MSK PROTOCOL COVER SHEET

A Randomized Trial of Early, Upfront Palliative Radiation Therapy versus Standard of Care for Patients with Highest Risk Asymptomatic or Minimally Symptomatic Bone Metastases

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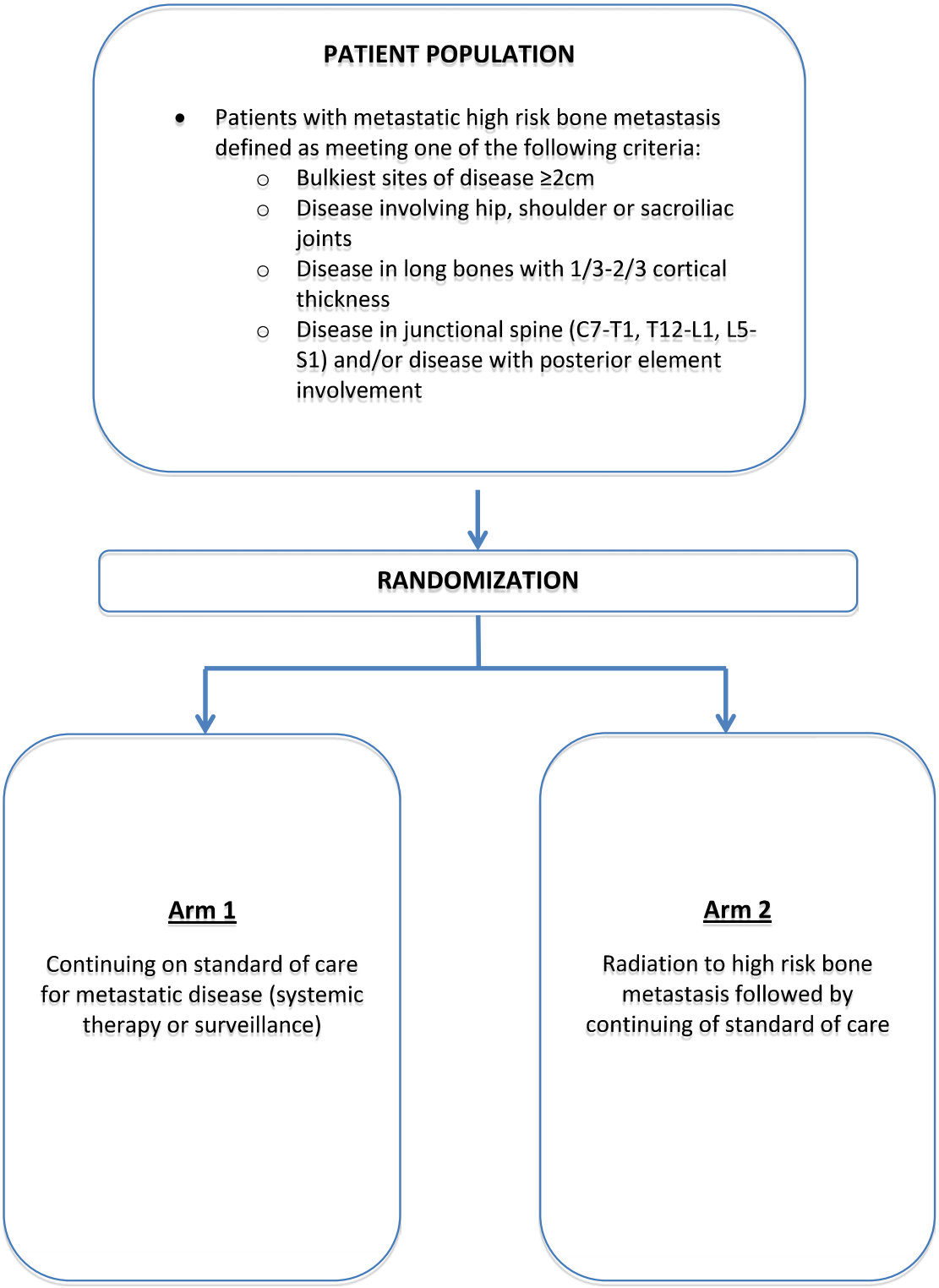
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title:	A Randomized Controlled Trial of Early, Upfront Palliative Radiation versus Standard of Care for Highest Risk Asymptomatic or Minimally Symptomatic Bone Metastases
Hypothesis:	Upfront, early palliative radiation of the highest risk asymptomatic or minimally symptomatic (non-opioid dependent) bone metastases in patients will lead to fewer skeletal-related events (SREs), defined as pathological fractures, spinal cord compression, or palliative radiotherapy or orthopedic surgery to bone.
Objectives:	**Primary Objective:** • To assess whether early palliative radiation of the highest risk asymptomatic/minimally symptomatic bone metastasis in patients with metastatic cancer can decrease the number of SREs, defined as pathological fractures, spinal cord compression, or palliative radiotherapy or orthopedic surgery for bone metastases. **Secondary Objectives:** • To compare the number of hospitalizations related to SREs between standard of care and upfront RT arms • To compare pain-related quality of life of between standard of care and RT arms, using the Brief Pain Inventory (BPI) form • To collect health care utilities in the standard of care and RT arms using the EuroQol Group EQ-5D-5L form • To compare pain-free survival (PFS) and overall survival (OS) between RT and standard of care arms. • To evaluate CTCAE v4 toxicity events in the upfront RT arms.
Patient Population:	Patients with metastatic solid tumors of metastatic disease.
Design:	Randomized, prospective trial.
Treatment Plan:	In this trial patients will be divided into 2 cohorts. Patients in Cohort 1 will undergo standard of care therapy for bone metastases. Patients in Cohort 2 will undergo upfront RT to ≤5 highest risk bone metastases first followed by standard of care therapy.
Number of Patients:	We plan to recruit 74 patients (see details of eligibility in the biostatistics section) to this protocol over 2 years.

