

## North Central Cancer Treatment Group

**Phase II Trial Evaluating Resection followed by Adjuvant Radiation Therapy (RT)  
for Patients with Desmoplastic Melanoma**

For any communications regarding this protocol,  
please call the protocol resource person on the following page.

Study Chairs: Barbara A. Pockaj, MD (Research Base)\*  
Mayo Clinic  
200 First Street, SW  
Rochester, MN 55905  
507/284-3559  
507/284-5280 (FAX)  
[pockaj.barbara@mayo.edu](mailto:pockaj.barbara@mayo.edu)

Richard L. Deming, M.D. (NCCTG)

Study Co-Chairs: Steven Schild, MD (Research Base)  
Svetomir N. Markovic, MD, PhD.  
James A. Martenson, MD  
John H. Donohue, M.D.  
Jan L. Kasperbauer, M.D.  
Richard Gray, MD  
Michael K. Gornet, MD  
Winston Tan, MD  
Steven J. Buskirk, MD

Pathology: David J. DiCaudo, MD (NCCTG)  
Lori Erickson, MD (Mayo)

Statistician: Jake Allred, MS.  
(507) 266-2874

DCT Supplied Investigational Agent(s): None

\*Investigator having NCI responsibility for this protocol.

<u>Document History</u>	<u>(Effective Date)</u>
Activation	July 11, 2003
Update 1	August 8, 2003
Addendum 1	April 9, 2004
Update 2	June 18, 2004
Update 3	August 26, 2005
Addendum 2	August 25, 2006
Addendum 3	August 31, 2007
Addendum 4	April 18, 2008
Addendum 5	June 6, 2008

<u>Study Participants</u>	<u>Date Activated</u>
Entire NCCTG	July 11, 2003

Add 3

## Protocol Resources

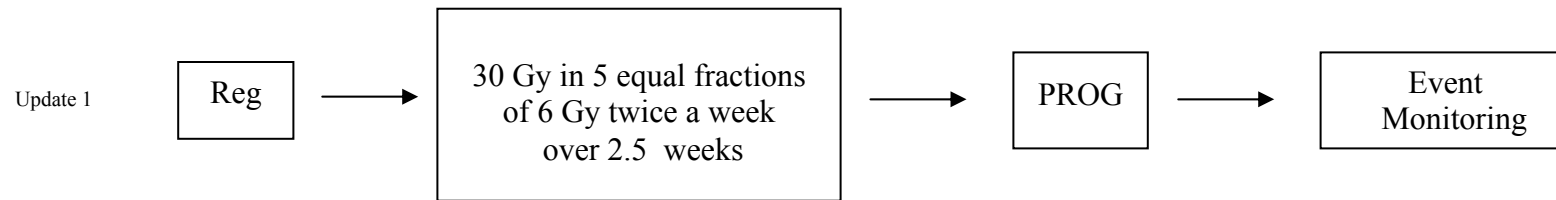
	<b>Questions:</b>	<b>Contact Name:</b>
Add 1	Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	Butch Kvittem NCCTG <i>Research Base</i> Quality Control Specialist Phone: (507) 284-3559 Fax: (507) 266-7240 E-mail: <a href="mailto:kvittem@mayo.edu">kvittem@mayo.edu</a>
Update 3 Add 4	Drug administration, infusion pumps, nursing guidelines	Stephanie Glasel, RN NCCTG <i>Research Base</i> Nurse Phone: (507) 284-2459 E-mail: <a href="mailto:glasel.stephanie@mayo.edu">glasel.stephanie@mayo.edu</a>  Evie Brennan, RN NCCTG Member Nurse Phone: (701) 234-7515 E-mail: <a href="mailto:eviebrennan@meritcare.com">eviebrennan@meritcare.com</a>
	Forms completion and submission	Carlene Dillavou NCCTG Member Clinical Research Associate Phone: (515) 244-7586 Email: <a href="mailto:cdillavou@uswestat.net">cdillavou@uswestat.net</a>
Add 2	Protocol document, consent form, regulatory issues	Sara Braun NCCTG <i>Research Base</i> Protocol Development Coordinator Phone: (507)538-8226 Fax: (507) 284-5280 E-mail: <a href="mailto:braun.sara@mayo.edu">braun.sara@mayo.edu</a>  Patricia A. Aggen NCCTG <i>Research Base</i> Protocol Coordinator Phone: 507/538-6232 Fax: 507/284-5280 E-mail: <a href="mailto:aggen.patricia@mayo.edu">aggen.patricia@mayo.edu</a>
Add 4	Radiation quality control	Kathryn M Scherger NCCTG <i>Research Base</i> Radiation Quality Control Coordinator Phone: (507) 266-0006 Fax: (507) 266-7240 E-mail: <a href="mailto:scherger.kathryn@mayo.edu">scherger.kathryn@mayo.edu</a>
Add 4	Paraffin-embedded tissue pathology	Christine R Maszk NCCTG <i>Research Base</i> Pathology Coordinator Phone : (507) 266-8919 Fax : (507) 284-9628 E-mail : <a href="mailto:maszk.christine@mayo.edu">maszk.christine@mayo.edu</a>
	Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	Patricia G McNamara NCCTG <i>Research Base</i> SAE Coordinator Phone: (507) 266-3028 Fax: (507) 284-9628 E-mail: <a href="mailto:mcnamara.patricia@mayo.edu">mcnamara.patricia@mayo.edu</a>
	Technical problems with electronic form entry	Vicki Bryhn NCCTG <i>Research Base</i> Data Management Specialist Phone: (507) (507) 266-5350 Fax: (507) 538-0906 E-mail: <a href="mailto:bryhn.vicki@mayo.edu">bryhn.vicki@mayo.edu</a>

