Cryocompression for Bortezomib-Induced Peripheral Neuropathy Among Multiple Myeloma Patients
Wake Forest Baptist Comprehensive Cancer Center (WFBCCC)
WFBCCC01119

Principal Investigator:

Roy Strowd, MD, Assistant Professor
Neurology
Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

Co-Investigators (alphabetical):

Vanessa Baute, MD, Associate Professor
Neurology
Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

James Caress, MD, Professor
Neurology
Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

Michael Cartwright, MD, Professor
Neurology
Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

Tiffany Statler, DMSc, MSPH, PA-C
Hematology and Oncology
Comprehensive Cancer Center of Wake Forest University
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

Francis O. Walker, MD, Professor
Neurology
Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

Cryocompression for Bortezomib-Induced Peripheral Neuropathy Among Multiple Myeloma Patients
Wake Forest Baptist Comprehensive Cancer Center (WFBCCC)
WFBCCC01119

Biostatistician: Fang-Chi Hsu, PhD
Biostatistics and Data Science
Comprehensive Cancer Center of Wake Forest University
Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC 27157
[redacted]

Study Coordinator: Denisse Funes Valencia
[redacted]

Regulatory Contact: Emily Teal, Regulatory Specialist
[redacted]

Participating Institution(s): Wake Forest Baptist Medical Center

Version Date: 02/04/22
Amended: 02/04/22

Confidential

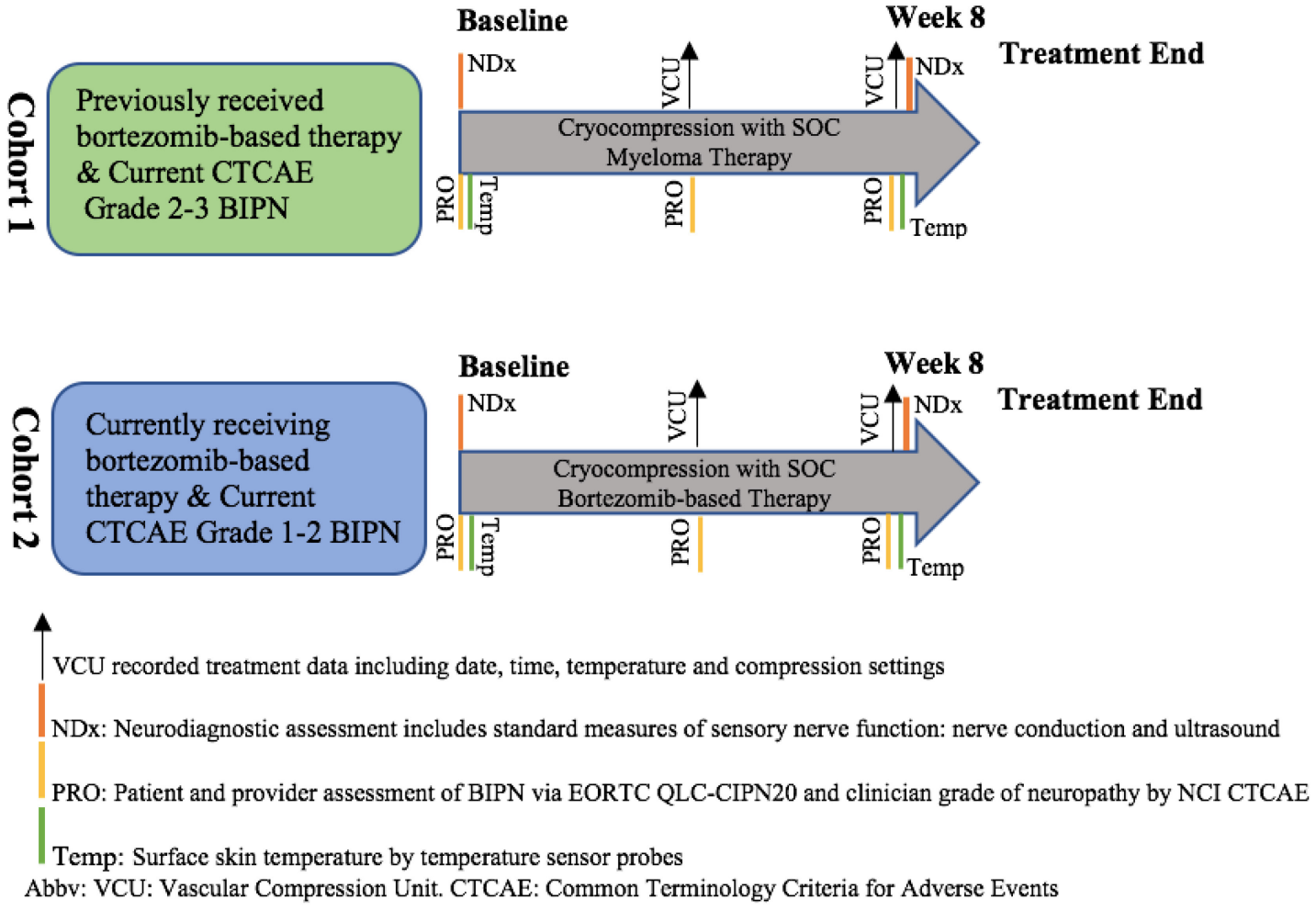
Table of Contents

1.0 Introduction and Background 7
2.0 Objectives 11
2.1 Primary Objective(s) 11
2.2 Secondary Objective(s) 11
2.3 Exploratory Objective(s) 11
3.0 Patient Selection 11
3.1 Inclusion Criteria 12
3.2 Exclusion Criteria 12
3.3 Inclusion of Women and Minorities 13
4.0 Methods 13
4.1 Registration Procedures 13
4.2 Study Calendar* 15
4.3 Study setting 16
4.4 Enrollment and Screening 16
4.5 Baseline Peripheral Nerve Assessment 17
4.6 Muscle Perfusion Assessment 17
4.6.1 Muscle Perfusion Ultrasound (Appendix J) 17
4.7 Treatment Initiation and Titration 17
4.8 Intervention: Home Cryocompression Treatments 18
4.9 Week 4 Assessment 18
4.10 Week 8 End of Treatment Assessment 19
5.0 Adverse Events List and Reporting Requirements 19
5.1 Adverse Event List for Cryocompression 19
5.2 Adverse Event List for Nerve Conduction Studies 19
5.3 Adverse Event List for Ultrasound 19
5.4 Adverse Event Characteristics 19
6.0 Study Outcomes and Study Measures 20
6.1 Primary Outcome 21
6.2 Secondary Outcomes 21
6.3 Exploratory Outcomes 21
7.0 Treatment Plan 21
7.1 Treatment Administration 21
7.2 Treatment Device 22

7.3 General Concomitant Medication and Supportive Care Guidelines 23
7.4 Duration of Therapy 24
7.5 Duration of Follow Up 24
7.6 Criteria for Removal from Study 24
8.0 Treatment Modifications 24
9.0 Correlative/Special Studies 25
10.0 Data Management 27
11.0 Statistical Considerations 28
11.1 Sample Size, Power, and Interim Analysis 28
11.2 Analysis of Primary Objective 28
11.3 Analysis of Secondary Objective 28
11.5 Estimated Accrual Rate 28
11.6 Estimated Study Length 29
12 Confidentiality and Privacy 29
13 Data Safety and Monitoring 29
14 Reporting of Unanticipated Problems, Adverse Events or Deviations 29
References 30
Appendix A – Subject Eligibility Checklist 34
Appendix B – Protocol Registration Form 37
Appendix C – Race & Ethnicity Verification Form 38
Appendix D – Mandatory STRC SAE Reporting Guidelines 39
Appendix E – Clinical Evaluation from History/Examination 39
Appendix F – Patient Reported Outcomes: EORTC QLQ-CIPN20 and PRO-CTCAE 49
Appendix G – Interim Concurrent Medications Form 51
Appendix H – Nerve Conduction Study Data Collection Form 52
Appendix I – Ultrasound Nerve Diameter Data Form 54
Appendix J – Muscle Perfusion Ultrasound 55
Appendix K – Physical Examination 56
Appendix L – Total Neuropathy Score – Clinical Version 57
Appendix M – In-Clinic Treatment Visit 58
Appendix N – Adverse Events Log 60
Appendix O – Home Cryocompression Treatment Log 61
Appendix P – CTCAE Neuropathy Grading Form 65

Appendix Q – Cohort 1 Chemotherapy Form 66
Appendix R – Cohort 2 Chemotherapy Form 68
Appendix S – 30-day Treatment Follow-up Form 70
Appendix T — Life Expectancy Confirmation 71
Appendix U – VCU Data Confirmation.....72

SCHEMA



VCU recorded treatment data including date, time, temperature and compression settings

NDx: Neurodiagnostic assessment includes standard measures of sensory nerve function: nerve conduction and ultrasound

PRO: Patient and provider assessment of BIPN via EORTC QLC-CIPN20 and clinician grade of neuropathy by NCI CTCAE

Temp: Surface skin temperature by temperature sensor probes

Abbv: VCU: Vascular Compression Unit. CTCAE: Common Terminology Criteria for Adverse Events

1.0 Introduction and Background

Peripheral neuropathy (PN) is broadly defined as damage to the peripheral nervous system caused by a primary lesion or dysfunction.[1] Chemotherapy-induced peripheral neuropathy (CIPN) is a common consequence of cytotoxic chemotherapies and results in length-dependent sensory predominant impairments with symptoms of numbness, tingling, burning and pain in hands and feet. CIPN is consistently associated with lower self-reported physical function and quality of life and may contribute to increased cancer mortality as patients often do not complete their full course of chemotherapy due to dose reductions, modifications, or treatment discontinuation. Although the underlying mechanisms of CIPN are only partially understood,[2] CIPN is a small fiber neuropathy that results in reduced nerve fiber density in the skin and can lead to physiologic changes in nerve conduction and anatomic changes in peripheral nerve anatomy.[3]

CIPN is a significant problem for cancer survivors. Prevalence rates of CIPN vary widely based on different patient populations, different grading systems and symptom assessments, but have been found in up to 80% of patients receiving chemotherapy.[4] CIPN is a dose-limiting side effect of many chemotherapeutics including paclitaxel, oxaliplatin, vincristine and bortezomib among other agents.[5] For bortezomib specifically, this agent is one of a class of proteasome inhibitors used for the treatment of multiple myeloma. Treatment-induced peripheral neuropathy is reported to occur in over 75% of bortezomib-treated patients[6-8] and was first reported in phase I trials.[9-11]

1.1 Bortezomib-induced peripheral neuropathy (BIPN)

Bortezomib-induced peripheral neuropathy (BIPN) is a length-dependent sensory neuropathy that presents as a “dying-back” distal axonopathy with numbness, tingling and paresthesia first developing in the hands and feet and often progressing to include neuropathic pain and even motor involvement in 10% of patients.[12,13] Peripheral neuropathy is a significant toxicity of bortezomib that typically begins within the first few cycles of treatment and reaches a plateau through cycle 5 with the risk of further progression with increasing cumulative dose.[14]