PROTOCOL SCHEMA



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To assess whether early palliative radiation of the highest risk asymptomatic or minimally symptomatic bone metastasis in patients with metastatic cancer can decrease the number of SREs, defined as pathological fractures, spinal cord compression, or palliative radiotherapy and orthopedic surgery to bone.

Secondary Objectives:

- To compare the number of hospitalizations related to SREs between standard of care and upfront RT arms
- To compare pain-related quality of life of between standard of care and RT arms, using the Brief Pain Inventory (BPI form
- To collect health care utilities in the standard of care and RT arms using the EuroQol Group EQ-5D-5L form
- To compare pain-free survival (PFS) and overall survival (OS) between RT and standard of care arms.
- To evaluate CTCAE v4 toxicity events in the upfront RT arms.

3.0 BACKGROUND AND RATIONALE

Radiation Therapy for Treatment of Bone Metastases

Patients with metastatic cancer are living longer due to advances in therapy. Bone metastases are a common manifestation for distant relapse for many solid tumors, and it is the third most common organ affected by metastases[1]. Bone metastases represent a prominent source of cancer related morbidity. A metastatic bone lesion can impair function and decrease quality of life due to acute or chronic pain. It can also cause pathologic fracture and spinal cord compression. These skeletal-related events (SREs) are frequently addressed with palliative radiation therapy (RT) as it is an extremely effective palliative treatment for bone metastases[2]. The current standard of care in patients with multiple bone metastases is to continue systemic therapy or observation, and patients are referred for consideration of palliative RT when the metastases become symptomatic. In the recently published American Society of Therapeutic Radiation Oncology consensus guideline, use of palliative radiation therapy in the treatment of painful bone metastases demonstrated a response rate of 70-80% in pain control across multiple studies[3]. For the treatment of spinal cord compression, prospective trial also demonstrated a response rate of 90% 3 months after RT[4].

Rational to Study Timing of Radiation

Early palliative care has been shown to improve the quality of life and even survival for patients with metastatic cancer[5,6]. More and more supportive oncology teams in cancer centers now advocate for early integration of radiation therapy in a patient"s palliative management course. While multiple randomized studies have evaluated the efficacy of different radiation therapy regimens in the treatment of symptomatic bone lesions[7,8], there has not been a study that examined the impact of early, upfront radiation for asymptomatic or minimally symptomatic (non-opioid dependent) bone metastases and its efficacy in preventing SREs.

To better understand the pattern of inpatient radiation oncology care, an institutional inpatient radiation oncology consult registry was created which demonstrated that 319 of the 1,151 inpatient consults requested between July 2015 and June 2016 were for evaluation of symptomatic bone metastases in patients who were hospitalized for acute or chronic pain. Among these patients, two-thirds went on to receive RT for pain management. The most common sites treated with RT were spine (50%), joints such as hip and shoulder (11%), and long bones such as femur and humerus (11%). The median survival of all patients who were evaluated was 4 months, and 9% percent of patients discontinued RT to transition to hospice care, 8% died before the end of planned RT. Our data showed that in this selected patient population admitted for pain management of bone metastases, the overall prognosis is poor. Nevertheless, 61% of treated painful bone metastases were diagnosed at >4 months prior to RT. While RT is an effective treatment modality for palliation, it does appear RT may be delivered too late. The proposed trial seeks to understand whether it is beneficial to patients with metastatic disease to change the treatment paradigm to one of early, upfront RT prior to the development of symptomatic disease.