\*No waivers of eligibility per NCI

**Index**

	Schema
1.0	Background
2.0	Goals
3.0	Patient Eligibility
4.0	Test Schedule
5.0	Stratification Factors
6.0	Registration Procedures
7.0	Protocol Treatment
8.0	Treatment Modification Based on Toxicity
9.0	Ancillary Treatment
10.0	Adverse Event (AE) Reporting and Monitoring
11.0	Treatment Evaluation
12.0	Descriptive Factors
13.0	Treatment/ Follow-up Decision at Evaluation of Patient
14.0	Radiation Studies
15.0	Radiation Therapy Information
16.0	Statistical Considerations and Methodology
17.0	Pathology Considerations
18.0	Records and Data Collection Procedures
19.0	Budget Considerations
20.0	References
	Appendix I – NCCTG Consent Form
	Appendix II – Radiation Therapy Quality Control Guideline
	Appendix III – Brief Fatigue Inventory

**Schema**



## 1.0 Background

Desmoplastic Melanoma (DM) is a rare variant of malignant melanoma. Published series have noted that DM occurs more commonly in elderly men on sun exposed skin surfaces, most commonly the head and neck followed by the extremities and the trunk (1-3).

These tumors are difficult to differentiate from other benign and malignant neoplasms leading to inaccurate diagnosis and inadequate treatment (4,5). Published recurrence rates for patients with DM vary from 25-50% (1-3). This has been attributed to the failure to excise clinically inapparent projections of tumor (4). This is in contrast to patients with other cutaneous melanoma who have a local recurrence rate of 2-13% depending on the tumor depth and presence of ulceration (6,7).

A recent retrospective study performed at the Mayo Clinic evaluated the natural history of DM and confirms the findings noted in the other series. We found the local recurrence rate to be 39% (8,9). A majority of these patients (61%) developed more than one local recurrence. For those patients who locally recurred the average depth of the original lesion was 10.6 mm compared to 4.7 mm who did not ( $p=0.016$ ). Local recurrence was 3 times more likely in patients who had unknown or positive margins (80%) than in patients with negative margins (24%),  $p<0.001$ . The local recurrence rate was much higher in DM patients with negative margins than in patients with other cutaneous melanomas. Local recurrence was a poor prognostic factor where the incidence of metastatic disease was 3 times higher in patients with local recurrence (52%) compared with patients without local recurrence (15%),  $p=0.006$ .

We found that the natural history of DM was also quite different from other cutaneous melanomas. Regional lymph node metastases are quite rare. Only one patient (1.7%) developed lymph node metastases after her third local recurrence. Other clinical series also reported a low incidence of lymph node metastases (8-15%) (1,2). This is in contrast to a lymph node metastases rate of at least 20% for patients with intermediate depth melanomas (10). The pattern of metastatic disease is also quite different than other cutaneous melanomas. DM has a propensity to metastasize to the lungs (81%), bone (25%), and brain (12.5%). Lung metastases occurs in only 18-36% of patients with cutaneous melanoma versus the more common sites of skin, subcutaneous, and distant lymph node metastases (11).

Overall the clinical behavior of DM mimics that of extremity soft tissue sarcoma rather than cutaneous melanoma. Extremity soft tissue sarcoma has a high incidence of local recurrence with surgery alone (up to 33%), rarely metastasizes to the regional lymph nodes (2-12%), and has a propensity to metastasize to the lungs (88%) (11-13).

The use of adjuvant radiation therapy in patients with cutaneous melanomas had demonstrated an improvement in local control when compared to historical data (14,15). These studies delivered hypofractionated radiation therapy (30-36 Gy) to patients at high risk of local and regional recurrence. Similar results have been demonstrated in patients with head and neck tumors (16). Adjuvant radiation therapy has also been shown to decrease the risk of nodal recurrences in patients with high-risk melanoma (19-21). There have been anecdotal reports of the use of radiation therapy in patients with high risk DM with excellent clinical results (17,18).

Radiation therapy has been effective treatment for the prevention of local recurrence in patients undergoing limb-sparing surgery for extremity soft tissue sarcoma (11-13). Local recurrence occurs at least 50% of the time when the surgical excision relies on enucleation only. If a wide local excision is performed with at least a 2 cm margin the local recurrence rate decreases to 12-31%. The addition of adjuvant radiotherapy reduces the local recurrence rate to less than 15%. The likelihood of local recurrence also is based on the grade of tumor and tumor size. Low grade, small tumors (<5 cm) may not need radiotherapy if adequate surgical margins are obtained.

In summary, the clinical behavior of DM is different from other cutaneous melanomas and more closely mimics that of extremity soft tissue sarcoma. Local recurrence is a significant clinical problem for patients with DM and carries a negative long-term impact. Clinical studies have shown that radiotherapy can reduce the risk of local recurrence in locally advanced malignant melanomas and extremity soft tissue sarcomas. We believe that patients with DM would benefit from radiotherapy to primary sites to control local recurrence. We propose this phase II study to determine if hypofractionated radiotherapy can decrease local recurrence rates and possibly bring about long term survival with acceptable morbidity.

## **2.0 Goals**

### **2.1 Primary Goals**

- 2.11 Assess the recurrence rates in patients with Desmoplastic Melanoma (DM)  $\geq 1$  mm deep treated with adjuvant radiotherapy after surgical resection.
- 2.12 Assess recurrence rates in patients with locally recurrent DM treated with adjuvant radiotherapy after surgical resection.

### **2.2 Secondary Goals**

- 2.21 Evaluate the impact of adjuvant radiation therapy after surgical resection on disease free and overall survival.
- 2.22 Evaluate the immediate and long-term morbidity of the addition of radiotherapy to surgery.