BIPN has been thought to result from mitochondrial dysfunction and calcium-dysregulation within the distal peripheral nerve axons.[15] Agents aimed at preventing nerve damage by interfering with proteosomal inhibition (e.g. the anti-tumor mechanism of action) risk reducing the efficacy of bortezomib. To date, there are no pharmacologic or alternative treatment modalities that have been proven efficacious to prevent or treat CIPN and more specifically BIPN. A recent NCI Symptom Management and Health-related Quality of Life Steering Committee symposium concluded that research was needed to understand the mechanisms of CIPN and to identify therapies to prevent or treat CIPN.[16] This group expressed particular interest in non-drug interventions. The NCI considers the development of adjuncts for the prevention and relief of CIPN as essential for patient care.[17]

1.2 Rationale and Clinical Data Supporting Cryotherapy with or without Compression for Treating BIPN

Cryotherapy independently or combined with compression is an attractive modality for treatment of BIPN. Safety and tolerability of cold and compression therapies have been studied in healthy subjects and both cold and compression therapies have previously been studied in the prevention of paclitaxel-induced peripheral neuropathy with favorable but inconclusive results (Table 1).[18-23]

Table 1: Prior studies evaluating cryotherapy with or without compression in patients with chemotherapy induced peripheral neuropathy

Author	Subject population	# of subjects	Treatment	Outcome measures	Exclusion criteria	Safety and Tolerability	Results
Eckhoff[24] September 2013	Enrolled in DBCG-07 READ trial	686/1725 enrolled patients	Frozen gloves and socks	Onset of neuropathy	N/A with specific regard to neuropathy		Incidences of DIPN was lower in patients wearing frozen gloves and socks compared to patients who did not ($p < 0.0001$)
Hanai[19] October 2017	Breast cancer patients treated weekly with paclitaxel; cumulative dose 960 mg/m2	44 enrolled • 4 did not undergo any intervention • 4 did not reach cumulative paclitaxel dose and therefore were not included in analysis	Elasto-Gel gloves and socks placed on the dominant side for 90 minutes, including duration of treatment, 15 minutes prior and 15 minutes post, replaced every 45 minutes	Tactile disturbance, thermosensory disturbance, vibration perception, performance speed Patient Neuropathy Questionnaire (PNQ)	Peripheral sensory/motor neuropathy (Grade>=2); neuralgia or edema; tumor metastasis to bone, soft tissue, or skin of the hands and feet; abscess of fingers or toes; Raynaud's symptoms; peripheral arterial ischemia; hand-foot syndrome	No patients dropped out due to cold intolerance. Reported AEs: • Pain (8.2%) • Sensory abnormalities (0.4%) • Feeling cold (4.2%)	Occurrences of CIPN (PNQ grades C-E) were prevented by cryotherapy (severe CIPN with grades D or E: hand 2.8% vs. 41.7%, OR= infinite, 95% CI = 3.32 to infinite, P<0.001; foot 2.8% vs. 36.1%, OR=infinite, 95% CI = 2.78)
Griffiths[18] April 2018	Taxane naïve female patients receiving paclitaxel therapy for breast cancer	33 enrolled; 29 randomized to treatment • 7 remained at study end	Elasto-Gel glove and sock randomized to dominant or non-dominant side for total of 210 minutes. • 15 minutes pre and post, 180-minute treatment • Replaced every 45 minutes	Neuropathic pain and pain sensitivity (NPSI & BPI, respectively)	Prior taxane therapy; history of peripheral neuropathy; diabetes mellitus; Raynaud's disease	Dropout due to discomfort precluded adequate power to fully understand the potential benefits of cryotherapy.	No significant differences in measures of neuropathy or pain between treated and untreated hands or feet
Younus[21] June 2016	Female patients with early breast cancer planned to receive dose-dense Adriamycin, cyclophosphamide, and Paclitaxel.	23 enrolled	Elasto-gel glove and boot to surgical side (right or left) for duration of paclitaxel infusion Replaced every 30 minutes	Neuropathy grade: NCIC CTC	Previous exposure to taxanes or with prior diagnosis of peripheral neuropathy from any etiology	No discontinuation of cryotherapy by any patient due to cold intolerability	Treated limbs did not develop neuropathy > grade 1 Control limbs developed grades 2 and 3 neuropathy Patients who switched to cryotherapy had improvement of neuropathy
Sundar[20] January 2017	Breast cancer patients scheduled to receive weekly paclitaxel chemotherapy	20 enrolled 2 did not complete all TNS and nerve conduction assessments	Continuous limb hypothermia to randomized limb	NCS and Total neuropathy pain score	Not provided.	Minimal discomfort reported; no serious or lasting adverse events	Mean skin temperature reduction of 1.5 +/- 0.7°C • Grade 3 PN (10%) • Grade 2 PN (10%) • Grade 1 PN (60%) Differences in nerve conduction parameters did not reach significance.

Cryotherapy modalities work by absorbing heat from the tissues being cooled.[25] Cryotherapy may reduce drug delivery to the distal nerve endings, decrease inflammation within the distal nerve microenvironment, or modulate peripheral pain stimuli through gating and peripheral feedback.[26,27] The velocity of nerve conduction fibers is decreased when cryotherapy is applied, therefore producing an analgesic effect. When tissue temperature is decreased 1°C, there is an associated 1.2 m-per-second decrease in motor nerve conduction velocity and a 2 m-per-second decrease in sensory nerve conduction velocity.[25] The benefits of combined cryocompression therapy include improved contact between the skin surface and cryotherapy, greater reduction of blood flow to treated area, and increased insulation effect which may further reduce tissue temperatures.[25,28]

In a pilot study investigating the safety and tolerability of hypothermia for preventing chemotherapy-induced neuropathy, it was determined continuous flow limb hypothermia is safe and well tolerated by healthy subjects for three hours without lasting or serious side effects. Continuous flow hypothermia provides a consistent low temperature throughout duration of therapy which is suspected to provide additional benefits when compared to intermittent replacement of ice packs or other cooling agents.[23]

In another pilot study assessing the use of continuous-flow limb hypothermia in reducing paclitaxel-induced peripheral neuropathy, the continuous-flow limb hypothermia achieved mean skin temperature reduction of 1.5 +/- 0.7°C and was well tolerated for the 3-hour treatment duration. With minimal discomfort reported and no serious or lasting adverse events, this study suggested that continuous-flow hypothermia is a safe and well tolerated method that may reduce paclitaxel-induced peripheral neuropathy.[20]

Treatments like cryotherapy or combined cryocompression therapy which act at the level of the nerve and will not limit the anti-tumor activity of bortezomib-based chemotherapy are ideal for clinical testing and translation in this population. BIPN is a dose-limiting side effect of bortezomib therapy resulting in increased morbidity secondary to decreased quality of life and increased mortality due to treatment discontinuation or dose-reduction. If cryocompression is feasible and shows a signal of activity, this would pave the way to a large study to establish this as the first treatment for BIPN.

1.3 Standard of Care Assessments of Nerve Function

CIPN manifests via several different pathophysiological mechanisms that can be assessed by currently available standard of care methods including physical examination, nerve conduction studies (NCS), peripheral nerve ultrasound, and patient-reported outcome measures. Each of these studies are standard of care for the assessment of sensory-predominant neuropathies such as CIPN.

Physical Examination: Physical exam with quantitative sensory testing (QST) uses tuning forks or monofilaments to objectively measure the sensory threshold for proprioception. QST may be a useful addition to self-reported symptoms as it is non-invasive, easily implemented, and well-correlated with self-reported CIPN symptoms. Although promising, it has not been shown to provide early detection of subclinical CIPN.[29,30]

Patient-Reported Outcome Measures: The European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 Questionnaire is a 20-item self-reported survey that is easy to administer and was validated across participants in four large cooperative group trials.[31] The

QLQ-CIPN20 sensory scale has been shown to be correlated with patient-reported symptoms from the Common Toxicity Criteria (0.79, $p < 0.00001$). For normative comparison, non-cancer patients tend to have very low scores on the QLQ-CIPN20 with a sum score average of 3.6 (standard deviation 7.2) and subtotals of 3.2 (7.3) for sensory measures, 3.8 (9.2) for motor, and 4.4 (10.7) for autonomic. The vast majority of non-cancer patients (90.1%) had a sum score of 0-10%; older age and self-reported comorbidities were associated with higher QLQ-CIPN20 scores. Based on the results from that study, age-matched normative data has been generated for the QLQ-CIPN20.[32] PRO-CTCAE is an item library containing 124 items reflecting 78 symptomatic cancer treatment-related symptoms.[33,34] Two PRO-CTCAE items address CIPN concerning the severity of the numbness and tingling and the degree that these symptoms have interfered with usual or daily activities. These items have previously been shown to have good psychometric properties.[35] The two PRO-CTCAE items have the potential of providing a feasible patient-reported measure in a clinic setting.

Nerve Conduction Studies (NCS): NCS measures impairment of electrical function in large peripheral nerves. NCS measures amplitude and latency of neuronal signaling. Reduction in the conduction velocity within a peripheral nerve indicates damage to the myelin, while reduction in the amplitude indicates axonal damage. Typical NCS findings suggestive of BIPN include low amplitude of sensory action potentials; predominantly affecting the sural nerve, as well as prolonged latency or loss of the H-reflex.[14,36] NCS can be mildly painful for the patient; requires expertise and time to administer and can only detect CIPN once it has progressed to the point that there is functional impairment of large peripheral nerves.[37] Other functional assays besides NCS have been investigated. Sudomotor testing is a novel technique. Although non-invasive, sudomotor testing tends to have wide variability which can make interpretation difficult and it has not yet been tested in chemotherapy-induced peripheral neuropathy. A nerve excitability study is a novel non-invasive functional assay that detects the threshold of current that is needed to elicit an action potential. Similar to US, this experimental technique has been shown that it can detect oxaliplatin-induced peripheral neuropathy.[38]

Peripheral Nerve Ultrasound (US): US is a non-invasive, non-irradiating, emerging imaging modality which can be used to assess peripheral nerves. Nerve fiber cross-sectional area (CSA), echogenicity, and vascularity are assessed and provide an indication of nerve health and potential pathology. The majority of US data have been published on detection of entrapment syndromes such as carpal tunnel syndrome. In these cases, the most common US findings include nerve enlargement, decreased echogenicity proximal to the entrapment, and an increase in nerve vascularity.[39] Other studies have found that US can detect other peripheral nerve lesions or neuropathies, with the most reliable finding a change in nerve CSA. Ultrasound measurements of the sensory sural nerve at the distal calf in healthy participants without neuropathy had an average CSA of 5.3 mm^2 with standard deviation 1.8 mm^2 for a normal reference range of 1.7-8.9 mm^2.[40] Another ultrasound study assessed the sural nerve more distally at the ankle and found a smaller CSA which was significantly enlarged ($p < 0.001$) in patients with diabetic polyneuropathy as compared to healthy controls (mean/standard deviation 2.59/0.96 mm^2 as compared to 1.40/0.59 mm^2).[41]

Each of these assessments including patient-reported outcomes, physical examination, NCS, and peripheral nerve ultrasound are standard of care for patients with sensory-predominant neuropathies such as CIPN and will be included in this trial to provide an objective assessment of peripheral nerve function. As standard of care tests, the risks of these studies are not different than those that would be encountered in routine clinical care for a patient undergoing comprehensive electrophysiological evaluation of peripheral nerve pathology.

