a summary of the conversation.

Serious Adverse Event Reporting

TROG TC fax: (08) 8222 2016

Your local ethics committee should be notified of all Serious Adverse Events.

This study will utilise the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for adverse events and serious adverse event reporting. A copy of the Criteria can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). It is advised that all involved investigators have access to a copy for reference.

TROG investigators should employ definitions of Serious Adverse Events as described in Section 10.0 (Serious Adverse Event Reporting) of the SC.20 protocol. Reports and supporting documentation must be submitted as follows:

All reportable serious adverse events must be reported within 24 hours (of investigator's knowledge of event) by fax to the TROG TC. Following the initial report by fax, a completed NCIC CTG Generic Serious Adverse Event form should be forwarded to the TROG TC by mail within 10 or 15 working days.

Reporting Secondary malignancies or myeloid dysplasia
Second malignancies or myeloid dysplasia must be reported on a Serious Adverse Event Report (SAE) form. Submit form and supporting documentation to the TROG TC within 15 working days of investigator's knowledge of the diagnosis.

TROG Trial Centre Mailing Address

TROG Trial Centre Data Manager
Department of Radiation Oncology
Royal Adelaide Hospital
North Terrace
Adelaide, SA 5000

AMENDMENT #1: 2004-MAY-20; AMENDMENT #4: 2006-MAR-24; AMENDMENT #5: 2009-AUG-07

TROG List of Contacts

	Contact	Tel. #	Fax #
TROG CO-CHAIR Royal Adelaide Hospital, Associate Professor	Dr Daniel Roos Email: Daniel.Roos@health.sa.gov.au	+61 (0)8 8222 4000	+61 (0)8 8222 2016
TROG TC Data Manager	Julie Butters Email: Julie.Butters@health.sa.gov.au	+61 (0)8 8222 4378	
TROG Senior Operations Manager	Ms Kathy Hall Email: kathy.hall@mater.health.nsw.gov.au	+61 (0)2 4921 1466	+61 (0)2 4921 1465

Documentation for Study

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

Form	To be completed	Due at TROG TC	Supporting Documentation Required
Form 1 Eligibility Checklist Initial Evaulation	Within one week prior to calling TROG TC to randomise the patient	within 6 weeks of randomisation (TROG TC)	none
Form 4 Radiotherapy Report	at the end of radiotherapy	within 6 weeks of the completion of treatment (TROG TC)	none
Form 5 Follow-up Report	every month for 6 months after RT, then at 9 and 12 months post RT	within 8 weeks of the date the patient was seen at the clinic, or telephone contact was made with the patient (TROG TC)	none
Form 6 Final Report	at the time of the patient's death	within 8 weeks of the patient's death (TROG TC)	autopsy report if done
Serious Adverse Event Report Form*	at time of the event	by Fax within 24 hours (TROG TC), forwarded by mail within 3 days. 2nd malignancies within 15 working days.	documentation of the event
Brief Pain Inventory Baseline Questionnaire**	Within one week prior to randomisation, day 1 of RT (if randomization > 7days or new analgesic regimen started since randomization)	submit with Form 1 or Form 4, as appropriate (TROG TC)	none
Brief Pain Inventory Follow-up Questionnaire	day 7, 14, months 1-6, 9 and 12	submit with Form 5 (TROG TC)	none
Acute Toxicity Questionnaire	at day 7 and day 14 after RT	submit with Form 5 (TROG TC)	None

* See earlier in this appendix for Serious Adverse Event reporting details for TROG patients.

** Worst pain score used to determine eligibility must come from the baseline Brief Pain Inventory completed prior to randomization.

AMENDMENT #2: 2005-MAR-01; AMENDMENT #5: 2009-AUG-07

APPENDIX X – PROCEDURES FOR RADIATION THERAPY ONCOLOGY GROUP (RTOG) PARTICIPATING SITES

Institution Eligibility for Participation

Prior to the recruitment of a patient for this study, investigators must be registered members of RTOG.

An investigator's agreement will be forwarded to all participating centres and should be returned to RTOG with names and signatures of all investigator's who intend to participate in the trial.

Ethics Approval and Informed Consent

Each participating centre must follow standard RTOG procedure with respect to obtaining ethics approval and informed consent. All regulatory documentation must be forwarded to CTSU (fax: 215-579-0206) for U.S. sites and RTOG Headquarters (fax: 215-574-0300) for Canadian sites.