Skeletal-Related Events as the Primary Endpoint

Skeletal-related events include fracture, spinal cord compression, and radiation or surgical interventions to bone such as for pain. SREs significantly impact health-related quality of life in patients with metastatic disease, and these events can also be distinctly measured and have been used as endpoints in clinical trials investigating therapies for bone metastases. Data from untreated arms of controlled trials of osteoclast inhibitors indicate that SREs ranged from 50-70% at 1-2 years, and treatment reduced the incidence to 38-50%[12,13]. A phase III trial evaluating zoledronic acid in patients with metastatic prostate cancer or renal cell carcinoma demonstrated SRE rates of ~50% in patients with prostate cancer and ~90% in patients with metastatic renal cell carcinoma at 1 year[14]. In another study, it was found that the baseline rate of SRE in patients with metastatic solid tumors with bone metastases was ~65% at 1 year, with the median time to SRE time being 155 days[15]. Radiation therapy significantly reduces the risk of SREs in patients with symptomatic bone metastases[16]. Nevertheless, no study to date has addressed the question whether RT to asymptomatic or minimally symptomatic highest risk bone

metastases would significantly reduce risk of developing SREs in patients with bone metastases.

Highest Risk Bone Metastases

There is a paucity of data on the definition of highest risk bone metastases. However, based on the retrospective data from our institution, the most commonly treated bone metastases in inpatients for pain were in the spine (51%), joints such as hip and shoulder (11%) and long bones such as femur and humerus (11%). Thus, we propose to define the highest risk lesions as: 1. bulkiest sites of osseous disease ≥ 2cm, 2. disease involving the hip (acetabulum, femoral head, femoral neck), shoulder (acromion, glenoid, humeral head), or sacroiliac joints 3. Disease in long bones with1/3-2/3 cortical thickness (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpus, phalanges) 4. Disease in junctional spine (C7-T1, T12-L1, L5-S1) and/or disease with posterior element involvement. Disease in the tibia or femur measuring > 2/3 cortical thickness is by Mirel's criteria at high-risk for a pathological fracture and should be treated surgically[17].

The use of preventative radiation in treating asymptomatic bone lesions is accepted, and has been documented in the literature[9,10]. In 2010, Harada et al. evaluated 72 patients with 84 femoral lesions who received palliative radiation therapy. Of the 72 patients, 66 patients had symptomatic metastases and 7 patients had asymptomatic metastases. The radiographic response after radiation was 42% 3 months after radiation and was not found to be associated with pain relief, suggesting that radiation is effective in treating symptomatic and asymptomatic lesions[11]. While radiation is frequently used to prevent bone metastases related complications from both symptomatic and asymptomatic bone lesions, the decision on whether radiation should be used for an asymptomatic bone lesion is extremely subjective as there has not been any prospective trial. We hope this study will allow us to gain knowledge on when radiation should be used to prevent SREs for future consensus.

Hospitalization

SREs are associated with significant health resource utilization. In a recent multicenter, observational study designed to describe cross-regional differences in health resource utilization of SREs in Europe and US, Durah et al.[18] reported 25% of reported SREs required inpatient hospitalization with mean of 18 days stay. Furthermore, 96% of the SREs resulted in inpatient and/or outpatient procedures, with radiation therapy to bone being the highest SRE type associated with highest number of procedures. In another study, 26% of SREs were associated with inpatient hospital stay with mean duration of 19.5 days[19]. Interventions that prevent the development of SREs have been shown to significantly reduce costs associated with SREs[20], accounting for the costs of interventions. SREs result in considerable health resource utilization and impose a substantial financial burden. This study will be investigating the impact of upfront radiation therapy on the number of hospitalizations related to SREs in patients with high risk bone metastases.

Innovation

The current standard of care of radiation for symptomatic bone lesions, which was established in the 1980s when the prognosis of patients with metastatic cancer was inferior to what it is now, and thus, may no longer be appropriate for metastatic cancer patients in the modern era of improved systemic therapy. There are several theoretical benefits to early, upfront RT of asymptomatic or minimally symptomatic bone metastases, such as reducing the risk for SREs. Furthermore, risks for developing painful bone metastases can be also reduced with early RT therefore improving pain-free survival and quality of life. Finally, there are significant direct and indirect costs associated with hospitalizations for painful bone metastases. This trial proposes the evaluation of a new treatment paradigm, in which bone metastases are treated with upfront RT before they become symptomatic in the outpatient setting.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a randomized (1:1) single institution trial in patients with metastatic solid tumors. Subjects will be randomized to receive either standard of care or upfront, early RT to high risk bone followed by standard of care therapy at the discretion of the treating medical oncologist. At the time of randomization, physicians will fill out the Lesions Identification Worksheet (Appendix) to document the ≤5 highest risk bone metastases per protocol definition to be followed during the protocol in both arms.

4.2 Intervention

4.2.1 Standard of Care

Patients randomized to Arm 1 will undergo appropriate therapy as determined by their oncologist. These patients will either continue their current therapy or be transitioned to a new standard of care therapy at the discretion of the treating oncologist. If randomized to Arm 1, these patients may undergo palliative RT for progressive, painful lesions (a skeletal related event) at time of symptom development (not upfront palliative RT).