2.0 Objectives

The primary objective of this two-arm, open label pilot study is to evaluate the feasibility of daily, 30-minute cryocompression treatments over an 8-week period in multiple myeloma patients. This will be studied in patients with established neuropathy (e.g. previously received bortezomib-based chemotherapy and have clinically documented CTCAE grade 2 or 3 neuropathies, Cohort 1) to explore its role in treating CIPN, and in patients with new-onset neuropathy (e.g. currently receiving bortezomib-based chemotherapy have clinically documented CTCAE grade 1 or grade 2 neuropathy, Cohort 2) to explore its role in preventing worsening of CIPN in patients receiving neurotoxic chemotherapy.

Specific objectives are:

2.1 Primary Objective(s)

2.1.1 To assess the feasibility of daily cryocompression therapy in multiple myeloma patients with BIPN.

2.2 Secondary Objective(s)

To obtain preliminary evidence of the clinical activity of cryocompression including:

2.2.1 To examine the change in patient-reported assessment of neuropathy based on the sensory, motor and autonomic neuropathy scores on the EORTC QLQ-CIPN20 (PRO) from baseline to 4 and 8 weeks after the start of cryocompression therapy.

2.2.2 To examine the change in physician graded assessment of peripheral neuropathy by NCI CTCAE v5.0 criteria from baseline to 4 and 8 weeks after the start of cryocompression therapy.

2.2.3 To assess the effect on sensory and motor nerve function via NCS (e.g. conduction velocity, latency, and amplitude) and neuro-ultrasound after 8 weeks of daily cryocompression therapy.

2.3 Exploratory Objective(s)

2.3.1 To explore the effect of 8 weeks of cryocompression on changes in muscle perfusion as measured by US.

2.3.2 To examine the associations among the peripheral nerve assessment measures (nerve conduction and peripheral nerve US) with the patient reported outcomes (EORTC QLQ-CIPN20, PRO-CTCAE) at baseline, week 4, week 8, and for the change from baseline to week 8.

3.0 Patient Selection

Two cohorts will be enrolled including multiple myeloma patients who have previously received (Cohort 1) or are actively receiving (Cohort 2) bortezomib-based chemotherapy and have clinically documented CTCAE grade 1, grade 2 or grade 3 neuropathy by CTCAE v5.0 criteria.

In Cohort 1, we will enroll multiple myeloma patients with established CTCAE Grade 2-3 BIPN who have previously received a bortezomib-containing regimen and are presently receiving a non-bortezomib containing regimen due to the presence of BIPN.

In Cohort 2, we will enroll multiple myeloma patients with new-onset CTCAE Grade 1-2 BIPN who are actively receiving a bortezomib-containing regimen.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed multiple myeloma (any ISS stage)

3.1.2 Clinical symptoms of bortezomib-induced peripheral neuropathy as measured by the NCI-CTCAE

3.1.2.1 Cohort 1: patients with clinically documented CTCAE grade ≥2 neuropathy
3.1.2.2 Cohort 2: patients with clinically documented CTCAE grade 1-2 neuropathy

3.1.3 Currently or previously received bortezomib-containing regimen

3.1.3.1 Cohort 1: patients who have previously received a bortezomib-containing regimen and have clinically documented neuropathy that is attributed to the bortezomib containing regimen
3.1.3.2 Cohort 2: patients who are currently receiving a bortezomib-containing regimen and have clinically documented neuropathy that is attributed to the bortezomib containing regimen

3.1.4 Age must be $\geq$ 18 years

3.1.5 ECOG $\leq$ 4

3.1.6 Life expectancy $\geq$ 6 months

3.1.7 Ability to understand and the willingness to sign an IRB-approved informed consent document

3.2 Exclusion Criteria

3.2.1 Self-reported or documented history of pre-existing peripheral neuropathy prior to initiation of bortezomib therapy

3.2.2 Other explanatory etiology for neuropathy

3.2.3 Presumptive evidence of congestive heart failure

3.2.4 Current deep vein thrombosis or pulmonary embolism (diagnosed within the past 6 months)

3.2.5 Current pulmonary edema

3.2.6 Unable to provide accurate medical history

3.2.7 Pregnant women are excluded from this study because they will not be receiving myeloma SOC therapy or bortezomib-based therapy per inclusion criteria

3.2.8 Current or previously documented inflammatory phlebitis; thrombophlebitis; decompensated cardiac insufficiency; arterial dysregulation; erysipelas; carcinoma or carcinoma metastasis in the affected extremity; decompensated hypotonia; venous or arterial occlusive disease; Raynaud's disease;

3.2.9 Current monoclonal gammopathy of undetermined significance (MGUS), Waldenstroms macroglobulinemia, or Castleman disease.

3.3 Inclusion of Women and Minorities

3.3.1 Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

3.3.2 The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on WFBCCC population estimates, we expect approximately 55% of participants to be women. Translating this to our sample size estimate of 24, we plan to enroll at least 13 women. We plan to enroll at least 23% Black or African American (N=5). Due to our catchment area population we do not expect accruals of individuals of Hispanic/Latino, American Indian/Alaska Native, or Asian ancestries; however, no one will be excluded if they meet the above outlined inclusion/exclusion study criteria. Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Methods

4.1 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

Contact Information:
Protocol Registrar [redacted]
Protocol Registrar FAX (336) 713-6772
Protocol Registrar [redacted]

*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

   Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient a study number
- register the patient on the study

4.2 Study Calendar*

	Screening (28 days)	Baseline Peripheral Nerve Assessment (Day 1-14 days)	Treatment Initiation and Titration Visit (Day 0, Week 1)	Home Cryocompression Intervention (Weeks 1 - 8)	Week 4 Visit (±10 days) Assessment	Week 8 Visit (±10 days) End of Treatment Assessment	30-day Follow-up
		Can occur on same day or different days					
Informed consent**	X						
Demographics	X						
Medical history	X						
BMI	X						
Concurrent meds	X				X	X	
Patient Reported Outcomes[a]	X				X	X	
Physical Examination[b]	X				X	X	
Neuropathy Grade[c]	X				X	X	
Neurological Examination[d]		X			X	X	
Nerve Conduction Study[e]		X				X	
Peripheral Nerve Ultrasound[f]		X				X	
Muscle Perfusion Ultrasound[g]		X				X	
Skin Temperature[h]			X			X	
Required Research Blood Draw[i]			X			X	
In-Clinic Cryocompression Treatment[j]			X			X	
Home Cryocompression Treatment[k]				X			
Recorded Cryocompression Parameters[l]						X	
Patient Treatment Log[m]				X			
VCU Recorded Treatment Data Report[n]					X	X	
Chemotherapy Treatment Info[o]						X	
Adverse Event Evaluation			X		X	X	X
30-day Treatment Follow Up[p]							X

*The Study Calendar represents an ideal schedule for the completion of study related activities; however, depending on patient and physician availability, the completion of these clinical tasks may occur at any clinical encounter. **The exceptions to this rule are the following: the informed consent should be signed before any research activity occurs.

a. Appendix F. Patient reported outcomes of bortezomib-induced peripheral neuropathy as measured by EORTC QLQ-CIPN20 and NCI-CTCAE.
b. Appendix K. Physical examination to include peripheral pulses and peripheral sensation.
c. Appendix P. Physician recorded neuropathy by grade NCI CTCAE v5.0 criteria.
d. Appendix L. Tibialis anterior strength, gastrocnemius strength, Achilles reflex, and sensory nerve assessment in the foot. Total Neuropathy Score will be completed at these time points.
e. Appendix H. Tibial motor response will include tibial amplitude (mV), latency (sec) and conduction velocity (m/sec). Sural sensory response will include amplitude (mV) and latency (sec).
f. Appendix I. Peripheral nerve ultrasound of the median nerve and superficial fibular nerve will be performed to document nerve cross sectional area and fascicular density.
g. Appendix J. Quantify muscle (thenar eminence) perfusion prior to and immediately after completing treatment administered in clinic.
h. Measure and record skin surface temperature prior to and immediately after (within 2 minutes) completing 30-minute treatment.
i. Two green top sodium heparin tubes: 6 ml x 2 blood sample.
j. Appendix M. In-clinic cryocompression treatment to be administered in designated treatment area; anticipate requiring ~ 60 minutes.
k. Patients will receive a 30-minute cryocompression treatment at home daily (within a 24-hour period) over an 8-week period.
l. Cryocompression parameters used during at-home treatments to be recorded by nursing staff.
m. Appendix O. Patients will self-record treatment daily including date and time as well as temperature and compression settings.
n. Each VCU records use with specific temperature and compression settings detailed by date and time. Recorded data will be collected every 4 weeks by TruTech Medical during in-home visit.
o. Appendix Q/Appendix R. Summary of chemotherapy regimen type and changes in regimen during the study.
p. Appendix S. Patients will receive a post cryocompression treatment call 30 days after treatment to ensure safety and review adverse events.

4.3 Study setting

Enrollment of participants will take place at WFBMC Comprehensive Cancer Center (CCC) outpatient clinics. Patients who are treated at satellite campuses including Lexington, Davie Medical Center and other Wake Forest affiliated sites will be candidates. Study related procedures including the initial treatment titration and subsequent follow up visits will occur at the WFBCCC.

4.4 Enrollment and Screening

Patients identified as having established grade 2 or 3 neuropathy (Cohort 1) or newly developed grade 1 or grade 2 neuropathy (Cohort 2) by NCI CTCAE v5.0 criteria will be brought to the attention of the research study nurse. Cohort 1 and Cohort 2 will be enrolled simultaneously. Treating clinicians will introduce the study and consent will be obtained by either the clinical or research team.

Clinical assessment will take place in the WFBCCC outpatient clinic and will include a focused history by one of the study investigators or research employees. The medical record will also be reviewed to confirm details of the medical history. The focused history will assess age, body-mass index (BMI), multiple myeloma staging, types and dosages of chemotherapy received, corticosteroid and analgesic use, and presence of comorbidities (diabetes, B12 deficiency, thyroid disorders, alcoholism, depression, carpal tunnel syndrome, sciatica). A physical examination will occur and will also assess peripheral pulses and peripheral sensation. Clinical symptoms of peripheral neuropathy of grade 1, grade 2 or grade 3 as measured by the NCI-CTCAE will be verified by administering the QLQ-CIPN20 questionnaire and PRO-CTCAE at this encounter. Physician reported neuropathy grade, physical examination, QLQ-CIPN20 questionnaire and PRO-CTCAE may be completed during baseline peripheral nerve assessment clinic visit if not performed during screening.