## **3.0 Patient Eligibility**

### **3.1 Required Characteristics**

- 3.11 Age  $\geq 18$  years.
- 3.12 ECOG performance status (PS) 0, 1, or 2.
- 3.13 Pathologically proven DM  $\geq 1$  mm in depth or locally recurrent DM. Recurrent tumor is defined as a tumor found  $\leq 2$  cm from the previous excision or within the surgical bed (which includes the extent of previous skin flaps).
- 3.14 DM resected with pathologically negative margins. Acceptable surgery includes standard wide local excision and Moh's surgery.
  - 3.141 Tumors on the trunk proximal extremities need to have a  $\geq 2$  cm negative margin. Tumors located on the head and neck and distal extremities will have an attempt at 2 cm negative margins but due to location and subsequent concern regarding cosmesis a margin  $< 2$  cm will be acceptable if margin is negative.
  - 3.142 Margins from tumors resected using the Moh's technique will be accepted if negative and best approximation of tumor width will be made.
- 3.15 RT is to begin  $\leq 8$  weeks after definitive surgical resection. This will allow for definitive healing from the wide local excision. Due to the nature of the disease, there is the potential

need for skin grafts and skin flaps to cover wounds which can be prone to wound healing issues. 8 weeks should allow adequate time for healing prior to radiation therapy.

- 3.16 Adjuvant systemic therapy (immunotherapy or chemotherapy) must be postponed until irradiation is completed.

The utility of adjuvant systemic therapy is unknown for patients with desmoplastic melanoma. There is a benefit for patients with cutaneous melanoma who have stage III disease but due to the fact the subset of DM is so small it is impossible to evaluate that group. There are reports of increased in field toxicity in patients who receive adjuvant interferon therapy (22,23). Severe subacute and late complications were seen in 5 out of 10 patients who received concurrent or sequential alpha-interferon therapy (22). The decision to treat these patients will be left up to the treating physician.

### 3.2 Contraindications

- 3.21 Previous irradiation to the same site.
- 3.22 Non-healing surgical wound.
- 3.23 Active infection at the surgical site.
- 3.24 Evidence of metastatic disease. Local nodal disease is still eligible for the trial.
- 3.25 Life expectancy <1 year.
- 3.26 Melanoma with focally desmoplastic features, in which the desmoplastic melanoma is not the predominant histologic pattern of the tumor, will be excluded. Non-desmoplastic neurotropic melanoma and non-desmoplastic spindle cell melanoma are also excluded.
- 3.27 Previous malignancy <5 years excluding basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma in situ (with the exception of patients who have stage I breast cancer who were adequately treated with adjuvant therapy and are currently disease free, and patients with stage I or II prostate cancer treated with prostatectomy or radiotherapy and are biochemically free of disease [for RRP PSA <0.3 and for radiotherapy PSA <2.0 above the post treatment nadir]).
- 3.28 Any of the following:
- Pregnant women
  - Women of childbearing potential who are unwilling to employ adequate contraception (condoms, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, abstinence, etc.)

Add 2

#### 4.0 Test Schedule

Add 3

Tests and Procedures	≤14 days prior to registration	Weekly during radiation therapy (weeks 1-3)	At completion of RT	Post completion of RT (Observation)	
				Q3 months (years 0-2)	Q 6 months (years 3-5)
Surgery/Evaluation of regional Lymph node disease	X <sup>1,6</sup>				
History and Exam, disease status, Wt, PS, toxicity	X <sup>2</sup>		X	X	X
Chest CT	X <sup>5</sup>				
Review of Pathology	X <sup>1,3,6</sup>				
Urine Pregnancy Test	X <sup>4</sup>				
CBC ANC, WBC, PLT, Hgb	X	X <sup>7</sup>	X		
Brief Fatigue Inventory		X <sup>8</sup>	X	X <sup>9</sup>	
CXR				X	X

1. Must be done ≤56 days of registration. Surgical excision may be performed at an outside institution but pathology must be reviewed by the treating institution to confirm diagnosis of DM and negative margins.
2. Prior to study entry the history and exam should assess functional status and suitability of the surgical site for radiation therapy. The history should also include the history of the primary lesion, pertinent past medical history which may impact tolerance to radiation therapy and overall survival. A physical exam should include a description of the site to be irradiated and the status of the regional lymph nodes.
3. If DM is recurrent attempts will be made to obtain original biopsy and treatment records for review and documentation. Attainment of the original biopsy is not a requirement for study enrollment.
4. For women of childbearing potential only. Must be done ≤7 days prior to registration.
5. A chest CT must be performed to rule out metastatic disease ≤ 84 days (12 weeks) prior to registration.
6. Regional lymph node disease may be assessed by clinical exam, elective lymph node dissection, or sentinel lymph node biopsy. Pathology evaluation will be done of the lymph nodes when applicable. A complete lymph node dissection will be done if the regional lymph nodes are found to have metastatic disease.
7. Weekly CBC is recommended but will be at the discretion of the treating radiation oncologist.
8. On days of RT Brief Fatigue Inventory must be evaluated prior to treatment.
9. See App. III for questions from the Brief Fatigue Inventory. During observation fatigue evaluation is only performed at 3 month visit.

Add 3

#### 5.0 Grouping factor: Desmoplastic melanoma type: ≥ 1mm deep vs. locally recurrent

## 6.0 Registration Procedures

- Add 4
- 6.1 To register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If you are unable to access the website, call the NCCTG Registration Office at (507) 284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).
- The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an NCCTG subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:
- Contact the NCCTG Registration Office (507) 284-4130. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
  - Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”
- 6.2 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: [www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). Guidelines can be found under Quick Fact Sheets.
- Add 4
- 6.3 Prior to accepting the registration/randomization, the remote registration/randomization application will verify the following:
- IRB approval at the registering institution
  - Patient eligibility
  - Existence of a signed consent form
  - Existence of a signed authorization for use and disclosure of protected health information. (USA institutions only)
- 6.4 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG member physician.
- 6.5 Treatment cannot begin prior to registration and must begin  $\leq 30$  days after registration.
- 6.6 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.
- 6.7 All required baseline symptoms must be documented and graded on the on-study form.
- 6.8 A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