4.2.2 Upfront, Early RT

Patients enrolled on Arm 2 of the study will undergo selective RT to 5 or less high risk bone metastases defined as 1. bulkiest sites of osseous disease ≥ 2cm, 2. disease involving the hip (acetabulum, femoral head, femoral neck), shoulder (acromion, glenoid, humeral head), or sacroiliac joints 3. disease in long bones with1/3-2/3 cortical thickness (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpus, phalanges) 4. disease in junctional spine (C7-T1, T12-L1, L5-S1) and/or disease with posterior element involvement. Bone metastases that are within 3cm of each other will be treated as one site. Patients may undergo systemic therapy concurrently with RT at the discretion of

treating radiation oncologist and medical oncologist. After completion of RT, patients will continue standard of care therapy per the treating oncologist.

4.2.3 Brief Pain Inventory Short Form

Patients enrolled on either arm will undergo assessment of patient reported cancer-specific pain questionnaire using the Brief Pain Inventory Short Form at baseline, 3 months, 6 months, 12 months and optionally but recommended within one week of any SRE (Appendix, ~5 minutes to complete). For patients randomized to receive upfront, early RT, they will complete the form once every 5 treatment days during RT. The Brief Pain Inventory is a validated method in rapidly assessing the severity of pain and its impact on functioning[21]. It is a 9 item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. Patients are asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10 point scale. Patients will be able to rate their pain on a 0 to 10 scale, 0 being no pain and 10 being the worst pain, for different time points (within the last 24 hours, on average, at the time of filling out the form). Patients will also be asked what treatments or medications they are receiving for pain from their understanding, and how much relief they received from the pain treatment and medications (0% being no relief and 100% being complete relief). Patients will also evaluate how much the pain has interfered with their activities and function (0 being does not interfere and 10 being completely interferes).

4.2.4 EuroQol, EQ-5D-5L

Patients enrolled on either arm will undergo assessment of patient reported health utilities using the EuroQol EQ-5D-5L questionnaire at baseline, 3 months, 6 months, 12 months, and optionally but recommended within one week of any SRE (Appendix, ~10 minutes to complete). For patients randomized to receive upfront, early RT, they will complete the form prior to RT. It is a standardized instrument created by the EuroQol Group as a measure of health utility[22,23]. It is a generic global quality of life measurement tool. It consists of a descriptive system that includes 5 dimensions (5D, each measured by a single item) (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can be assessed on 5 levels (5L) (no problems, slight problems, moderate problems, severe problems, and extreme problems). Respondents are asked to indicate which response option best describes their health “today”.

Respondents are asked to indicate their health state by marking the box associated with the most appropriate statement in each of the 5 dimensions, resulting in a one digit number expressing the level selected for that dimension (1-5 from no problems to extreme problems, note these do not carry numeric value and should not be summarized as such)

- The digits for the 5 dimensions are then combined into a 5-digit code describing the respondent"s overall health state

- The 5-digit health states are then transformed to overall index values (sometimes called preference values, utilities, or QALY weights) based on country-specific value sets provided by the EuroQol Group. The United States value set will be used to obtain the overall index values and are available at http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html for the current study. The index value has interpretive anchors at 0 (dead) and 1 (best possible health).
- In order to minimize missing values on the overall index value, missing values are given a numeric value of 9; ambiguous values (i.e. two responses to the same question) are also given a numeric value of 9 and are accounted for in the published overall index values.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Radiation Therapy

Radiation therapy will be delivered according to department standards. For this protocol, total dose and dose fractionation may be delivered at the discretion of the treating radiation oncologist according to department standards. All techniques including conventional, 3D-CRT, or IMRT technique may be used. Image guidance at the time of treatment delivery to verify patient positioning may be chosen at the discretion of the treating radiation oncologist according to department standards.

5.2 Systemic Therapy

Standard of care systemic therapy, including chemotherapeutics, targeted therapies, immunomodulatory agents, and hormonal therapies will be delivered at the discretion of the treating medical oncologist. Patients may receive systemic therapy concurrently and there are no restrictions on initiation of systemic agents after radiotherapy including immunotherapy and hormonal therapy, the timing of which will be determined by a consensus between the treating medical and radiation oncologists.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.1 Subject Inclusion Criteria

- Histologically confirmed solid tumor malignancy with greater than 5 sites of metastatic disease detected on imaging.
- Has high risk bone metastases that are asymptomatic or minimally symptomatic (not requiring opioids). High risks metastases are defined as: 1. bulkiest sites of osseous disease ≥ 2cm, 2. disease involving the hip (acetabulum, femoral head, femoral neck),

shoulder (acromion, glenoid, humeral head), or sacroiliac joints 3. disease in long bones with1/3-2/3 cortical thickness (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpus, phalanges) 4. disease in junctional spine (C7-T1, T12-L1, L5-S1) and/or disease with posterior element involvement.

- ECOG performance status 0 – 2.
- Age ≥ 18 years.
- Able to provide informed consent.
- Patients at reproductive potential must agree to practice an effective contraceptive method. Women of childbearing potential must not be pregnant or lactating.