Participants will be scheduled for the NCS and ultrasound to occur prior to start of treatment/treatment initiation visit.

4.5 Baseline Peripheral Nerve Assessment

Peripheral nerve evaluation will be performed in the Diagnostic Neurology clinic at WFBMC. Patients will undergo abbreviated neurological examination, nerve conduction study, and peripheral nerve ultrasound. Bilateral testing will be performed. Studies will include:

4.5.1 Neurological Examination (Appendix L)

Bilateral neurological exam will include tibialis anterior strength, gastrocnemius strength, Achilles reflex, and sensory nerve assessment in the foot. The exam will be recorded in the EMG/NCV report. TNS will be completed by the study team/providers.

4.5.2 Nerve Conduction Study (Appendix H)

Bilateral nerve conduction studies will be performed as outlined below to assess motor and sensory nerve function at baseline. Tibial motor response will include tibial amplitude (mV), latency (sec) and conduction velocity (m/sec). Sural sensory response will include amplitude (mV) and latency (sec). Median nerve assessment will include amplitude (mV), latency (sec) and conduction velocity (m/sec).

4.5.3 Peripheral Nerve Ultrasound (Appendix I)

Bilateral peripheral nerve ultrasound of the median and sural nerves will be performed to document nerve cross sectional area and vascularity. Cross sectional area will be measured as the perimeter of the nerve at standard anatomic sties (median: distal wrist crease and sural 10 cm above lateral malleolus).

4.6 Muscle Perfusion Assessment

Muscle perfusion evaluation will be performed in the Diagnostic Neurology clinic at WFMBC.

4.6.1 Muscle Perfusion Ultrasound (Appendix J)

Bilateral muscle ultrasound of the thenar eminence will be performed to document muscle vascularity. Patients will undergo ultrasound of the thenar eminence at rest. A repeat ultrasound will be performed after a 1-minute (10 seconds of active muscle engagement, alternating with 5 seconds of rest) muscle activation exercise. Studies will be performed prior to- and status post cryocompression treatment bilaterally.

4.7 Treatment Initiation and Titration

At the treatment titration visit, concurrent medications will be reviewed. Therapy wraps will be placed on the patient's non-dominant hand and foot. The vascular compression unit (VCU) will be turned on and the treatment temperature decreased as tolerated to the goal temperature setting of 46° F. Continuous cryotherapy temperature of the VCU ranges from 43-49° F to allow for treatment

modification if patient is intolerant to goal temperature. Recommended compression therapy of 30 mmHg will be applied in conjunction with continuous cryotherapy but may be modified to improve tolerability with settings ranging from 15 mmHg to 50 mmHg. Final treatment settings will be recorded (Appendix M).

Skin surface temperature of bilateral hands and feet will be monitored and recorded prior to and within 2 minutes of successful completion of the cryotherapy treatment. Treatment tolerability will be assessed at intervals of 10 minutes from treatment start to end of 30-minute continuous cryotherapy using visual analog scale (VAS). Perfusion of the thenar eminence will be measured prior to and immediately following treatment by neuro-muscular ultrasound.

We will use a personalized rather than a standardized treatment plan for several reasons: 1) this represents actual clinic practice, 2) CIPN is manifested in different ways in different patients, and 3) there is insufficient information in the published literature to inform an appropriate, "one-size-fits-all" cryocompression treatment protocol.

4.8 Intervention: Home Cryocompression Treatments

Participants will be instructed to complete a daily 30-minute cryocompression treatment at home over an 8-week period. The first home cryocompression treatment will be scheduled by the Study Coordinator to occur at the patient's home within 7 days of initial treatment titration performed in clinic.

TruTech Medical will arrange an in-service to be performed at the patient's home. The in-service will comprise approximately 45-60 minutes of patient's time and will consist of delivery and set-up of home VCU. Specific operation instructions, wrap fitting and FAQ sheet will be provided by TruTech. For patients who reside outside of TruTech's service territory, the patient will receive a VCU to take home during treatment initiation visit. For these patients, the in-service will be performed by TruTech either via telephone call or at the time of patient's treatment initiation visit. All patients will be instructed to contact TruTech Medical with questions or concerns regarding operation or malfunction of VCU.

Patients will complete home cryocompression treatment on non-dominant hand and foot for 30 continuous minutes each day for the duration of the study. Unilateral treatment will allow for comparison of symptoms on either side of the patient's body with each patient serving as his/her own control; therefore, a control group is not needed. Patients will log each treatment into a treatment diary (Appendix O). Patients may complete the 30-minute session at any time of day. The entire 30 minutes should be completed at one sitting. Patients are not recommended to divide the session (for example do NOT complete 15 minutes in the morning and 15 minutes in the evening). If a patient has to temporarily stop a session of treatment, it should be resumed as soon as possible and noted in the home treatment diary.

4.9 Week 4 Assessment

All patients will be scheduled for interval follow-up to occur 4 weeks after treatment initiation visit (referred to as Week 4 assessment). Physical examination and clinical symptoms as measured by NCI-CTCAE will performed as in Section 4.4. The QLQ-CIPN20 questionnaire and PRO-CTCAE will also be administered at these encounters. Concurrent medications and adverse events will be reviewed and recorded. Home treatment diary will be reviewed and collected.

4.10 Week 8 End of Treatment Assessment

All patients will be scheduled for a follow-up assessment to occur 8 weeks (+/-10 days) after treatment titration visit (referred to as Week 8 assessment), regardless of whether they have completed all cryocompression treatments. The same protocol will be performed as described in Section 4.5 with addition of the QLQ-CIPN20 and PRO-CTCAE as described in Section 4.4. Peripheral neuropathy grade, as measured by the NCI-CTCAE, will be assessed at this time. At the end of Week 8 assessment and in-clinic treatment, the patient will return VCU device and all device accessories as well as all other study-related items.

5.0 Adverse Events List and Reporting Requirements

5.1 Adverse Event List for Cryocompression

5.1.1 Common adverse events reported with cryocompression therapy include the following:

Skin irritation
Feeling that skin is cool/cold
Pain or discomfort at the site of treatment

5.2 Adverse Event List for Nerve Conduction Studies

5.2.1 Standard risks include mild procedural pain, discomfort and bruising.

5.3 Adverse Event List for Ultrasound

5.3.1 Ultrasound is a safe procedure. Patients may experience a slight warming or coldness from the gel.

5.4 Adverse Event Characteristics

5.4.1 **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

5.4.2 **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 4 5.1, 5.2 and 5.3 above) for expedited reporting purposes only.

5.4.3 **Attribution** of the AE:

Definite – The AE **is clearly related** to the study treatment.
Probable – The AE **is likely related** to the study treatment.
Possible – The AE **may be related** to the study treatment.
Unlikely – The AE **is doubtfully related** to the study treatment.
Unrelated – The AE **is clearly NOT related** to the study treatment.

5.5 STRC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

5.6 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

6.0 Study Outcomes and Study Measures

Listed below are the primary, secondary and exploratory outcomes. Given that this is a pilot study, other parameters associated with nerve conduction and ultrasound studies will be captured and may be used for exploratory analyses.

6.1 Primary Outcome

6.1.1 The primary outcome measure will be feasibility of daily 30-minute cryocompression treatments with a target of 60% compliance. Compliance will be measured by VCU recorded data. Patient study treatment diary will also be compared and when discrepancies exist, resolved either by asking the patient or discussing with the Study PI. Compliance is defined as completion of 60% of prescribed treatment days. Completion of at least 25 of 30 minutes on each day will be considered completion of therapy on the prescribed day.

6.2 Secondary Outcomes

6.2.1 Patient-reported assessment of neuropathy based on sensory, motor and autonomic neuropathic pain scores on the EORTC QLQ-CIPN20 (PRO) at baseline, and at 4 and 8 weeks of cryocompression therapy.

6.2.2 Physician graded assessment of peripheral neuropathy as measured by NCI-CTCAE v5.0 criteria at baseline, and at 4 and 8 weeks of cryocompression therapy.

6.2.3 Sensory and motor nerve function via NCS (e.g. conduction velocity, latency, and amplitude) and neuro-ultrasound at baseline and after 8 weeks of cryocompression therapy.

6.3 Exploratory Outcomes

6.3.1 Muscle perfusion will be measured by US at baseline and after 8 weeks of cryocompression therapy.

6.3.2 The peripheral nerve assessment measures with the patient reported outcomes (EORTC QLQ-CIPN20, PRO-CTCAE) at baseline, week 4, week 8, and for the change from baseline to week 8.

6.4 Covariates

6.4.1 Age

6.4.2 Multiple Myeloma staging

6.4.3 Types/doses of systemic therapy

6.4.4 Use of analgesics or treatments for neuropathy

7.0 Treatment Plan

7.1 Treatment Administration

Cryocompression treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 5.1.

7.2 Treatment Device

7.2.1 Device Name



7.2.1.1 Proprietary name: VascuTherm 5
7.2.1.2 Common name: Intermittent, external pneumatic compression device
7.2.1.3 Classification name: Compressible limb sleeve

7.2.2 Device Description

7.2.2.1 Physical Description: The VascuTherm 5 device consists on a reusable pump (VascuTherm unit) and hand and foot/ankle single-patient use inflatable wraps (VascuTherm wraps). The hand treatment wrap consists of a one-piece slip-on VascuTherm wrap and does not require adjustments to secure wrap in place. The foot/ankle treatment wrap is secured into place with pre-placed Velcro attachments across the forefoot and the high ankle area.



Figure 1







Figure 2



Figure 3



Figure 4



Figure 5

7.2.2.2 Therapy Modality: The VascuTherm unit thermal control therapy provides chilled fluid to the wrap affixed to the extremity therapy site to reduce pain and compresses the treatment site for optimum performance and fluid transfer. The VascuTherm unit also contains a deep vein thrombosis (DVT) mode that will not be utilized in this trial.

7.2.2.3 Safety Features: The VascuTherm systems utilizes a microprocessor control with multiple sensors to ensure patient safety and system functionality, and to provide consistent and repeatable therapy modalities. Alarms are both visual on the unit display and audible. Alarms are in place to detect a potentially unsafe situation and to terminate therapy to protect the patient and the system.

7.2.3 Indications and Usage

Indications:

1. Disorders associated with vascular or lymphatic insufficiency such as chronic venous insufficiency, venous stasis ulcers, post-mastectomy edema and chronic lymphedema.
2. Reduction of edema associated with soft tissue injuries such as burns, postoperative edema, and ligament sprains
3. Localized thermal therapy (hot or cold) for post traumatic and post-surgical and/or medical conditions.

In addition, the VascuTherm 5 is used to decrease the risk of DVT and aids the blood flow back to the heat. VascuTherm 5 may be used to treat and assist healing of cutaneous ulceration, reduce wound healing time, enhance arterial circulation, and reduce compartmental pressures.