The sample consent form provided by the NCIC CTG is satisfactory as a template for RTOG centres and is supplied as Appendix VIII to the protocol. RTOG centres should add the Radiation Therapy Oncology Group to the list of organizations with access to patients' records.

Patient Registration

To register a patient, RTOG institutions will:

- Access the protocol and forms on the NCIC CTG web site (see the 0433 title page with the link and password on the RTOG web site, http://www.rtog.org/);
- Access, print, and complete NCIC CTG's Form 1 (Eligibility Checklist and Initial Evaluation);
- Print and complete the demographic information form for 0433 on the RTOG web site, http://www.rtog.org/;
- Fax the completed NCIC CTG Form 1 to RTOG Headquarters (215-574-0300; 8:30 AM to 4:00 PM, Eastern Time, Monday through Friday).

When RTOG Headquarters receives the faxed NCIC CTG Form 1 from the RTOG institution, Headquarters will confirm patient eligibility and regulatory compliance before the patient will be registered to this study. Upon confirmation of eligibility and regulatory compliance, RTOG Headquarters will register the patient on the NCIC CTG web site and then will call the RTOG institution to confirm registration.

When registration is complete, the RTOG institution will mail the NCIC CTG Form 1 to:

NCIC CTG
Attn: SC.20 Clinical Trials Assistant
c/o Queen's University
10 Stuart Street
Kingston, ON K7L 3N6

NCIC CTG will provide patient enrollment information to RTOG Headquarters monthly. This information then will be processed for reimbursement of RTOG sites.

NOTE:

- For eligibility questions, refer to the "List of Contacts" on the last page of the NCIC CTG protocol;
- RTOG Headquarters and NCIC CTG will not generate patient calendars/labels for RTOG institutions (see Appendix III of the protocol, which describes the form submission schedule).

Case Report Forms
The CRFs must be downloaded from the NCIC CTG web site (see the 0433 title page with the link and password on the RTOG web site, http://www.rtog.org/).

Data Submission
RTOG Headquarters and NCIC CTG will not generate patient calendars for RTOG institutions.

Patients will be evaluated according to the schedule in Appendix I. RTOG participants will submit data at the required intervals in Appendix III. Expected submission timelines also are repeated on the page 1 header of each data form. Include the NCIC CTG protocol number (SC.20) as well as the RTOG study number (0433) and the patient's case number on all forms.

All Case Report Forms and data must be sent to:

NCIC CTG
Attn: SC.20 Clinical Trials Assistant
c/o Queen's University
10 Stuart Street
Kingston, ON K7L 3N6

NCIC CTG will send queries regarding data and forms due reports to RTOG Headquarters, and RTOG will forward the queries to RTOG institutions. RTOG Investigator's responses to queries should be submitted directly to NCIC CTG.

Centre Performance Monitoring
The timeliness and quality of data submission are monitored for all centres. The results will be reported twice a year and centres must reach a minimum standard for performance. Guidelines for submission times are listed in Appendix III.

On-Site Monitoring/Auditing
No on-site monitoring has been planned for RTOG centres.

Source Documenting Telephone Calls
Telephone calls in which information is exchanged that is pertinent to the trial should be recorded and filed in the source documents. The record should cite the date, caller's name and position and a summary of the conversation.

Serious Adverse Event Reporting
RTOG investigators should employ definitions of Serious Adverse Events as described in Section 10.0 (Serious Adverse Event Reporting) of the SC.20 protocol. Reports and supporting documentation must be submitted to NCIC CTG within 10 working days.

Your local ethics committee should be notified of all Serious Adverse Events.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for adverse events and serious adverse event reporting. A copy of the Criteria can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

RTOG Contact:

William Hartsell, MD
Advocate Good Samaritan Cancer Center
3815 Highland Avenue
Downers Grove, IL 60515
TEL: 630-275-2300
FAX: 630-275-2390
William.Hartsell-MD@advocatehealth.com