## 7.0 Protocol Treatment

- Add 1
- 7.1 RT must begin within 8 weeks of surgical excision. Healing should be adequate to begin RT safely. Patients will receive a total of 30 Gy in 5 fractions of 6 Gy prescribed to Dmax, administered twice-a-week (Monday and Thursday or Tuesday and Friday) over approximately 2.5 weeks. Treatment will be administered with electrons only. If the tumor is located in the head or neck region and its depth was  $\leq 4$  mm depth, then 2 cm margins between the estimated tumor bed (incision) and the block edges will be used. If the tumor is located in the head or neck region and its depth was greater than 4 mm, then 3 cm margins between the estimated tumor bed (incision) and the block edges will be used. If the tumor is in a non-head and neck region, then 3 cm margins between the estimated tumor bed (incision) and the block edges will be used. The incision is to be demarcated with a radio-opaque marker at the time of simulation. Simulation films should be taken. Radiotherapy will be accomplished with electrons. The electron energy can be altered to treat to specific depths. A point at the center of the incision at a depth equal to the thickness of the tumor on the pathology report should receive at least 90% of the prescribed (Dmax) dose. Additionally for thinner tumors, a point at the center of the field and 1.5 cm below the incision should receive at least 80% of the prescribed dose. Bolus should be used as necessary to achieve a surface dose of at least 90% of the prescribed dose. Bolus can also be used to decrease the penetration of a high-energy beam. None of the lung, spinal cord, eye, or brain (dose-limiting structures) can receive  $\geq 24$  Gy (this requirement is absolute and may lead to compromises in other treatment parameters in unusual circumstances). CT-derived treatment planning is to be performed when the field includes one of these dose-limiting structures. The CT should be performed with a radio-opaque marker on the incision. In situations with a dose-limiting structure within the field,

isodose plans should be performed at 1 cm increments throughout the field length with the dose-limiting structure denoted on the isodoses plan. See Appendix II for other treatment planning reporting requirements. Central axis contours with isodoses shown are to be performed in all patients and is satisfactory alone in those with no dose-limiting structure in the field. The 95% (28.5 Gy), 90% (27 Gy), and 80% (24 Gy) isodoses are to be shown.

Add 1 7.2 Radiotherapy will not be given to the first echelon lymph nodes unless necessary to give adequate therapy to the primary tumor bed.

Add 1 7.21 Radiation therapy will not be given to the lymph node basin even if the lymph nodes are positive.

7.211 Based on recent review of all patients treated at the Mayo Clinic Rochester and Mayo Clinic Scottsdale, there was only one patient out of 59 patients who had lymph node metastases. These lymph node metastases occurred after the third local recurrence. We do not think the risk of lymph node metastases is great enough to warrant irradiation (8, 9).

## 8.0 Treatment Modifications Based on Toxicity

If a patient develops any grade 3 toxicity felt to be due to radiation therapy, they will have a treatment break until the toxicity severity decreases to grade 2 at which time, they are to resume and complete therapy. This break in treatment is usually no more than 1 week. The patient will go to event monitoring if the treatment break is greater than two weeks.

Studies using similar radiation therapy protocols have demonstrated very low toxicity. Morris reported toxicity in 24 of 41 patients and were minimal and self-limited such as transient erythema (15), desquamation (2), acute parotiditis which resolved without antibiotic therapy (2), xerostomia where one required treatment with acyclovir for cold sores (2), local edema (1), fibrosis (1), telangectasias (1), and upper extremity weakness which resolved with physical therapy (1) (14). The Sidney Melanoma Unit found that there were few severe acute side effects in 174 patients. Two patients developed pain following irradiation in the jaw after irradiation of the parotid and upper neck. Two patients developed severe late complications following neck radiation. Subsequent lymphedema was observed in 58% of patients with axillary edema and 66% of patients with groin irradiation (15).

Add 2

## 9.0 Ancillary Treatment

Skin changes are common complications of radiation therapy. Usual care will be provided. For dry skin aloe vera based product will be prescribed. If the skin becomes erythematous and/or there is pruritis, topical steroid cream will be prescribed. The addition of antihistamines will be used for severe pruritis. Patients experiencing pain will be prescribed pain medication.

## 10.0 Adverse Event (AE) Reporting and Monitoring

10.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for adverse event monitoring and reporting. The CTC version 2.0 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 CTC version 2.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTC. Next, determine whether the event is expected or unexpected (refer to Section 15.0 and/or product literature) and if the adverse event is related to the medical treatment or procedure (see Section 10.12). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) or as part of the routinely reported clinical data.

Expedited adverse event reporting requires submission of a written report to the NCCTG Operations Office. Expedited reports are to be completed within the timeframes specified in Section 10.2. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).

### 10.12 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the treatment.

Probable - The adverse event *is likely related* to the treatment.

Possible - The adverse event *may be related* to the treatment.

Unlikely - The adverse event *is doubtfully related* to the treatment.

Unrelated - The adverse event *is clearly NOT related* to the treatment..

### 10.2 Expedited Adverse Event Reporting Requirements (based on *NCI Guidelines: Expedited Reporting Requirements for NCI Investigational Agents, January 2001 Version*)

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE <sup>1</sup>	Other Grade 4 or 5 <u>Or</u> Any Hospitalization During Treatment <sup>2</sup>	Secondary AML/MDS <sup>3</sup>
FDA Form 3500 (MedWatch) to NCCTG within 5 days <sup>4</sup>	X	X		
Notification form: Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form to NCCTG within 5 working days <sup>2,4</sup>			X	
NCI/CTEP Secondary AML/MDS Report Form to NCCTG within 15 working days <sup>4</sup>				X

1. Any increased incidence of a known AE that has been reported in the package insert or the literature, including adverse event resulting from a drug overdose.
2. If the FDA Form 3500 (MedWatch) has been completed, this form does not need to be completed. Any death more than 30 days after the patient's last study treatment or procedure which has an attribution of at least possibly treatment related must be reported as a Grade 5 AE, with CTC type and attribution assigned.
3. Reporting for this AE required during or after treatment.
4. Fax to the NCCTG Operations Office, Fax 507-284-1902.