7.2.4 Contraindications

The use of the VascuTherm 5 device is contraindicated in patients with either suspected or observed DVT or pulmonary embolism; deep acute venal thrombosis; inflammatory phlebitis; pulmonary edema; thrombophlebitis; decompensated cardiac insufficiency; arterial dysregulation; erysipelas; carcinoma or carcinoma metastasis in the affected extremity; decompensated hypotonia; venous or arterial occlusive disease; Raynaud's disease; poor peripheral circulation as these diagnoses were not studied during device development. Patient's with known hyposensitivity to pain in treated extremity should also avoid cryocompression therapy.

The following patients must use the VascuTherm therapy systems for temperature contact therapy under the supervision of a physician if they are:

- Individuals with extremities non sensitive to pain
- Individuals with extremely low blood pressure
- Individuals with Raynaud's Disease
- Hypersensitive to cold
- Children
- Diabetics

7.2.5 Technological Characteristics

The VascuTherm 5 has the same performance characteristics as predicate devices. The pneumatic control circuitry is a microprocessor-controlled system. Multiple safety redundancies are built into the system including: high and low temperature alarms, alarms for unit malfunction situations, and system malfunction overpressure safety via a pressure vent switch. Power is supplied via 110 VAC line current.

The surface contact temperature range is microprocessor controlled in cooling from 43°F to 49°F and to 105°F in heating mode.

The compression pump pressure ranges from 30 mmHg to 50 mmHg, +/- 5 mmHg. The compression pump default pressure is 30 mmHg. Compression cycle time consists of 20 seconds of inflation, followed by 40 seconds of deflation.

7.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Patients may continue neuropathic pain medications for neuropathy symptoms prescribed prior to enrolling in clinical trial. It is not recommended to initiate or dose-escalate neuropathic pain medications during patient's participation in trial; however, this decision will be left to the patient's treating clinician. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

7.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 8 weeks or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

7.5 Duration of Follow Up

Following recruitment, patients will be scheduled for neurodiagnostic assessments within 14 days. Cryocompression treatments will occur daily over 8 weeks, after which patients will return within 10 days for end-of-treatment follow-up assessment. All patients will receive a follow-up telephone call 30 days (+/- 5 days) after their end-of-treatment assessment to identity whether any adverse events have occurred. Follow-up for serious adverse events and mortality after the last cryocompression treatment is administered will take place during the routine clinic visits that the patient will have during the 30-day follow-up window.

7.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 7.4 applies.

8.0 Treatment Modifications

The target cryotherapy temperature and compression settings for all patients is 46°F and 30 mmHg respectively. During in-clinic treatment initiation visit, the VCU will be turned on and the temperature setting progressively decreased to target treatment temperature of 46°F. Once target temperature has been reached, the target compression setting of 30 mmHg will be applied and treatment will continue for 30-minutes. For patients who cannot tolerate target treatment parameters during in-clinic treatment titration visit, modifications will be prescribed.

Cryotherapy Temperature Settings
43°F
44°F

45°F
46°F – Target treatment temperature
47°F
48°F
49°F

Compression Settings
15 mmHg
30 mmHg – Target compression setting
50 mmHg

General treatment parameters include cryotherapy temperature ranging from 43°F - 49°F and compression settings ranging from 15 mmHg to 50 mmHg +/- 5 mmHg.

If patient is unable to tolerate target treatment parameters during in-clinic titration visit, compression setting will be decreased to 15 mmHg and temperature setting will remain at target temperature of 46°F. If patient is still unable to tolerate treatment parameters, adjunct compression therapy will be discontinued and treatment temperature of 46°F will be maintained. Any additional treatment parameter modifications due to intolerance will result in treatment temperature increase of 1°F without the use of concurrent compression.

	Temperature (°F)	**Compression (mmHg)**
Target treatment parameters	46	30
Treatment modification 1	46	15
Treatment modification 2	46	0
Treatment modification 3	47	0
Treatment modification 4	48	0
Treatment modification 5	49	0
Treatment modification 6	Any other combination of temperature and/or compression settings not listed above.	

Once treatment parameters have been established during in-clinic treatment titration visit, patient will continue daily 30-minute treatment sessions (as described in Section 4.7) at the treatment parameters established for a total of 8 weeks. If at any point during the 8-week treatment course patient becomes intolerant to treatment parameters, patient may, with the guidance of either study personnel or TruTech Medical staff, modify treatment parameters as outlined above. All treatment modifications will be recorded by the patient and either study personnel or TruTech Medical staff.

9.0 Correlative/Special Studies

Venous blood will be sampled at the time of peripheral nerve assessment (e.g. pre-treatment and end-of-treatment) to explore potential circulating markers of peripheral nerve health.

If the patient will undergo regularly scheduled phlebotomy on the day of peripheral nerve assessment, this blood draw will be preferentially added to the routinely collected specimens. Some participants may require an additional blood draw if insufficient blood samples were collected or regularly scheduled blood draw is not planned on the date of peripheral nerve assessment. For the purposes of this study, 24mL of venous blood (12mL at each of two draws) will be collected in a sodium heparin (green-top) collection tube and then transferred directly to Dr. Shiozawa's lab for processing. Serum will be stored in Dr. Shiozawa's lab.

Blood Sample Preparation

1. Email notification will be sent to Matt Eber (meber@wakehealth.edu), Sun Park (shpark@wakehealth.edu) and Yusuke Shiozawa (yshiozaw@wakehealth.edu) the day before the blood collection.

2. Blood will be collected in a green-top vacutainer tube containing heparin (60 USP Units of Lithium Heparin/6mL tube), and immediately inverted 8-10 times to prevent coagulation. **Attention: Protocol #: CCCWFU # (TBD) and the OnCore PID in addition to the other standard information should be on the tube**

3. Samples will then be transported from the Cancer Center to the Shiozawa lab (Lab: 3-6624, 3-5119, Office: 6-8743).

10.0 Data Management

Informed Consent Document	EPIC
Protocol Registration Form	WISER/OnCore
Clinical Evaluation from History/Exam	WISER/OnCore
EORTC QLQ-CIPN20 (neuropathy scale)	REDCap
PRO-CTCAE Numbness and Tingling	REDCap
Nerve Conduction Study Data Collection Form	WISER/OnCore
Ultrasound Digital Artery Perfusion Form	WISER/OnCore
Muscle Perfusion Ultrasound	WISER/OnCore
In-Clinic Treatment Visit	WISER/OnCore
Adverse Events Log	WISER/OnCore
CTCAE Neuropathy Grading Form	WISER/OnCore
Chemotherapy Form	WISER/OnCore
Cryocompression Treatment Form	WISER/OnCore
30-day Treatment Follow-up Form	WISER/OnCore

11.0 Statistical Considerations

11.1 Sample Size, Power, and Interim Analysis

The primary goal of this study is to provide preliminary data for future studies. The power calculation is performed based on the Simon's two-stage optimum design (http://cancer.unc.edu/biostatistics/program/ivanova/simonstwostagedesign.aspx). The null hypothesis that the compliance proportion ≤ 0.25 will be tested against the alternative that the compliance proportion ≥ 0.60. In the first stage, 5 patients will be accrued. The study will be terminated if 1 or 0 patients complete the treatment. If the study goes on to the second stage, a total of 12 patients will be studied. If the total number for compliance is greater than or equal to 6, the null hypothesis will be rejected. This design yields a type I error rate of 0.049 and power of 0.808. Thus, we plan to recruit a total of 12 patients per cohort, which should give us greater than 80% power to reject the null hypothesis. The sample size of 12 per cohort has also been recommended for pilot studies.[42] This is because the increased gain in precision of the estimated difference between the two cohorts begins to asymptote after 12 per cohort, and that there is a similar asymptote for the gain in the precision to estimate the variance.

11.2 Analysis of Primary Objective

Because this is a pilot study, analyses will be primarily descriptive to estimate variances and effect sizes for future work. The primary outcome measure will be feasibility of daily 30-minute cryocompression treatments measured by compliance. As in Section 6.1 compliance is defined as completion of 60% of prescribed treatment days. Completion of at least 25 of 30 minutes on each day will be considered completion of therapy on the prescribed day. The proportion of compliance and its 95% confidence interval will be calculated for each cohort.

11.3 Analysis of Secondary Objective

The primary goals of the secondary objectives are to provide preliminary data on the effect of the intervention on the secondary outcomes of interest. The continuous outcome measures (Objective 2.2.1, EORTC QLQ-CIPN20 motor and autonomic neuropathic pain subscale; Objective 2.2.2, NCI CTCAE v5.0 criteria; Objectives 2.2.3, Peripheral Nerve Assessments) will be displayed graphically with individual trajectories. We will estimate means and standard deviations for each cohort at each time point for the continuous measures. We will also compute the means and standard deviations for the changes between each follow-up time point and baseline per cohort. Follow-up measure and baseline measure will also be compared by paired t-test. The correlation between the measures at the follow-up time point and baseline will be also estimated.

Further, for the binary outcomes (e.g., CTCAE measures), they will be assessed using frequencies by time point per cohort. The odds ratio between the measures at the follow-up time point and baseline will be also estimated.

11.4 Analyses of Exploratory Outcomes

The analysis approach is the same as the analysis plan for the continuous outcome measures specified in Section 11.3.

11.5 Estimated Accrual Rate

2-4 participants per month: We need 6 months to finish the recruitment.

11.6 Estimated Study Length

12-24 months

12 Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

13 Data Safety and Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

14 Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References

1. Amato AA. *Neuromuscular disorders.* New York, NY [u.a.]: MaGraw-Hill; 2008.

2. Donna R Rivera, Patricia A Ganz, Meghan S Weyrich, Hanna Bandos, Joy Melnikow. Chemotherapy-associated peripheral neuropathy in patients with early-stage breast cancer: A systematic review. *Journal of the National Cancer Institute*. 2018;110(2).

3. Simon N, Danso M, Alberico T, Basch E, Bennett A. The prevalence and pattern of chemotherapy-induced peripheral neuropathy among women with breast cancer receiving care in a large community oncology practice. *Qual Life Res*. 2017;26(10):2763-2772. https://www.ncbi.nlm.nih.gov/pubmed/28664460. doi: 10.1007/s11136-017-1635-0.

4. Seretny M, Currie G, Sena E, et al. Cn-16 incidence, prevalence and predictors of chemotherapy induced peripheral neuropathy: A systematic review and meta-analysis. *Neuro-Oncology*. 2014;16(suppl 5):v49. doi: 10.1093/neuonc/nou243.16.

5. Magge RS, DeAngelis LM. The double-edged sword: Neurotoxicity of chemotherapy. *Blood Rev*. 2015;29(2):93-100. doi: 10.1016/j.blre.2014.09.012 [doi].

6. Jackson G, Einsele H, Moreau P, Miguel JS. Bortezomib, a novel proteasome inhibitor, in the treatment of hematologic malignancies. *Cancer Treat Rev*. 2005;31(8):591-602. doi: S0305-7372(05)00199-4 [pii].

7. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348(26):2609-2617. doi: 10.1056/NEJMoa030288 [doi].

8. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *Br J Haematol*. 2004;127(2):165-172. doi: BJH5188 [pii].

9. Carol Aghajanian, Steven Soignet, Don S. Dizon, et al. A phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. *Clinical Cancer Research*. 2002;8(8):2505-2511. http://clincancerres.aacrjournals.org/content/8/8/2505.abstract.

10. Robert Z. Orlowski, Thomas E. Stinchcombe, Beverly S. Mitchell, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. *Journal of Clinical Oncology*. 2002;20(22):4420-4427. http://jco.ascopubs.org/content/20/22/4420.abstract. doi: 10.1200/JCO.2002.01.133.

11. Christos N. Papandreou, Danai D. Daliani, Darrell Nix, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. *Journal of Clinical Oncology*. 2004;22(11):2108-2121. http://jco.ascopubs.org/content/22/11/2108.abstract. doi: 10.1200/JCO.2004.02.106.

12. Gupta S, Pagliuca A, Devereux S, J Mufti G, Schey S. Life-threatening motor neurotoxicity in association with bortezomib. *Haematologica.* 2006;91(7):1001. http://www.haematologica.org/cgi/content/abstract/91/7/1001.

13. Badros A, Goloubeva O, Dalal JS, et al. Neurotoxicity of bortezomib therapy in multiple myeloma: A single-center experience and review of the literature. *Cancer*. 2007;110(5):1042-1049. doi: 10.1002/cncr.22921 [doi].

14. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol*. 2006;24(19):3113-3120. doi: JCO.2005.04.7779 [pii].

15. Xin-Yan Pei, Yun Dai, Steven Grant. Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor bortezomib and histone deacetylase inhibitors. *Clinical Cancer Research*. 2004;10(11):3839-3852. http://clincancerres.aacrjournals.org/content/10/11/3839.abstract. doi: 10.1158/1078-0432.CCR-03-0561.

16. Dorsey S, Janelsins M. Chemotherapy induced peripheral neuropathy: Developing novel trials informed by translational science. 2017.

17. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(18):1941-1967. https://www.ncbi.nlm.nih.gov/pubmed/24733808. doi: 10.1200/JCO.2013.54.0914.

18. Griffiths C, Kwon N, Beaumont JL, Paice JA. Cold therapy to prevent paclitaxel-induced peripheral neuropathy. *Support Care Cancer*. 2018. doi: 10.1007/s00520-018-4199-9 [doi].

19. Hanai A, Ishiguro H, Sozu T, et al. Effects of cryotherapy on objective and subjective symptoms of paclitaxel-induced neuropathy: Prospective self-controlled trial. *JNCI: Journal of the National Cancer Institute*. 2017;110(2):141-148. doi: 10.1093/jnci/djx178 [doi].

20. Sundar R, Bandla A, Tan SS, et al. Limb hypothermia for preventing paclitaxel-induced peripheral neuropathy in breast cancer patients: A pilot study. *Front Oncol*. 2017;6:274. doi: 10.3389/fonc.2016.00274 [doi].

21. Younus J, Kligman L, Jawaid D. The impact of cold therapy on the incidence and severity of paclitaxel induced peripheral neuropathy: A pilot study. *Journal of Solid Tumors.* 2016;6(2).

22. Ohno T, de Kerckhove C, Mine T, et al. How compression therapy could be alleviating chemotherapy-induced peripheral neuropathy: A study of skin microcirculation homeostasis across all CIPN grades. *JCO*. 2015;33(15):e20670. http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.e20670. doi: 10.1200/jco.2015.33.15_suppl.e20670.

23. Aishwarya Bandla, Raghav Sundar, Lun-De Liao, et al. Hypothermia for preventing chemotherapy-induced neuropathy - a pilot study on safety and tolerability in healthy controls. *Acta oncologica (Stockholm, Sweden)*. 2016;55(4):430-436. https://www.ncbi.nlm.nih.gov/pubmed/26360921. doi: 10.3109/0284186X.2015.1075664.

24. Eckhoff L, Knoop A, Jensen M-, Ejlertsen B, Ewertz M. Risk of docetaxel-induced peripheral neuropathy among 1,725 danish patients with early stage breast cancer. *Breast Cancer Res Treat*. 2013;142(1):109-118. https://www.ncbi.nlm.nih.gov/pubmed/24132874. doi: 10.1007/s10549-013-2728-2.

25. Merrick MA, Jutte LS, Smith ME. Cold modalities with different thermodynamic properties produce different surface and intramuscular temperatures. *Journal of athletic training*. 2003;38(1):28. https://www.ncbi.nlm.nih.gov/pubmed/12937469.

26. Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. *Br J Sports Med*. 2006;41(6):365-369. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2465313/. doi: 10.1136/bjsm.2006.031237.

27. Melzack R, Jeans ME, Stratford JG, Monks RC. Ice massage and transcutaneous electrical stimulation: Comparison of treatment for low-back pain. *Pain*. 1980;9(2):209-217. doi: 0304-3959(80)90008-1 [pii].

28. Weber K. The technical benefits of icing. https://www.thermotekusa.com/ckfinder/userfiles/files/The%20Technical%20Benefits%20of%20Icing.pdf.

29. Forsyth P, Balmaceda C, Peterson K, Seidman A, Brasher P, Deangelis L. Prospective study of paclitaxel-induced peripheral neuropathy with quantitative sensory testing. *J Neurooncol*. 1997;35(1):47-53. https://www.ncbi.nlm.nih.gov/pubmed/9266440. doi: 1005805907311.

30. Hershman D, Weimer L, Wang A, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast Cancer Res Treat*. 2011;125(3):767-774. https://www.ncbi.nlm.nih.gov/pubmed/21128110. doi: 10.1007/s10549-010-1278-0.

31. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. *European Journal of Cancer*. 2005;41(8):1135-1139. https://www.sciencedirect.com/science/article/pii/S0959804905001607. doi: 10.1016/j.ejca.2005.02.012.

32. Mols F, van de Poll-Franse L, Vreugdenhil G, et al. Reference data of the european organisation for research and treatment of cancer (EORTC) QLQ-CIPN20 questionnaire in the general dutch population. *European Journal of Cancer*. 2016;69:28-38. https://www.narcis.nl/publication/RecordID/oai:dare.uva.nl:publications%2F48d1dd1b-16b1-45fb-899e-aadfc42c5cdb.

33. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *JAMA Oncology*. 2015;1(8):1051-1059. http://dx.doi.org/10.1001/jamaoncol.2015.2639. doi: 10.1001/jamaoncol.2015.2639.

34. Basch E, Reeve BB, Mitchell SA, et al. Development of the national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Journal of the National Cancer Institute*. 2014;106(9):dju244. https://search.proquest.com/docview/1615758113. doi: 10.1093/jnci/dju244.

35. Knoerl R, Gray E, Stricker C, et al. Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. *Support Care Cancer*. 2017;25(11):3437-3446. https://www.ncbi.nlm.nih.gov/pubmed/28577231. doi: 10.1007/s00520-017-3764-y.

36. Umapathi T, Chaudhry V. Toxic neuropathy. *Curr Opin Neurol*. 2005;18(5):574-580. doi: 00019052-200510000-00016 [pii].

37. G Cavaletti, G Bogliun, L Marzorati, et al. Grading of chemotherapy-induced peripheral neurotoxicity using the total neuropathy scale. *Neurology*. 2003;61(9):1297-1300. https://www.ncbi.nlm.nih.gov/pubmed/14610145. doi: 10.1212/01.WNL.0000092015.03923.19.

38. Susanna B. Park, David Goldstein, Cindy S.-Y. Lin, Arun V. Krishnan, Michael L. Friedlander, Matthew C. Kiernan. Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. *Journal of Clinical Oncology*. 2009;27(8):1243-1249. http://jco.ascopubs.org/content/27/8/1243.abstract. doi: 10.1200/JCO.2008.19.3425.

39. Walker FO, Cartwright MS, Wiesler ER, Caress J. Ultrasound of nerve and muscle. *Clin Neurophysiol*. 2004;115(3):495-507. doi: 10.1016/j.clinph.2003.10.022 [doi].

40. Cartwright MS, Passmore LV, Yoon J, Brown ME, Caress JB, Walker FO. Cross-sectional area reference values for nerve ultrasonography. *Muscle & Nerve*. 2008;37(5):566-571. https://onlinelibrary.wiley.com/doi/abs/10.1002/mus.21009. doi: 10.1002/mus.21009.

41. Arumugam T, Razali SNO, Vethakkan SR, Rozalli FI, Shahrizaila N. Relationship between ultrasonographic nerve morphology and severity of diabetic sensorimotor polyneuropathy. *European Journal of Neurology*. 2016;23(2):354-360. https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.12836. doi: 10.1111/ene.12836.

42. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics*. 2005;4(4):287-291. https://onlinelibrary.wiley.com/doi/abs/10.1002/pst.185. doi: 10.1002/pst.185.

Appendix A – Subject Eligibility Checklist

IRB Protocol No.	**CCCWFU Protocol No.** WFBCCC0119
Study Title: Cryocompression for Bortezomib-Induced Peripheral Neuropathy Among Multiple Myeloma Patients	
Principal Investigator: Roy Strowd MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Patients must have histologically or cytologically confirmed multiple myeloma (any ISS stage)	☐	☐	
Clinical symptoms of bortezomib-induced peripheral neuropathy as measured by the NCI-CTCAE • Cohort 1: patients with clinically documented CTCAE grade ≥2 neuropathy • Cohort 2: patients with clinically documented CTCAE grade 1-2 neuropathy	☐	☐	
Currently or previously received bortezomib-containing regimen Cohort 1: patients who have previously received a bortezomib-containing regimen and have clinically documented neuropathy that is attributed to the bortezomib containing regimen Cohort 2: patients who are currently receiving a bortezomib-containing regimen and have clinically documented neuropathy that is attributed to the bortezomib containing regimen	☐	☐	
Age must be ≥ 18 years	☐	☐	
ECOG ≤ 4	☐	☐	
Life expectancy ≥ 6 months	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document.	☐	☐	

Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Self-reported or documented history of pre-existing peripheral neuropathy prior to initiation of bortezomib therapy	☐	☐	
Other explanatory etiology for neuropathy	☐	☐	
Presumptive evidence of congestive heart failure	☐	☐	
Current deep vein thrombosis or pulmonary embolism (diagnosed within the past 6 months)	☐	☐	
Current pulmonary edema	☐	☐	
Unable to provide accurate medical history	☐	☐	
Pregnant women are excluded from this study because they will not be receiving myeloma SOC therapy or bortezomib-based therapy per inclusion criteria	☐	☐	
Current or previously documented inflammatory phlebitis; thrombophlebitis; decompensated cardiac insufficiency; arterial dysregulation; erysipelas; carcinoma or carcinoma metastasis in the affected extremity; decompensated hypotonia; venous or arterial occlusive disease; or Raynaud's disease;	☐	☐	
Current monoclonal gammopathy of undetermined significance (MGUS), Waldenstroms macroglobulinemia, or Castleman disease.	☐	☐	

This subject is ☐ Eligible **/** ☐ Ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐ Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight:_____.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling [redacted] *between 8:30 AM and 4:00 PM, Monday – Friday.*

Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at [redacted] *or registra@wakehealth.edu, respectively.*

Appendix C – Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   ☐ Hispanic or Latino/a
   ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   ☐ White or Caucasian
   ☐ Black or African American
   ☐ American Indian or Alaskan Native
   ☐ Asian
   ☐ Native Hawaiian or Other Pacific Islander
   ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D – Mandatory STRC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the

confirmation.