AMENDMENT #3: 2005-JUL-04; AMENDMENT #4: 2006-MAR-24

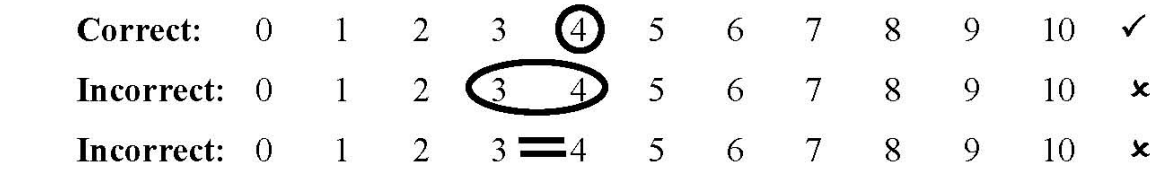
APPENDIX XI - GUIDELINES FOR PATIENTS

The following pages contain guidelines to assist patients in completing the SC.20 questionnaires. Please give them to each patient before he or she completes the baseline questionnaires and allow the patient to take them home for reference when completing future questionnaires. They are also available from the SC.20 website in both English and French.

SC.20 GUIDELINES FOR PATIENTS

Thank you for agreeing to take part in this study. You are being asked to fill out three types of forms at different times before and after your radiation treatment. This document will give you some guidelines on how to fill out these forms so that the researchers can best use the information that you give them. If you have any questions, please contact the clinical research associate or study nurse that has been working with you on the study.

1. When a question asks you to give your answer by circling a number, please choose only the one number that best describes your answer.



2. When you are filling out the Brief Pain Inventory, please answer the questions about the area that was treated with radiation for the study. For the forms that are done after your treatment, this area will be marked on the body diagram in question # 1 of the form.

3. When you are asked about the medication you have been taking in question # 5 of the Brief Pain Inventory, please list all of the pain medications you actually took in the 24 hours before you started filling out the form.
   - The name of the medication goes in the first column
   - The strength of <u>each</u> pill or patch (or other type of medication) goes in the second column.
   - How you took the medication goes in the third column
   - The number of pills you have taken goes in the fourth column.

   If you did not take any medication, please write "no medication" in the table.

   Please see the next page for some examples.

e.g. You took two 50 mg tablets of Medication A by mouth three times and one 30 mg tablet of Medication B by mouth twice in the 24 hours before you filled in the form:

Name of medication	Strength (mg/pill)	Route of Administration	Number of pills/ Administrations per day	
Medication A	50 mg	mouth	2 tablets 3 times a day	✓
Medication B	30 mg	mouth	1 tablet twice a day	✓

e.g. You are being given 25 mcg/h Medication C by patch. You change your patch every three days. When you have extra pain, you take one 10 mg tablet of Medication D. In the 24 hours before you filled in the form, you had taken one tablet of Medication D.

Correct:

Name of medication	Strength (mg/pill)	Route of Administration	Number of pills/ Administrations per day	
Medication C	25 mcg/h	patch	1 patch every 3 days	✓
Medication D	10 mg	mouth	1 tablet	✓

Incorrect:

Name of medication	Strength (mg/pill)	Route of Administration	Number of pills/ Administrations per day	
Medication C	25 mcg/h	patch	1 patch every 3 days	✓
Medication D	10 mg	mouth	as needed	✗

This is incorrect because it does not tell the researchers how many pills you actually took before filling in the form.

4. Question # 6 on the Brief Pain Inventory asks about how much pain relief you get from your medication and the radiation treatment. Please do your best to answer this question, even if you have not taken any pain medication before filling in the form. It will tell the researchers how much pain relief the radiation treatment has given you.

Thank you for your contribution to this research study.

APPENDIX XII – PROCEDURE FOR FRENCH PARTICIPATING SITE

1.) Investigators

Pr. J.L. Lagrange (jean-leon.lagrange@hmn.aphp.fr)
Dr. C. Diana (Christian.diana@hmn.aphp.fr)

Service de Radiothérapie
Hôpital Henri Mondor
51, Avenue du Maréchal De Lattre de Tassigny
94010 Créteil cedex
FRANCE

Tel: 33 (0)1 49 81 45 24
Fax: 33 (0)1 49 81 25 89
Tel secrétariat 33 (0)1 49 81 25 97

2.) Randomization procedure

All randomizations will be done centrally by the Radiotherapy service of Henri Mondor Hospital (Pr. Lagrange and Dr. Diana) after a review of the eligibility criteria, by using a web-based system provided by NCIC CTG. In addition to fulfilling the eligibility criteria outlined in section 4.1 of the protocol:

- Patients need to be covered by medicare, and
- Women of child-bearing potential must use contraception to participate in the study in France.

These requirements will be checked by the investigators at Henri Mondor Hospital prior to randomizing each patient.