All forms noted above are available for downloading from the NCCTG website. Upon receipt of the above reports, the NCCTG Operations Office will forward reports to all regulatory agencies (including NCI, FDA, and others) as applicable. Specifically, and in accordance with the relevant section of the *NCI Guidelines: Expedited Reporting Requirements for NCI Investigational Agents*, the Operations Office will forward FDA Form 3500 (MedWatch) reports to the FDA and to NCI within the allotted (total) 10 working days and using one of the cited submission mechanisms.

- 10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Toxicity Criteria (CTC) Version 2.0 grading unless otherwise stated:

Category	Adverse Event/Symptoms	Baseline	Each evaluation
Dermatology/Skin	Alopecia		X
	Radiation dermatitis		X
Gastrointestinal	Anorexia	X	X
	Nausea	X	X
	Odynophagia	X	X
	Vomiting	X	X
Fatigue	Fatigue <sup>1</sup>	X	X
Pain	Pain due to radiation		X

<sup>1</sup>Fatigue will be monitored using questions from the Brief Fatigue Inventory<sup>24</sup>. See Appendix III.

- 10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3:
- 10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
  - 10.312 Grade 3, 4, and 5 AEs and deaths within 30 days of the patient's last treatment, regardless of attribution to the study treatment or procedure, with the exception of signs or symptoms definitely related to the patient's disease or disease progression.
  - 10.313 Any death more than 30 days after the patient's last study treatment or procedure which is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTC type and attribution assigned.

**11.0 Treatment Evaluation**

- 11.1 During active radiotherapy the patients will be monitored for any toxicity secondary to the treatment. All toxicities will be recorded and ancillary treatment will be used to treat these toxicities.
- 11.2 After radiotherapy is completed the patient will be followed every 3 months for the first 2 years and then every 6 months for years 3-5.
- 11.3 Date and site of local recurrence, regional recurrence, and systemic metastases will be recorded.
- 11.4 Date and cause of death will be recorded.
- 11.5 Subsequent morbidity secondarily to the radiotherapy will be recorded.
- 11.6 If a patient refuses therapy prior to receiving radiotherapy, they will be canceled. Only on-study forms need to be submitted.
- 11.7 Premature discontinuation of therapy: If the patient decides to discontinue the study due to unacceptable toxicity or any other reasons, after RT has started, the patient will go to event monitoring. The date of discontinuation, the reason the patient discontinued RT, and the total dose received should be recorded.

**12.0 Descriptive Factors:** None.

**13.0 Treatment/Follow-up Decisions at Evaluation of Patient**

Patient will continue to be followed until there is recurrence: local, regional, or systemic. At the time of recurrence, the best possible treatment will be offered to the patient that may include surgery, further radiotherapy, immunotherapy, or chemotherapy.

**14.0 Radiation Studies:** None.

**15.0 Radiation Therapy Information**

See Section 18.0 for guidelines of submission of dosimetry information.

**16.0 Statistical Considerations and Methodology**

- 16.1 Accrual: A total of 40 eligible patients with desmoplastic melanoma  $\geq 1$  mm deep and 20 eligible patients with locally recurrent DM will be accrued.
  - 16.11 Inclusion of Women and Minorities: This study will be available to all eligible patients, regardless of race or ethnic group. The planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings. Based on the Mayo accrual to other NCCTG melanoma clinical trials, we expect approximately 60% of patients registered onto this study to be female, and 4% to be of a minority racial grouping.

## 16.2 Definition of endpoints and analysis plan:

- 16.21 The primary endpoint is the incidence of local recurrence within 2 years after treatment. The properties of the binomial distribution will be used to construct a 95% confidence interval for the true 2 year local recurrence rate. The Kaplan-Meier (25) method will be used if some patients are lost to follow-up.

For the sample of 40 patients with  $DM \geq 1$  mm, assuming incidence follows a binomial distribution, the maximum width of the 95% confidence interval for the 2 yr. local recurrence rate is  $\pm 16\%$ .

For the sample of 20 patients with local recurrent DM, assuming incidence follows a binomial distribution, the maximum width of the 95% confidence interval for the 2 yr. Local recurrence rate is  $\pm 22\%$ .

### 16.22 Secondary endpoints include:

16.221 Incidence of regional and systemic metastasis: Incidences will be calculated for each cohort and 95% confidence intervals will be constructed using the properties of the binomial distribution.

16.222 Survival time: Survival time is defined as the time from randomization to death due to any cause. The median survival time will be estimated using the method of Kaplan-Meier (25).

16.223 Failure time: Failure time is defined as the time from randomization to death due to any cause or disease progression. The median failure time will be estimated using the method of Kaplan-Meier.

16.224 Toxicity: The maximum grade of each type of toxicity will be recorded for each patient. For each toxicity reported, the percentage of patients reporting/experiencing any degree of that toxicity as well as the percentage of patients reporting/ experiencing a severe degree (Grade 3 or higher on the NCI CTC scale) will be determined.

Add 2

16.225 Fatigue Assessment: A portion of the Brief Fatigue Inventory will be used to determine fatigue changes throughout the course of radiation. Patients will fill out the questionnaire at baseline, weekly during radiation, and 3 months after the beginning of radiation. Fatigue will be defined as: minor if the patient answers 0-3 (on a 10 point scale), mild for answers of 4-6, and severe for answers of 7-10. The percentage of patients that have worsened (improved) fatigue from baseline to the radiation stage will be calculated. We will also compare fatigue levels at baseline to the 3 month visit. Worsened fatigue is defined as going from minor to mild, minor to severe, or mild to severe. Improved fatigue is defined as going from severe to mild, severe to minor, or mild to minor.