3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do

not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars



Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate

suspension of enrollment shouldbe considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

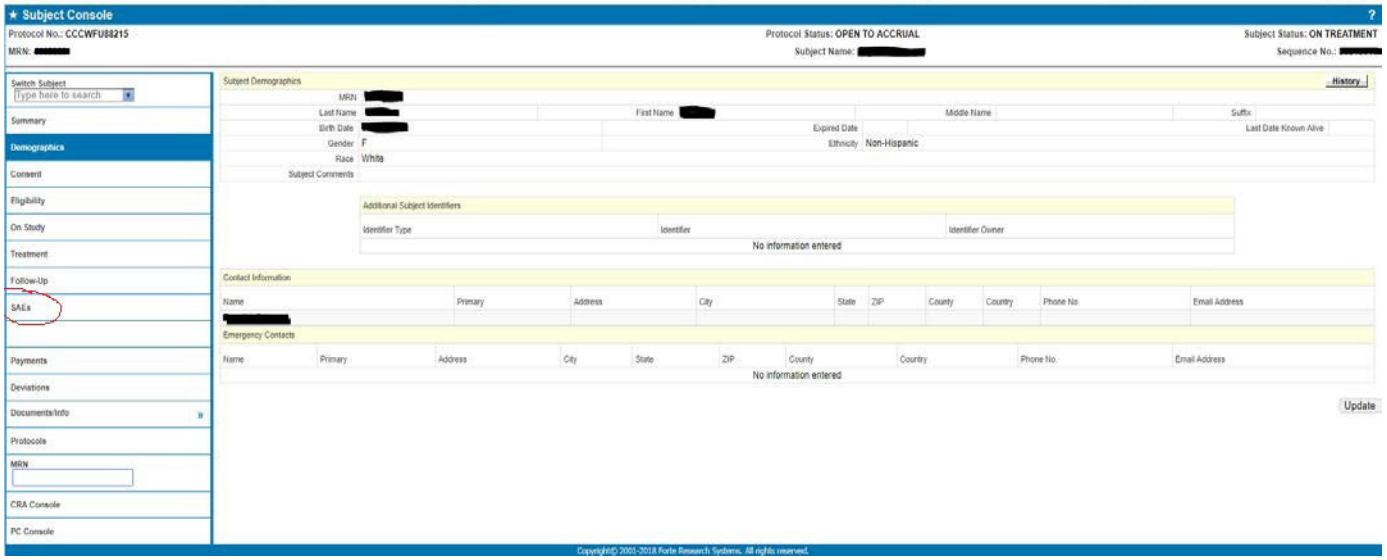
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

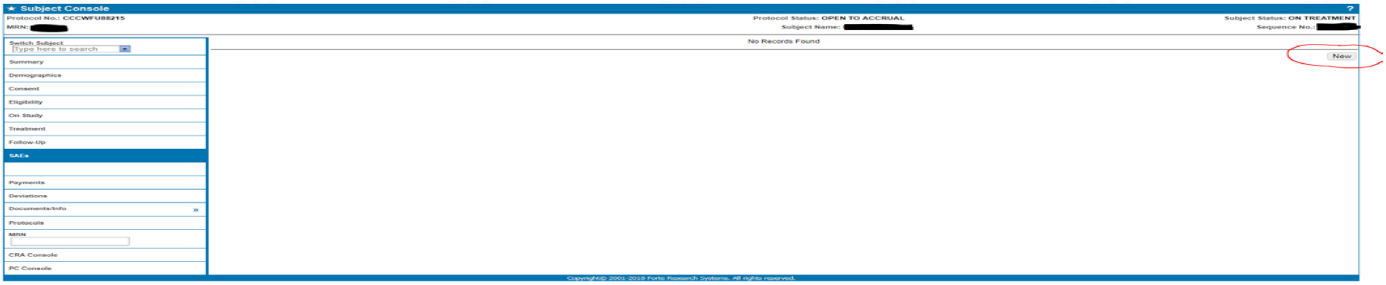
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

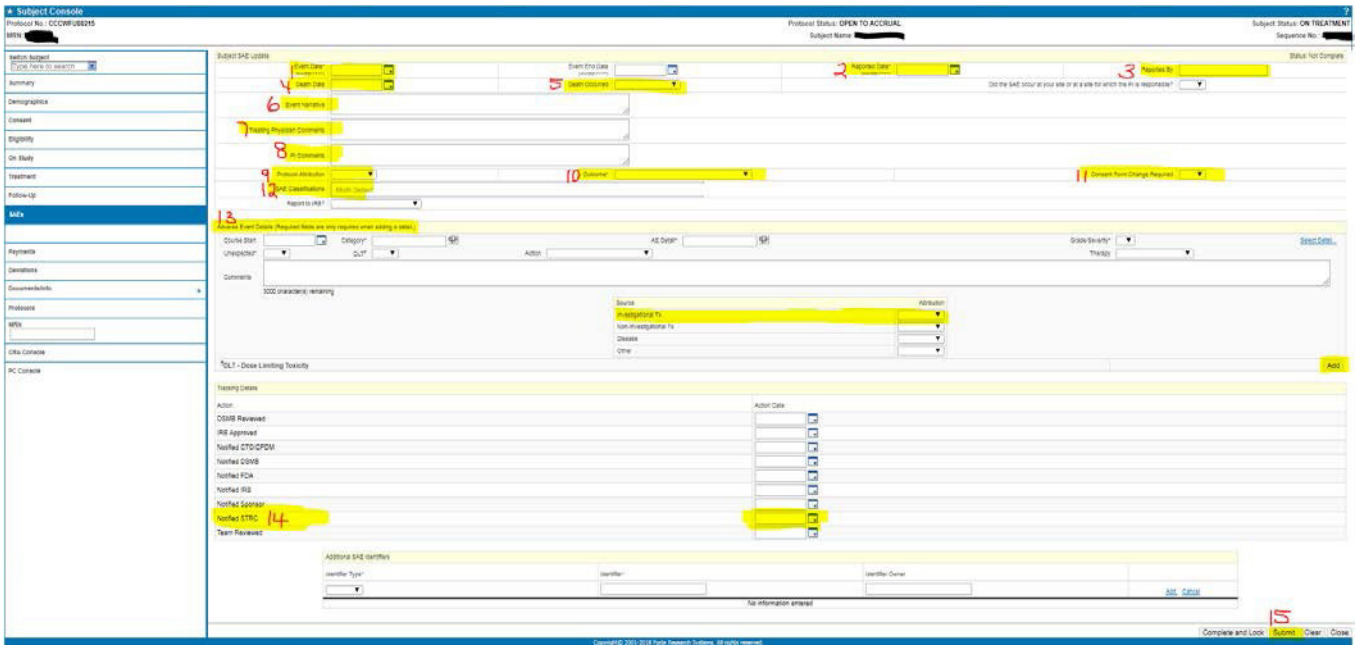
Screen Shot 1:



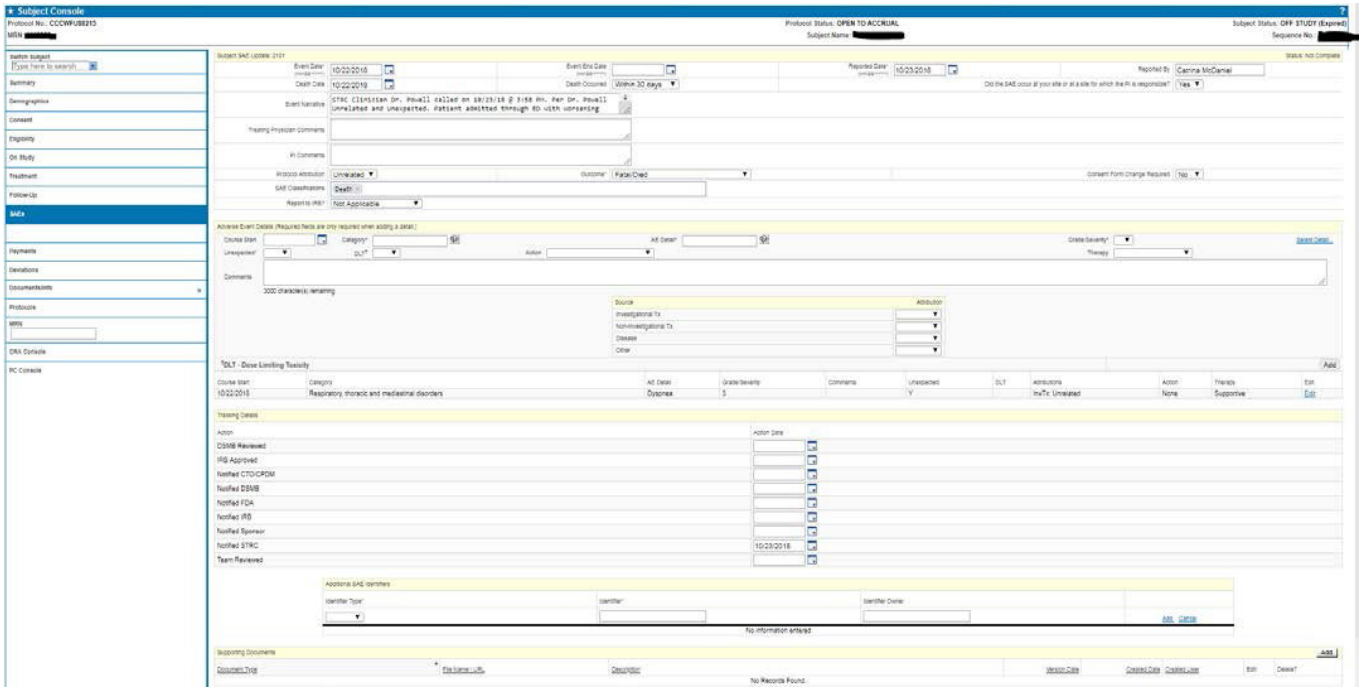
Screen Shot 2:


Subject Console
Protocol No.: CCCWFU88215
Protocol Status: OPEN TO ACCRUAL
Subject Status: ON TREATMENT
Subject Name:
Sequence No.:
Switch Subject
Type here to search
Summary
Demographics
Consent
Eligibility
On Study
Treatment
Follow-Up
SAEs
Payments
Deviations
Documents/Info
Protocols
MRN
CRA Console
PC Console
No Records Found
New
Copyright© 2001-2018 Forte Research Systems. All rights reserved.