The Radiotherapy service will inform the DRCD (Département de la Recherche Clinique et du Développement, contact: Mr Christophe AUCAN) and the URC (Unité de Recherche Clinique, contact: Miss Pauline Jouany) by mail at each randomization.

3.) Ethical, Regulatory and Administrative issues

Rôle du promoteur

Il est défini par la loi 2004-806 du 9 août 2004. Dans cette recherche, l'AP-HP sera le promoteur de la recherche effectuée en France, et la Délégation Régionale à la Recherche Clinique qui en assure les missions réglementaires aura un rôle décisionnel.

Soumission du protocole au CPP

En accord avec l'article L.1123-6 du Code de la Santé, le protocole de recherche sera soumis à un Comité Protection des Personnes (CPP) de l'Ile de France, après accord du promoteur (avec l'attestation d'assurance et la quittance de droit fixe). L'avis de ce comité sera notifié dans le formulaire adressé à l'autorité compétente par le promoteur avant le démarrage de la recherche.

Déclaration CNIL

La loi prévoit que la déclaration doit avoir été faite avant le début effectif de la recherche.

- La DRRC en qualité de promoteur effectuera une déclaration à la CNIL, en relation avec le responsable du fichier informatique, lors de sa déclaration annuelle simplifiée si la recherche fait l'objet d'un contrôle qualité des données par un ARC et entre dans le champ d'application de la méthodologie de référence CNIL MR-001.
- **En sont exclues les recherches en génétique identifiante, épidémiologie ou l'étude des comportements, les recherches qui comportent des données sensibles en termes de confidentialité (identité complète des personnes ou numéro de sécurité sociale collecté).** Dans ce cas, ainsi que pour les recherches non monitorées, le responsable du fichier assure lui-même la déclaration unitaire de la recherche auprès du Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé puis de la CNIL.

Documentations de la recherche

Avant de démarrer la recherche, l'investigateur coordonnateur fournira au représentant du promoteur de la recherche une copie de son curriculum vitæ personnel daté et signé et comportant son numéro d'inscription à l'Ordre des Médecins, de même que tous les investigateurs.
La version du protocole acceptée avant soumission avec ses annexes sera signée conjointement par l'investigateur coordonnateur et le représentant du promoteur. Le cas échéant, le responsable scientifique sera également signataire.
Lors de chaque nouvelle version du protocole, rendue nécessaire par des amendements et/ou demandes des autorités, un nouveau numéro et la date seront attribués et les mêmes signatures recueillies.

Chaque investigateur s'engagera à respecter les obligations de la loi et à mener la recherche selon les B.P.C. et en respectant les termes de la déclaration d'Helsinki. Pour ce faire, un exemplaire daté et signé de l'engagement scientifique (document type DRRC) par chaque investigateur de chaque service clinique participant d'un centre sera remis au promoteur.

Contrôle de Qualité et Assurance Qualité

La recherche sera encadrée selon les procédures opératoires standard de l'AP-HP promoteur.

Le déroulement de la recherche dans les centres investigateurs et la prise en charge des sujets sera faite conformément à la déclaration d'Helsinki et les Bonnes Pratiques.

Procédures de monitoring

Les représentants du promoteur effectueront des visites des centres investigateurs au rythme correspondant au schéma de suivi des patients dans le protocole, aux inclusions dans les différents centres et au niveau de risque qui a été attribué au protocole.
D'abord, avant inclusions, pour une ouverture de chaque centre avec mise en place du protocole et prise de connaissance avec les investigateurs.

Lors des visites suivantes, les cahiers d'observation seront revus au fur et à mesure de l'état d'avancement de la recherche par les ARCs représentant le promoteur qui en contrôleront le bon remplissage et assureront la validation des données. L'investigateur principal de chaque centre et les autres investigateurs qui incluent ou suivent des sujets participant à la recherche acceptent de recevoir des représentants du promoteur nommés par l'AP-HP à intervalles réguliers.

Lors de ces visites sur site et en accord avec les Bonnes Pratiques Cliniques, les éléments suivants seront revus :
- respect du protocole de la recherche et des procédures qui y sont définies,
- examen des documents source et confrontation avec les données reportées dans le cahier d'observation,
- assurance de qualité des données recueillies dans le cahier d'observation : exactitude, données manquantes, cohérence des données, selon les règles édictées par les procédures de la DRRC,

Gestion des Evénements Indésirables

Définitions :

Evénement indésirable

Toute manifestation nocive et non recherchée survenant chez une personne pendant une recherche, qu'elle soit considérée ou non comme liée à celle-ci.