- 16.3 Monitoring: The principal investigator and the study statistician will review the study periodically (at least twice a year) to identify accrual, toxicity, and endpoint problems that might be developing. The study statistician will prepare a report containing accrual, adverse event, and efficacy data

which will be submitted to the Mayo Clinic Comprehensive Cancer Center Data and Safety Monitoring Board (MCCCC DSMB) on an annual basis.

The adverse event profile of this technique will be examined at least every 2 months.

Add 2

16.31 If among the first 10 patients enrolled onto this trial experience, 3 or more patients develops a grade 3 toxicity at least likely to be related to treatment, or 2 or more patients develops a grade 4+ toxicity at least likely to be related to treatment, enrollment will be suspended so that the adverse event data can be examined and a trial recommendation will be formulated and presented to the MCCCC DSMB.

16.32 At any point in study after 11 or more patients have been enrolled, if 30% or more of these patients report a grade 3+ toxicity considered at least likely to be related to treatment, or if 10% or more of these patients report a grade 4+ toxicity at least likely to be related to treatment, enrollment will be suspended so that the adverse event data can be examined and a trial recommendation will be formulated and presented to the MCCCC DSMB.

## Add 5 **17.0 Pathology Considerations**

Review is being performed by an external reviewer not located at the NCCTG Research Base. Please ship specimens and appropriate materials as indicated below:

- Diagnostic slides
- Op and path reports
- Pathology Reporting form

**The Pathology Submission Form must be sent to the NCCTG Operations Office at Mayo Clinic Rochester. Please do not send this form to the external reviewer listed below.**

Add 4

Mayo Clinic Rochester and its affiliate sites should submit the materials to: Dr. Lori Erickson, Hilton-11, Mayo Clinic, Rochester, MN 55905 for review.

For all other NCCTG memberships, materials should be sent to the Scottsdale Primary CRA:

Linnea Loserth  
 Mayo Clinic Arizona  
 Cancer Clinical Research Unit-CP21B  
 13400 E. Shea Blvd.  
 Scottsdale, AZ 85259

Linnea Loserth will accession the pathology materials and forward the materials to Dr. David DiCaudo for review.

After review is completed, the pathologist will return all pathology materials to:

NCCTG Operations Office  
 Attn: PC Office  
 RO\_FF\_03\_24-CC/NW Clinic  
 200 First Street SW  
 Rochester, MN 55905

The Pathology Coordinators will return the diagnostic slides to the submitting institution following central review..



1. Refer to the instructions in Section 17.0.
2. For patients who do not receive any scheduled radiation therapy, submit the radiation therapy reporting form with the reason radiation was not given. For patients who receive partial/complete radiation therapy, submit the following materials  $\leq 14$  days after the last day of radiation:
  - a. RT reporting form.
  - b. Daily treatment records.
  - c. Dosimetry calculations and isodose curves.
  - d. Copies of representative simulation films of all treated fields.
  - e. Copies of representative port films of all treated fields.
3. On days of radiation therapy, Brief Fatigue Inventory must be completed prior to treatment.
4. If a patient is still alive after 5 years after registration, no further follow-up is required.

**19.0 Budget**

- 19.1 Current therapy will be billed to the patient's insurance company since this treatment is considered within the realm of therapy for melanoma.
- 19.2 Tests to be research funded: None.
- 19.3 Other budget concerns

**20.0 References**

1. Quinn MJ, Crotty KA, Thompson FJ, et al: Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 people. *Cancer* 83(6):1128-1135, 1998.
2. Skelton HG, Smith KJ, Laskin WB: Desmoplastic malignant melanoma. *Journal of the Am Acad of Derm*, 32(5):71-725, May 1995.
3. Bruijn JA, Mihm MC, Barnhill RL: Desmoplastic melanoma. *Histopathology* 20:197-205, 1992.
4. Smithers BM, McLeod GR, Little JH: Desmoplastic melanoma: patterns of recurrence. *World J Surg* 16:186-190, 1992.
5. Whitaker DC, Argenyi Z, Smith AC: Desmoplastic malignant melanoma: rare and difficult to diagnose. *Journal of the Am Academy of Derm* 26(5):704-709, 1992.
6. Balch CM, Soong S, Smith T, et al: Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. *Ann Surg Oncol* 8:101-108, 2001.
7. Heaton KM, Sussman JJ, Gershenwald JE, et al: Surgical margins and prognostic factors in patients with thick (>4 mm) primary melanoma. *Ann Surg Oncol* 5:332-328, 1998.
8. Jaroszewski DE, Pockaj BA, Bite U, et al: Desmoplastic melanoma: lessons learned from the past and now with sentinel lymph node biopsy. *Fifty-Third Annual Meeting of the Southwestern Surgical Congress Abstract # 24*, April 2001.
9. Jaroszewski DE, Pockaj BA, Bite U, et al: Desmoplastic melanoma: lessons learned from the past and now with sentinel lymph node biopsy. *Am J Surg*. 2001; 182:590-595.
10. Balch CM, Soong S, Ross MI, et al: Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). *Ann Surg Oncol* 7:87-97, 2000.
11. Kirkwood J: Melanoma. In DeVita VT, Hellman S, Rosenberg SA: eds. *Biologic Therapy of Cancer*, 2<sup>nd</sup> ed. Pennsylvania: J.B. Lippincott Company 388-411, 1995.
12. Wylie JP, O'Sullivan B, Culton C, et al: Contemporary radiotherapy for soft tissue sarcomas. *Sem Surg Oncol* 17:33-46, 1999.
13. Pisters PW: Combined modality treatment of extremity soft tissue sarcomas. *Ann Surg Oncol* 5:464-472, 1998.
14. Morris KT, Marqueses CM, Holland JM, et al: Prevention of local recurrence after surgical debulking of nodal and subcutaneous melanoma deposits by hypofractionated radiation. *Annals of Surg Onc* 7(9):680-684, 2000.
15. Stevens G, Thompson JF, Firth I, et al: Locally advanced melanoma: results of postoperative hypofractionated radiation therapy. *Cancer* 88:88-94, 2000.