6.2 Subject Exclusion Criteria

- Previous radiotherapy to the intended treatment site that precludes developing a treatment plan that respects normal tissue tolerances.
- Serious medical co-morbidities precluding radiotherapy.
- Pregnant or lactating women.
- Target lesion(s) is/are complicated bone metastases that include clinical or radiological evidence of spinal cord compression or impending pathological fracture.
- Leptomeningeal disease.
- Malignant pleural effusion.
- Absolute neutrophil count (ANC) <1.0 K/mcL and platelet count <50 K/mcL at time of enrollment.
- Patients whose entry to the trial will cause unacceptable clinical delays in their planned management.

7.0 RECRUITMENT PLAN

A member of the patients treatment team, the site protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC) will identify potential research participants. If the investigator is a member of the treatment team, s/he will screen their patient"s medical records for suitable research study participants. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The site principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the

treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

The following tests must be completed prior to enrollment unless otherwise specified:

Prior to study entry (randomization):

- Standard of care biopsy proving malignancy, with clinical documentation consistent with metastatic disease, per physician discretion.

Within 6 weeks (42 days) of study entry (randomization):

- CT CAP, FDG-PET/CT scan, MRI Total Spine or NaF-PET can be used, imaging study is at the discretion of the treating physician.
- Other local imaging studies that include the target lesion(s) can also be used as baseline imaging at the discretion of the treating physician.

Within 4 weeks (28 days) of study entry (randomization):

- CBC with differential
- Comprehensive metabolic panel (CMP=Na, K, Cl, CO2, BUN, Creatine, Ca, Glucose, total protein, albumin, alk phos, total bilirubin, AST and ALT).
- Complete medical history including current medications, comorbidities and performance status
- Physical exam including weight, height and vital signs (O2 saturation, blood pressure, heart rate, respiratory rate, and temperature).
- BPI short form and EQ-5D-5L .
- Lesion Identification Worksheet should be completed by physicians

9.0 TREATMENT/INTERVENTION PLAN

Patients who have metastatic cancer and greater than 5 sites of disease will be enrolled. Patients may also have newly diagnosed stage IV disease. Patient will be randomized to standard of care therapy or to receive RT to selective bone metastases prior to continuation of standard therapy.

9.1 RT

Patients will undergo RT to each lesion using one of the dose and fractionation regimens in the table below. Accounting for the patient's global clinical status, the treating radiation oncologist should select a RT regimen that would result in optimal lesion local control while not exceeding local normal tissue radiation tolerance:

Total Dose	Fractions	Dose per Fraction	Verification Imaging
2000cGy	5	400cGy	MV or KV
3000cGy	10	300cGy	MV or KV
3000cGy	5	600cGy	KV and CBCT
3500cGy	5	700cGy	KV and CBCT
2400cGY	3	800cGy	KV and CBCT
2700cGy	3	900cGy	KV and CBCT
2400cGy	1	2400cGy	KV and CBCT

Patients will first be simulated using appropriate immobilization as determined by the treating radiation oncologist. This will be followed by acquisition of a CT scan in the treatment position. The use of intravenous or oral contrast will be at the discretion of the treating radiation oncologist. Dose constraints will be followed according to department standards and will depend on the radiation technique and total dose prescribed.

The treating radiation oncologist must delineate the gross tumor volume (GTV). Clinical target volume (CTV) will be defined as the GTV plus a margin required for microscopic extension of tumor. The planning target volume (PTV) should expand the CTV by an amount necessary to account for uncertainty in patient positioning and treatment delivery.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All patients in Arm 2 (RT arm) will be assessed for toxicities according to CTCAE v 4.0 and pain score using BPI short form once every 5 treatment days. Only patients in Arm 2 (RT arm) will have radiation treatment related adverse event evaluation. Following randomization, all patients in Arm 1 and Arm 2 will be scheduled for follow-up at 3 months (+/- 4 weeks), 6 months (+/- 4 weeks), 12 months (+/- 4 weeks), and receive the following assessments:

- CBC with differential
- Imaging studies (Follow-up imaging at the discretion of the treating physicians)
- History and physical
- Performance status
- Adverse event evaluation (CTCAE V 4.0) (Excluding Arm 1 patients)
- BPI Short Form
- EQ-5D-5L
-

In the event of an SRE, the following assessments should be completed within one week. As it may not be feasible that the research team will be notified of all SREs within one week, or a patient may not be able to come to MSK, these assessments are optional, but highly recommended:

- CBC with differential
- Imaging studies (Follow-up imaging at the discretion of the treating physician)
- History and physical
- Performance status
- Adverse event evaluation (CTCAE v 4.0)
- BPI Short Form
- EQ-5D-5L

. If patient is unable to come in for a follow-up appointment or within one week of an SRE occurring, a telephone follow-up will suffice. The CBC with differential, history and physical, performance status and imaging studies will be deferred. If the patient has had any of these assessments completed locally, records should be obtained to fulfill these requirements. If the attending physician is able, the adverse event evaluation can be completed over the phone.