Effet indésirable

Réaction nocive et non voulue à un traitement expérimental : médicament (quelle que soit la dose administrée), dispositif, traitement chirurgical…) utilisé chez l'homme.

Effet ou événement indésirable grave

Effet ou événement indésirable ayant entraîné :

- Le décès
- La mise en jeu du pronostic vital
- Une invalidité ou une incapacité importantes ou durables
- Une hospitalisation ou prolongation d'hospitalisation
- Une anomalie ou malformation congénitale
- Autre : tout effet indésirable jugé comme grave par le professionnel de santé, en particulier les événements nécessitant une intervention pour éviter l'une des conséquences notées ci-dessus, et certains résultats d'examens paracliniques.

Effet indésirable inattendu

Effet indésirable dont la nature, la gravité ou l'évolution ne correspondent pas aux informations contenues dans le résumé des caractéristiques du produit, la brochure investigateur ou autre référentiel reconnu par les autorités.

Obligations des investigateurs :

Evénements indésirables non graves :

Tout événement indésirable - non grave suivant la définition précédente - observé lors de la recherche et dans ses suites devra être reporté dans le cahier d'observation dans la section prévue à cet effet.
Un seul événement doit être reporté par item. L'événement peut correspondre à un symptôme, un diagnostic ou à un résultat d'examen complémentaire jugé significatif. Tous les éléments cliniques ou paracliniques permettant de décrire au mieux l'événement correspondant doivent être reportés.
Tout patient présentant un événement indésirable doit être suivi jusqu'à la résolution ou la stabilisation de celui-ci, et l'évolution en sera notée sur la page correspondante.

Evénements indésirables graves :

Les investigateurs doivent informer, **en temps réel**, l'AP-HP-promoteur d'éventuels événements indésirables graves tels que définis ci-dessus.
L'investigateur envoie les copies des feuillets-type événements indésirables graves du cahier d'observation de la recherche, décrivant l'EIG, par fax, à la DRRC au nom du chef de projet en charge de la recherche au 01 44 84 17 99 dans les 48 heures, (après si possible un appel téléphonique immédiat au 01 44 84 17 23 en cas de décès ou d'une menace vitale inattendus).
L'investigateur devra pour chaque événement indésirable grave émettre un avis médical sur la relation pouvant exister entre l'apparition de l'évènement et le protocole.

Les bilans cliniques, les examens diagnostiques et les examens de laboratoire appropriés seront mis en route afin d'identifier l'origine de la réaction et les résultats de ces explorations ainsi que l'évolution clinique seront rapportés.

Tout fait nouveau survenu dans la recherche ou dans le contexte de la recherche provenant de données de la littérature ou de recherches en cours doit aussi être notifié au promoteur très rapidement.

Dans le cas des effets indésirables graves qui satisfont aux définitions de la section 10 du protocole, les chercheurs rempliront le rapport d'événement indésirable grave du GEC INCC et le télécopieront à l'attention du coordonnateur de l'étude SC.20 au GEC INCC, dans les délais prescrits.

Déclaration des événements indésirables graves aux Autorités de Santé :

Elle sera assurée par le pôle de pharmacovigilance de la DRRC, après analyse d'imputabilité de chaque cas. Toutes les suspicions d'effet indésirable grave inattendu (non présent dans le RCP ou la brochure investigateur du ou des produits utilisés dans la recherche) seront déclarées par le promoteur à l'autorité compétente dans les délais légaux.

En cas d'effet indésirable grave inattendu dû à l'un des traitements de la recherche ou la recherche elle-même, le CPP et les investigateurs de la recherche devront être informés.

Transcription des données dans le cahier d'observation

Toutes les informations requises par le protocole doivent être fournies dans le cahier d'observation et une explication donnée par l'investigateur pour chaque donnée manquante.
Les données devront être transférées dans les cahiers d'observation au fur et à mesure qu'elles sont obtenues qu'il s'agisse de données cliniques ou para-cliniques Les données devront être copiées de façon nette et lisible à l'encre noire dans ces cahiers (ceci afin de faciliter la duplication et la saisie informatique).
Les données erronées dépistées sur les cahiers d'observation seront clairement barrées et les nouvelles données seront copiées sur le cahier avec les initiales et la date par le membre de l'équipe de l'investigateur qui aura fait la correction.
L'anonymat des sujets sera assuré par la mention au maximum des 3 premières lettres du nom et des 2 premières lettres du prénom du sujet sur tous les documents nécessaires à la recherche, ou par effacement par les moyens appropriés (blanc correcteur…) des données nominatives sur les copies des documents source, destinés à la documentation de la recherche.
Les données informatisées sur un fichier seront déclarées à la CNIL selon la procédure adaptée au cas.