16. Ang KK, Peters LJ, Weber RS, et al: Postoperative radiotherapy for cutaneous melanoma of the head and neck region. *Int J Radiation Oncol Biol Phys* 30:795-798, 1994.
17. Kevanagh BD, Campbell RL, Patterson JW, et al: Desmoplastic malignant melanoma of the palatal alveolar mucosa: sustained disease-free survival after surgery and postoperative radiotherapy. *Oral Surg, Oral Path, Oral Rad, Endodontics* 89:465-470, 2000.
18. Jennings TA, Okby NT, Schroer KR: Parotid involvement by desmoplastic melanoma. *Histopathology* 29(2):165-170, 1996.
19. Lee JR, Gibbs JF, Proulx GM, et al. Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. *Int J Rad Oncol Biol Phys.* 46:467-474. 2000.
20. Corry J, Smith JG, Bishop M, Ainslie J. Nodal radiation therapy for metastatic melanoma. *Int J Rad Oncol Biol Phys.* 44:1065-1069, 1999
21. Ballo MT, Strom EA, Zagars GK, et al. Adjuvant irradiation for axillary metastases from malignant melanoma. *Int J Rad Oncol Biol Phys.* 52:964-972, 2002
22. Hazard LJ, Sause WT, Noyes RD. Combined adjuvant radiation and interferon-alpha 2b therapy in high-risk melanoma patients: the potential for increased radiation toxicity. *Int J Rad Oncol Biol Phys.* 52: 796-800, 2002.
23. Thomas R, Stea B. Radiation recall dermatitis from high-dose interferon alfa-2b. *J Clin Oncol.* 20:355-357, 2002.
24. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, Huber SL. The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. *Cancer.* 85:1186-1196, 1999.
25. Kaplan E, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 53: 457-481, 1958

## Appendix I

### NCCTG Consent

**TITLE: N0275, Phase II Trial Evaluating Resection followed by Adjuvant Radiation Therapy (RT) for Patients with Desmoplastic Melanoma**

**PARTICIPANTS: Dr. Barbara Pockaj and colleagues**

**This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.**

**Why is this study being done?**

This study is being done to find out what effects (good and bad) radiation therapy has on you and your desmoplastic melanoma.

**How many people will take part in the study?**

The plan is to have about 60 people take part in this study.

**What will happen in the study?**

<i>Pre-Study</i>	<ul style="list-style-type: none"><li>• <i>Urine and pregnancy test, if applicable.</i></li><li>• <i>History and exam, including entire skin exam</i></li><li>• <i>Routine blood tests (CBC)</i></li><li>• <i>Chest CT</i></li></ul>
<i>During Radiation Therapy</i>	<ul style="list-style-type: none"><li>• <i>Radiation therapy twice a week (Monday and Thursday or Tuesday and Friday) over about 2½ weeks</i></li><li>• <i>CBC weekly</i></li><li>• <i>Evaluation of Radiation Toxicity</i></li></ul>
<i>After Radiation Therapy</i>	<ul style="list-style-type: none"><li>• <i>Evaluation of Radiation Toxicity and Local Recurrence every 3 months for 2 years including a history and physical, entire skin exam, and CXR</i></li><li>• <i>Evaluation of Radiation Toxicity and Local Recurrence every 6 months for 3 more years, including a history and physical, entire skin exam and CXR</i></li></ul>

If you take part in this study, you will have urine and pregnancy tests, if applicable, routine blood tests, and an entire skin exam before you begin radiation therapy.

During treatment you will receive radiation therapy (with x-rays or electrons) twice a week (Monday and Thursday or Tuesday and Friday) over about 2½ weeks for a total of 5 radiation treatments. You will also be evaluated for radiation toxicity and have a CBC done weekly during treatment.

After radiation therapy is completed, you will be evaluated for radiation toxicity and local recurrence and have a CXR and entire skin exam (H&P) done every three months for two years, and then every six months for three years.

**How long will I be in the study?**

This study will have about a five-year follow-up, but how long you will be in the study will depend on how you do with the radiation therapy and how your cancer acts. Even if you stop the radiation therapy, we will still want to keep contact with you.

**Are there reasons I might leave the study early?**

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the study doctor if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped. You will be told of important new findings or any changes in the study or procedures that may affect you.

**Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG), or released to researchers outside of NCCTG for future unspecified use?**

No.

**What are the risks of the study?**

While you are taking part in this study, you are at risk for these side effects. You should talk to your study doctor and/or your medical doctor about these side effects. There also may be other side effects that are not known. Other drugs may be given to lessen side effects. Many side effects go away shortly after radiation therapy is stopped, but in some cases side effects can be serious, long lasting, or may never go away. The side effects can be mild or can lead to death.

Radiation therapy: Mild to moderate nausea, vomiting, and loss of appetite are common side effects to radiation treatments. Dehydration is a possible side effect. Other side effects may include difficulty in swallowing, thirst, dry/sore throat, persistent cough, skin reaction/irritation, scarring at the site of radiation, loss of hair, and/or fatigue.

There is not enough medical information to know what the risks might be to an unborn child of a man or woman who takes part in this study. Men who are able to father a child and women who can become pregnant must use one of these birth control plans during this study: condoms, diaphragm, birth control pills, injections, intrauterine device (IUD), surgical sterilization, under the skin implants, abstinence. Another choice is for your sexual partner to use one of these birth control plans. Women who can become pregnant must have a pregnancy test before taking part in this study. For the pregnancy test, urine will be tested within 7 days before you enter the study. You will be told if you are pregnant or not. If the pregnancy test is positive, you will not be able to take part in the study.