Additionally, the BPI Short Form and EQ-5D-5L can be completed over the phone or sent to the patient via mail, fax or electronic mail by the physician, physician office assistant or research staff. For SRE, it is preferred that the BPI Short Form and EQ-5D-5L are completed over the phone if patients are unable to come in for a follow-up appointment. If the patient cannot be reached by phone or prefers to complete the questionnaires personally, the questionnaires will be sent via mail, fax or electronic mail. The questionnaires sent directly to patients must be blank forms with no patient identifiers, only study ID numbers. If questionnaires are sent via mail, the patient must be provided with a pre-filled business envelope that will allow patients to return it with no expense. Patients must also have the option of returning questionnaires by electronic mail or fax. If a patient is unable to come in for a follow-up appointment or complete the questionnaires over the phone, the method by which questionnaires are sent to patients and the method by which questionnaires are returned will be determined based on the patient's preference or if they are unable to be contacted by phone, the contact information on file for the patient as some patients may not have access to a phone, fax or electronic mail.

	Prior to randomization	Within 4 weeks prior to randomization	Once every 5 treatment days during radiation	3 months following randomization +/- 4 weeks	6 months following randomization +/- 4 weeks	12 months following randomization +/- 4 weeks	Within one week of SRE[4]
Standard of care biopsy of a metastatic lesion or pathology review confirming metastatic cancer[1]	X						
CBC with differential		X		X	X	X	X
CMP		X					
Imaging studies[5]		X		X[2]	X[2]	X[2]	X[2]
History and physical		X		X[3]	X[3]	X[3]	X[3]
Performance status		X		X	X	X	X
Adverse event evaluation (CTCAE v 4.0)			X	X	X	X	X
BPI Short Form		X	X	X	X	X	X
EQ-5D-5L		X		X	X	X	X
Lesions Identification Worksheet		X					

[1] For patients with prostate cancer, an elevated PSA consistent with metastatic disease is adequate in the absence of a biopsy.

[2] Follow up imaging at the discretion of the treating physician. The same imaging modality is encouraged for assessment between time points.

[3] Patient's height is not needed at follow ups and SRE.

[4] All assessments following an SRE are optional, but highly recommended

[5] Baseline imaging can be obtained within 6 weeks of study entry

11.0 TOXICITIES/SIDE EFFECTS

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used to evaluate toxicities. Adverse events will depend on the sites receiving RT and the normal tissues adjacent to those sites.

All patients undergoing RT are likely to experience fatigue within the first several months of treatment. RT toxicities will depend on the region treated as well as the regimen. If surgery is needed on the radiated bone, patient can also be at higher risk for infection. Additional possible toxicities associated with RT include and not limited to, by site:

Thorax

Likely
- Musculoskeletal: chest wall pain
- Dermatologic: skin erythema, soft tissue edema, hyperpigmentation
- Gastrointestinal: esophagitis

Less likely
- Pulmonary: cough, shortness of breath, pneumonitis

Rare but serious
- Cardiac: pericardial effusion, pericarditis
- Neurosensory: transverse myelitis, brachial plexopathy
- Gastrointestinal: esophageal stenosis, perforation, fistula formation.
- Musculoskeletal: rib fractures

Abdomen/Pelvis

Likely
- Dermatologic: skin erythema, soft tissue edema, hyperpigmentation
- Gastrointestinal: nausea, vomiting, diarrhea (during therapy)

Less likely
- Hematologic: decrease in blood counts leading to infection
- Genitourinary: bladder irritation

Rare but serious
- Gastrointestinal: bowel ulceration, GI bleeding, fistula formation, bowel obstruction, radiation induced liver disease
- Renal: radiation nephropathy with permanent decline in renal function
- Neurosensory: transverse myelitis, brachial plexopathy

Spine

Likely
- Dermatologic: skin erythema, soft tissue edema, hyperpigmentation
- Gastrointestinal (risk depends on proximity to esophagus or bowel): esophagitis (cervical/thoracic spine), radiation laryngitis or pharyngitis (upper cervical spine), nausea and vomiting (during therapy).

Less likely
- Pulmonary: pneumonitis (thoracic spine)
- Hematologic: decrease in blood counts leading to infection

- Neurosensory: pain flare

Rare but serious

- Musculoskeletal: vertebral body compression fracture
- Neurosensory: transverse myelitis, brachial plexopathy
- Gastrointestinal: esophageal or bowel ulceration, GI bleeding, fistula formation, bowel obstruction, esophageal perforation

11.1 Adverse Event Reporting

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version v4.03 for adverse event (AE) reporting. After informed consent is signed, study site personnel will record the occurrence and nature of each patient"s pre-existing conditions, including clinically significant signs and symptoms of the disease. During the study, site personnel will record any change in the pre-existing condition(s), and the occurrence and nature of any new adverse events.

All AEs related to protocol procedures are reported. All AEs occurring after the patient receives the first dose of radiation therapy must be reported in regard to their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, and/or radiation modality via CRF. If a patient"s radiation treatment is discontinued as a result of an AE, personnel must clearly report the circumstances and data leading to any dosage reduction or discontinuation of treatment.