Amendements au protocole de la recherche

La DRRC doit être informée de tout projet de modification du protocole par l'investigateur coordonnateur. Les modifications devront être qualifiées en substantielles ou non.
Tout amendement au protocole de la recherche, devra être notifié au CPP s'il entraîne des modifications substantielles, c'est-à-dire si les modifications prévues sont susceptibles, d'une manière ou d'une autre, de modifier les garanties apportées aux personnes qui se prêtent à la recherche biomédicale *(modification d'un critère d'inclusion, prolongation d'une durée d'inclusion, participation de nouveaux investigateurs.....).*

Extension de la recherche

Toute extension de la recherche (modification profonde du schéma thérapeutique ou des populations incluses, prolongation des traitements et ou des actes thérapeutiques non prévus initialement dans le protocole) devra être considérée comme une nouvelle recherche.

Responsabilité

L'Assistance Publique-Hôpitaux de Paris est le promoteur de cette recherche. En accord avec la loi sur les recherches biomédicales, elle a pris une assurance auprès de la compagnie GERLING KONZERN pour toute la durée de la recherche, garantissant sa propre responsabilité civile ainsi que celle de tout intervenant (médecin ou personnel impliqué dans la réalisation de la recherche) (loi n°2004-806, Art L.1121-10 du CSP).
L'Assistance Publique - Hôpitaux de Paris se réserve le droit d'interrompre la recherche à tout moment pour des raisons médicales ou administratives; dans cette éventualité, une notification sera fournie à l'investigateur.

Rapport final de la recherche

Le rapport final de la recherche sera écrit par le NCIC CTG qui est responsable de la coordination de la recherche et de l'analyse des données. Ce rapport devra être adressé au promoteur dans les meilleurs délais après la fin effective de la recherche. Un rapport doit être transmis à l'autorité compétente ainsi qu'au Comité dans un délai de un an, après la fin de la recherche, s'entendant comme la dernière visite de suivi du dernier sujet inclus. Ce délai est rapporté à 90 jours en cas d'arrêt prématuré de la recherche.

Publications et propriétés des données

L'AP-HP est propriétaire des données recueillies dans les centres participants en France et pour lesquels l'AP-HP s'est portée promoteur. Aucune utilisation ou transmission à un tiers ne peut être effectuée sans son accord préalable.
L'Assistance Publique- Hôpitaux de Paris doit être mentionnée comme étant le promoteur de la recherche biomédicale et comme soutien financier le cas échéant. Les termes « Assistance Publique- Hôpitaux de Paris » doivent apparaître dans l'adresse des auteurs.

AMEND #1: 2004-MAY-20 ; #2: 2005-MAR-01; #4: 2006-MAR-24 ; ADMIN UPDATE #1: 2006-SEP-20
LIST OF "CONTACTS"

PATIENT REGISTRATION
All patients must be registered by telephone with NCIC CTG before any treatment is given.

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to telephone registration. Starting doses will also be calculated at registration.	Sara Rushton Clinical Trials Assistant NCIC CTG Email: srushton@ctg.queensu.ca	(613) 533-6430	(613) 533-2941
STUDY SUPPLIES Forms, Protocols	Available on NCIC CTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Carolyn Wilson SC.20 Study Coordinator NCIC CTG Email: cwilson@ctg.queensu.ca or: Dr. Ralph Meyer Physician Coordinator NCIC CTG E-Mail: rmeyer@ctg.queensu.ca		
STUDY CHAIR	Dr. Edward Chow Study Chair E-Mail: Edward.Chow@sunnybrook.ca	(416) 480-4998	(416) 480-6002
SERIOUS ADVERSE EVENT REPORTING See protocol section 10.0 for details of reportable events.	Carolyn Wilson SC.20 Study Coordinator NCIC CTG	(613) 533-6430	(613) 533-2941

For TROG contact information please see Appendix IX.
For RTOG contact information please see Appendix X.