**Are there benefits to taking part in this study?**

This study may not make your health better. Although we hope to control your melanoma and stop further tumor growth, no benefit is guaranteed.

**What other choices do I have if I don't take part in this study?**

You do not have to be in this study to receive treatment for your condition. Your other choices may include other investigational drugs or treatments. There is also the choice of getting no active treatment of the cancer but giving care and support to make you as comfortable as possible during the course of the disease. Your doctor can talk to you about your disease and how helpful other treatments are. You should talk to your doctor about each of these choices before you decide if you will take part in this study.

**What are the costs of tests and procedures?**

You and/or your health plan will need to pay for all tests and exams that are part of this study because they are needed for your regular medical care. Before you take part in this study, you should call your health insurer to find out if the cost of these tests and/or exams will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

**Who can answer my questions?**

You may talk to Dr. Barbara Pockaj calling the Mayo operator at telephone (507) 284-2511 at any time about any question you have on this study.

You can get information about policies, the conduct of the study, or the rights of research subjects from Cindy L. Boyer, Administrator of the Mayo Foundation Office for Human Research Protection, telephone (507) 284-2329.

**Where can I get more information about clinical trials?**

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI Web site: <http://www.cancer.gov/>

**What happens if I am injured because I took part in this study?**

You will not get free medical care or money for any bad side effects from taking part in this study. Medical services will be given at the usual charge.

**What are my rights if I take part in this study?**

You do not have to take part in this study, but if you do, you can stop at any time. Your medical care now or in the future will not be affected if you take part in this study or not.

You do not give up any of your rights by taking part in this study.

**What about confidentiality?**

Data from this study may be written up. Your name and other identifying data will not be given outside of North Central Cancer Treatment Group (NCCTG) without written permission unless the law allows it. Your medical record will be used by the researchers in this study. Your medical records may be made

available to the NCCTG, the National Cancer Institute, and/or the Food and Drug Administration as stated in federal rules, or to the Office for Human Research Protections.

**I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to participate in this study.**

\_\_\_\_\_  
(Date)                      \_\_\_\_\_  
(Printed Name of Participant)

\_\_\_\_\_  
(Signed Name of Participant)

\_\_\_\_\_  
(Date)                      \_\_\_\_\_  
(Printed Name of Individual Obtaining Consent)

\_\_\_\_\_  
(Signed Name of Individual Obtaining Consent)

## Appendix II

### Radiation Therapy Quality Control Guidelines

See Section 7.0 for treatment parameters.

- Add 1
1. Tumor bed Coverage (protocols require a 2-3 cm radiographic margin on the simulation film from the incision). Simulation and CT should be performed with a radio-opaque marker on the incision.
    - a. No deviation--coverage +/- 1 cm of specified.
    - b. Minor deviation--coverage +/- >1 to 2 cm of specified.
    - c. Major deviation-->2 cm of specified.
- Add 1
2. Regarding spinal cord/eye/lung/brain (dose-limiting structures) limits:  $\leq 24$  Gy
    - a. No deviation--dose-limiting structure:  $< 105\%$  of specified.
    - b. Minor deviation--dose-limiting structure: 106-110% of specified.
    - c. Major deviation--dose-limiting structure:  $> 110\%$  of specified.
- Add 1
3. Isodoses--point dose calculations are not satisfactory. Composite isodose plots are required at central axis and all dose-limiting structures must be shown on the isodose plot. This will require CT-based dosimetry for fields that include any of the above-mentioned, dose-limiting structures, at 1 cm intervals throughout the field length. For tumor sites distant from dose-limiting structures, a central axis composite isodoses plan will suffice. A radio-opaque marker should be placed on the incision for the CT and shown on the dosimetry plan. The 95% (28.5 Gy), 90% (27 Gy), and 80% (24 Gy) isodoses must be shown on the plan. The depth of the tumor bed (tumor thickness) should be shown on the isodose plots. Simulation films (with radio-opaque marker on the incision) are required for submission.
    - a. No deviation--isodoses are submitted as required and doses within 95-110% of specified.
    - \*b. Minor deviation--isodose information incomplete or doses within 90-94% or 111-120% of specified.
    - \*c. Major deviation--no isodoses submitted or doses  $< 90\%$  or  $> 120\%$  of specified.

\*Submission deviations would only occur if isodose information is incomplete or not submitted after there has been a request to submit complete isodose information.
  4. Other parameters including dose per fraction, total dose, etc.
    - a. No deviation-- $< 5\%$  protocol specification.
    - b. Minor deviation-- $> 5\%$  to 10% protocol specification.
    - c. Major deviation-- $> 10\%$  of protocol specification.

5. Normal structures are only to be included within the radiation field in as much as this is necessary to treat the primary tumor volume. A minor deviation will result when normal structures are unnecessarily included, but this is not felt to result in unacceptable toxicity, which would interfere with the scientific aims of the protocol. A major deviation will result when normal structures are unnecessarily included in the radiation therapy field and such inclusion is felt likely to result in a major increase in toxicity which would potentially compromise the scientific goals of the study.
6. Any individual minor deviation will result in an overall score of minor deviation; any major deviation will result in an overall score of a major deviation. Multiple minor deviations will not add up to a major deviation.

**NORTH CENTRAL CANCER TREATMENT GROUP**

**BRIEF FATIGUE INVENTORY**

Protocol # N0275

Patient ID # \_\_\_\_\_ Initials: \_\_\_\_\_

L F M

Local ID # \_\_\_\_\_ Institution \_\_\_\_\_

Date:   /   /      
m m d d y y y y

**Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes \_\_\_\_\_ No \_\_\_\_\_**

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right **NOW**.

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

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **USUAL** level of fatigue during the past 24 hours.

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

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **WORST** level of fatigue during the past 24 hours.

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