Events leading to the clinical outcome of death due to disease progression will be included as part of the safety and efficacy analyses for this study.

If a death is considered related to treatment, the death should be reported as a Serious Adverse Event and appropriate guidelines followed for SAE reporting. Any clinically significant findings from labs, vital sign measurements, and other procedures should be reported as well.

11.2 Definitions of Adverse Events

11.2.1 Adverse Event (AE)

Defined as any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or, procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure, whether or not considered to be related. Resources containing information on AEs include monthly transcripts, assessment forms obtained after each clinic visit, and hospital progress and discharge notes. Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported appropriately.

11.2.2 Related or Possibly Related AE

An AE is “related or possibly related to the research procedures,” if in the opinion of the principal investigator, it is more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder, or condition of the subject, or by other circumstances unrelated to the research are not “related or possibly related”. If there

is any question whether or not an AE is related or possibly related, Grade 3 or higher AE should be reported to the PI and IRB.

11.2.3 Unexpected AE

An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the foreseeable risk of adverse events associated with the research procedures described in protocol-related documents, such as the IRB approved research protocol, informed consent document, product labeling and package inserts, and; (b) the characteristics of the subject population being studied, including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor profile for the adverse event. AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol.

11.2.4 Attribution to Radiation Therapy

For reporting purposes, attribution is the assessment of the likelihood that an adverse event is caused by the research agent, or protocol intervention. The attribution is assigned by the principal investigator after considering the clinical information, the medical history of the subject, and the past experience with the research agent/intervention.

This is recorded using one of the following five categories:

- Unrelated
- Unlikely Related
- Probably Related
- Possibility Related
- Definitely Related

Related events are those which are most certainly caused by the procedures involved in the research.

Possibly related events are those which may have been caused by the procedures involved in the research.

Not related events are those which are due to an underlying disease, disorder, or condition of the subject, or due to other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Unknown events are those which have an unclear relationship to the procedures involved in the research, both because more information is needed, and will be provided in follow-up, or because there is no way to make a determination.

11.3 Follow-up of Adverse Events

All adverse events will be followed up according to Good Clinical Practice.

During Treatment: Throughout the duration of the study, site personnel will track any change in the condition(s), the occurrence, and the nature of any AEs, and record the highest grade of the adverse event per cycle on the CRF. CTCAE grading will be assigned before each visit for any adverse events experienced during the previous visit period.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Primary Outcome Measurement

The primary endpoint of this study is the number of skeletal related events (SREs), which will be defined as pathological fractures, spinal cord compression, or palliative radiotherapy and orthopedic surgery to bone.

12.2 Secondary Outcome Measurements

Patients on both arms will be followed for accumulation of surrogates of health care cost, including number and duration of hospitalizations for SREs.

All study participants will be assessed for health related quality of life, measured using the BPI questionnaires, and health utilities using the EQ-5D-5L form.

Patients enrolled on both arms of the study will also be included in an analysis of pain-free survival, defined as time from study entry to start of opioids or death. Patients enrolled on both arms of the study will also be included in an analysis of overall survival, defined as time from study entry to death.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study if any of the following criteria are met, after review by the principal investigator:

1. A change in the patient"s medical status unrelated to RT results in the patient being unable to comply with the protocol.
2. Patient is unable to continue follow-up as outlined within the protocol
3. Patient is found to be ineligible based on the criteria in section 6.0 of this protocol.
4. Patient requests to withdraw from the protocol.
5. Patient death.

Otherwise, patients will continue on protocol until 12 months have elapsed since date of randomization or until an SRE occurs.

14.0 BIOSTATISTICS

The primary objective of this study is to compare the rate of skeletal related events (SRE) from the date of randomization to death or 12 months, whichever occurs first, between patients who received standard of care versus upfront, early palliative RT to high-risk bone metastases. We expect 60-80% of the enrolled patients can be followed for 1 year. An SRE is defined as pathological fractures, spinal cord compression, or palliative radiotherapy and orthopedic surgery for bone pain. Data suggest that the event rate is around 60% in the standard of care arm[12,13,17]. In our institutional experience, 75% of inpatient radiation consultation led to palliative radiation for painful bone

metastasis, an SRE. Furthermore, 61% of these lesions were diagnosed at least 4 months prior to undergoing RT. We believe 60% estimated event rate at 1-year is a conservative estimate.

The primary endpoint is a binary variable and the rate refers to proportion and is defined as the number of lesions that had SRE divided by the total number of target lesions. This analysis is lesion-based so an SRE (or no SRE) at one site does not affect the status of other sites from the same patient. We estimate that the investigational arm has the event rate around 30%. Radiation therapy is extremely effective in alleviating pain due to bone metastases with 70-80% pain control. By preventing the development of significant bone pain, which often leads to SREs, RT can effectively reduce SREs. To this end we will analyze at least 66 patients with valid SRE endpoint (randomized 1:1 to each arm) to achieve >80% power in detecting such a difference using a two-sample, one-sided proportion test with alpha<0.05. Since patients who withdraw before the endpoint can be evaluated will not be included in the analysis (i.e., it will NOT be an intent-to-treat analysis) we will over-accrue to account for withdrawals to ensure a minimum of 33 patients in each arm (subject to stratification, see Section 15.2) who can contribute the analyzable endpoint of SRE. We believe an additional 10% would be sufficient so totally we expect to randomize 74 patients. A small portion of patients (<15%) may have multiple lesions, in which case they will be treated as independent analysis units. In other words, the eventual effect sample size may be slightly higher than 66 because this objective will be analyzed per lesion.

Palliative radiation therapy is a well-established, frequently used treatment for patients with metastatic disease. It is often the standard of care for patients with symptomatic metastatic lesion. It is extremely unlikely to be more toxic or cause earlier deaths.

We expect to enroll all 74 patients within 2 years.

Secondary objectives will be analyzed per patient. Unless otherwise specified, all endpoints are defined within the time window from the date of randomization to death or 12 months, whichever occurs first.

To compare the number of hospitalizations related to SREs between standard of care and upfront, early palliative RT arms we will employ a Wilcoxon rank sum test.

To compare quality of life between standard of care and RT arms, using the Brief Pain Inventory (BPI) and EuroQol Group EQ-5D-5L forms, we will test the difference (between the two arms) of the survey results at the following time points: 3 months, 6 months, 12 months and optionally but recommended within one week of any SRE. The individual quantitative scores derived from the BPI, and the utility scores as well as the overall health scores derived from EQ-5D-5L, will be summarized at these assessment times using descriptive statistics (means and standard deviations, medians and quartiles). Differences between the two arms in terms of these quantitative scores at various time points of interest will be evaluated for both statistical and clinical significance using Wilcoxon rank

sum tests and established minimally important differences (MIDs) for the various measures, respectively. For scale scores with no established MIDs, the "half standard deviation" rule will be applied (i.e., differences of a half standard deviation will be considered clinically significant). At the conclusion of the study data at each time point will be presented, the number of patients in each group at a given time point will be documented, and the mean EQ-5D-5L and BPI scores for each group will be plotted over time and longitudinal pattern will be examined with the possibility of proposing more complicated regression methods such as the linear mixed models. The categorical answers (e.g., YES vs NO) from EQ-5D-5L will be compared between the two arms using Fisher‟s test at each time point as well and odds ratios together with confidence intervals will be computed. Other non-quantifiable answers (e.g., treatment receiving for pain) will be summarized descriptively. For the last question in BPI, the score for pain interference on the BPI Short Form is the mean of the 7 interference questions as long as at least 4 are completed.

For comparing pain-free survival and overall survival between the two arms, both of which are time to event endpoint (time from randomization to start of opioids or death which is not necessarily within 12 months from randomization), we will use log-rank test.

To evaluate CTCAE v4 toxicity events in the upfront RT arms, we will tabulate all toxicities and summarize the CTCAE v4.03 scores and present descriptive statistics. This will be done at 3 months, 6 months, and 12 months from randomization.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff is responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Patients will be randomized to the standard of care therapy arm or the early, upfront RT followed by standard of care therapy arm. For patients enrolled, immediately after consent is obtained, the CRC at MSKCC will register participants in the Clinical Trial Management System (CTMS).Once the participant‟s eligibility is established, the registration will be finalized and the participants will be randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and will be stratified by disease histology and planned standard of care. After

treatment arm is determined by randomization, the CRCs will notify physicians at MSKCC of the treatment arm within 24 hours of randomization. All data will be collected and analyzed at MSKCC.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the (CRC) include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of activities
of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

An assigned (CRC) will work with the principal investigators to ensure proper adherence to the protocol, eligibility verification, informed consent and data accuracy.

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

With the help of the CRC, the principal investigator will review each case at the time of enrollment to verify eligibility. The CRC will work with the principal investigator to ensure that the protocol is followed carefully.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance, and data verification audits, therapeutic response, and staff education on clinical research QA) and department procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees, including the *Data and Safety Monitoring Committee (DSMC)* for phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center"s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation

17.0 PROTECTION OF HUMAN SUBJECTS

Every effort will be made to protect the rights of human subjects per institutional policy. A full discussion of the risks, benefits, expected toxicities, alternatives and treatment options will be undertaken. No additional financial costs or burdens will result as a consequence of joining the study. Informed consent is a prerequisite for enrollment on the study.

In accordance with institutional policy, privacy and confidentiality of medical records will be strictly observed. All data pertaining to the study will also be protected. The study is entirely voluntary. Patients who do not wish to participate in the study will be offered all treatment options including those considered to be the standard of care.

17.1 Privacy

MSK"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant"s last investigational treatment/intervention. Any events that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1 – Brief Pain Inventory Short Form

Appendix 2 – EuroQol EQ-5D-5L

Appendix 3 – Lesions Tracking Worksheet