Screen Shot 3:



Screen Shot 4:



Appendix E – Clinical Evaluation from History/Examination

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Instructions: To be filled out by medical staff at screening, baseline or treatment initiation visit.

1. Oncologic history

a. Diagnosis (ICD-10): _____

b. ISS Stage: _____

c. Current chemotherapy:

Name	Dose	Start Date of regimen (mm/dd/yy)	Current cycle number	Standard dose?
☐				Yes No*
☐				Yes No*
☐				Yes No*
☐				Yes No*
☐ Other (specify):				Yes No*

*If reduced, specify dose:_____ mg/m^2

*If reduced, is CIPN reason for reduction? ☐ Yes ☐ No ☐ Other:_____

d. Other current cancer therapy: ☐ Other: _____

e. Other prior cancer therapies (excluding 1c.) for most recent cancer. Mark all that apply:
☐ Chemotherapy ☐ Radiation ☐ Stem-cell Transplant
☐ Other: _____ ☐ None

Chemotherapy Regimen Name	Total # of Treatments	Date of Last Treatment (mm/dd/yy)
1.		__ __ / __ __ / __ __
2.		__ __ / __ __ / __ __
3.		__ __ / __ __ / __ __
4.		__ __ / __ __ / __ __
5.		__ __ / __ __ / __ __
6.		__ __ / __ __ / __ __

Stem Cell Transplant	Condition Regimen	Dose	Date of Transplant (mm/dd/yy)
1.			__ __ / __ __ / __ __
2.			__ __ / __ __ / __ __

Other	Dose	Date of Last Treatment (mm/dd/yy)
1.		__ __ / __ __ / __ __
2.		__ __ / __ __ / __ __

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

2. Date of Onset of CIPN (mm/dd/yy): __ __/__ __/__ __

3. BMI: ___ ___

4. Medical history (check all that apply, if unknown can be left unchecked):
   - ☐ Thyroid Disorder: If yes: ☐ Hyperthyroidism ☐ Hypothyroidism
   - ☐ Vitamin B12 deficiency
   - ☐ Peripheral vascular disease (claudication, arterial bypass, untreated aneurysm ≥6cm)
   - ☐ Cerebrovascular disease (history of TIA or CVA)
   - ☐ Alcoholism
   - ☐ Carpal tunnel syndrome
   - ☐ Sciatica
   - ☐ Diabetes: If yes, end organ damage? Yes ☐ No ☐
   - ☐ AIDS
   - ☐ Depression
   - ☐ Other major medical condition; specify

     _____

4. Concurrent medications and supplements

a. List all prescription and over-the-counter medications (includes prescription supplements)

Medication Name	Is it PRN?		Medication Name	Is it PRN?	
1.	yes	no	11.	yes	no
2.	yes	no	12.	yes	no
3.	yes	no	13.	yes	no
4.	yes	no	14.	yes	no
5.	yes	no	15.	yes	no
6.	yes	no	16.	yes	no
7.	yes	no	17.	yes	no
8.	yes	no	18.	yes	no
9.	yes	no	19.	yes	no
10.	yes	no	20.	yes	no

b. List all supplements taken regularly

Supplement Name	Taking?		If yes, is it taken for neuropathy?		If yes, is it PRN?	
Multivitamin	yes	no	yes	no	yes	no
B12	yes	no	yes	no	yes	no
B vitamin complex	yes	no	yes	no	yes	no
Vitamin C	yes	no	yes	no	yes	no
Vitamin E	yes	no	yes	no	yes	no
Vitamin D	yes	no	yes	no	yes	no
Calcium	yes	no	yes	no	yes	no
Iron	yes	no	yes	no	yes	no
Probiotics	yes	no	yes	no	yes	no
Fiber	yes	no	yes	no	yes	no
Tumeric	yes	no	yes	no	yes	no
Fish oil/omega-3/flaxseed	yes	no	yes	no	yes	no

Other:_____	yes	no		yes	no	yes	no
Other:_____	yes	no		yes	no	yes	no

Appendix F – Patient Reported Outcomes: EORTC QLQ-CIPN20 and PRO-CTCAE

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Instructions: To be filled out by patient.

Visit: ☐ Baseline
☐ Week 4
☐ Week 8

EORTC QLQ-CIPN20

Patients sometimes report that they have these following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

DURING THE PAST WEEK	Not at all	A little	Quite a bit	Very much
1) Did you have tingling fingers or hands?	1	2	3	4
2) Did you have tingling toes or feet?	1	2	3	4
3) Did you have numbness in your fingers or hands?	1	2	3	4
4) Did you have numbness in your toes or feet?	1	2	3	4
5) Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
6) Did you have shooting or burning pain in your toes or feet?	1	2	3	4
7) Did you have cramp in your hands?	1	2	3	4
8) Did you have cramp in your feet?	1	2	3	4
9) Did you have problems standing or walking because of a difficulty in feeling the ground under your feet?	1	2	3	4
10) Did you have difficulty in distinguishing between hot and cold water?	1	2	3	4
11) Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
12) Did you have difficulty in manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
13) Did you have difficulty in opening a jar or bottle because of weakness in your hand?	1	2	3	4
14) Did you have difficulty because your feet dropped downwards?	1	2	3	4
15) Did you have difficulty in climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
16) Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
17) Did you have blurred vision?	1	2	3	4
18) Did you have any difficulty in hearing?	1	2	3	4

Please answer the following question only if you drive a car: **19) Did you have difficulty using pedals?** **Or mark: ☐ Not applicable: I do not drive a car**	1	2	3	4

PRO-CTCAE
As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please mark the one box that best describes your experiences over the past 7 days.

PRO-CTCAE™ Symptom Term: Numbness & tingling				
a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very Severe
b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO-CTCAE™ is subject to NCI's Terms of Use

1. Are you currently taking any medications or supplements (such as gabapentin/Neurontin, amitriptyline/Elavil, nortriptyline/Pamelor, vitamin B12, pain medications) for your neuropathy?

☐ No

☐ Yes

1a. What are you taking? _____
1b. When did you start taking this? _____

2. Are you currently doing anything else to treat your neuropathy (such as meditation, massage, yoga)?

☐ No

☐ Yes

2a. What are you doing? _____
2b. When did you start doing this? _____

Appendix G – Interim Concurrent Medications Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Instructions: Fill this form out at week 4 visit and week 8 visit.

Visit: ☐ Week 4
☐ Week 8

Date of Visit (mm/dd/yy): __ __/__ __/__ __

Current Medications List

Prescription Medications:

Name of Medication	Dose	Units	Frequency	Condition Medication Taken For	Start date (mm/dd/yy)	Stop date (mm/dd/yy)	Formulation	Route	Notes

Appendix H – Nerve Conduction Study Data Collection Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Visit: ☐ Baseline
☐ Week 8

Treatment Side: ☐ Right
☐ Left

Instructions:

- Use the OnCore PID and visit to Identify the Sample
- Date is the date of experimentation and listed before the technique. Use the following format (mm/dd/yy)
- Do not erase entries. If an entry is incorrect, cross the entry out with one line, initial, and write in the correct entry. Please write neatly.

Motor Nerve Conduction Worksheet

Date of Nerve Conduction Study: _ _ / _ _ / _ _

Nerve/Sites	Latency (ms)	Amplitude (mV)	Segments	Velocity (m/s)
Right Median				
Wrist				
Elbow				
Left Median				
Wrist				
Elbow				
Right Tibial				
Ankle				
Pop Fossa				
Left Tibial				
Ankle				
Pop Fossa				

Sensory Nerve Conduction Worksheet

Date of Nerve Conduction Study: _ _ / _ _ / _ _

Nerve/Sites	Onset Latency (ms)	Peak Latency (ms)	Amplitude (mV)	Segments	Velocity (m/s)
Right Sural					
Ankle (Calf)					
Left Sural					
Ankle (Calf)					

Appendix I – Ultrasound Nerve Diameter Data Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ _ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Visit: ☐ Baseline
☐ Week 8

Treatment Side: ☐ Right
☐ Left

To be used for determination of sural and median nerve diameters.
Date of Procedure (mm/dd/yy): __ __/__ __/__ __

Nerve	**Side**	**Area (mm2)**	**Vascularity**
Sural	Left		yes no NA
Sural	Right		yes no NA
Median: Wrist	Left		yes no NA
Median: Wrist	Right		yes no NA
Other: _____			yes no NA

LEGEND

Vascularity: describes presence of vascular activity *within* nerve; **NA** (not available)
Other: Includes *Persistent Median Artery (PMA), Bifid Nerve, Trifid Nerve, FDS in CTS,* etc.

Person recording information: _____

Appendix J – Muscle Perfusion Ultrasound

OnCore PID: __ __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Visit: ☐ Baseline
☐ Week 8

Treatment Side: ☐ Right
☐ Left

Date of Procedure (mm/dd/yy): __ __/__ __/__ __

Site	**Side**	**Pre-Treatment**		**Post-Treatment**	
Thenar eminence	Right	# of sites	Degree of activity	# of sites	Degree of activity
			☐ Low ☐ Medium ☐ High		☐ Low ☐ Medium ☐ High

Site	**Side**	**Pre-Treatment**		**Post-Treatment**	
Thenar eminence	Left	# of sites	Degree of activity	# of sites	Degree of activity
			☐ Low ☐ Medium ☐ High		☐ Low ☐ Medium ☐ High

Appendix K – Physical Examination

OnCore PID: __ __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Visit: ☐ Baseline
☐ Week 4
☐ Week 8

Date of Examination (mm/dd/yy): __ __/__ __/__ __

Please mark the following examination information as A = ABNORMAL or N = NORMAL.

Systems	**Exam (A or N)**	**Brief Description if Abnormal on Exam**
HEENT		
Cardiovascular		
Pulmonary		
Gastrointestinal		
Musculoskeletal		
Skin		
Neurologic		
Other		

Appendix L – Total Neuropathy Score – Clinical Version

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Instructions: To be completed in outpatient clinic at WFBMC as part of peripheral nerve assessment.

Visit: ☐ Baseline
☐ Week 4
☐ Week 8

Date of Examination (mm/dd/yy): __ __/__ __/__ __

	Score				
Scale	**0**	**1**	**2**	**3**	**4**
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knee or elbow or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomic symptoms, n	0	1	2	3	4 or 5
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness (MRC 4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Paralysis (MRC 0–1)
Deep tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent

The Total Neuropathy Score – Clinical is a reduced version of the TNS that assesses only the signs and symptoms that are apparent during a clinical examination. The table above is a summary of the key elements.

TNS will be completed by the study team/providers.

Appendix M – In-Clinic Treatment Visit

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Date of Visit (mm/dd/yy): __ __/__ __/__ __

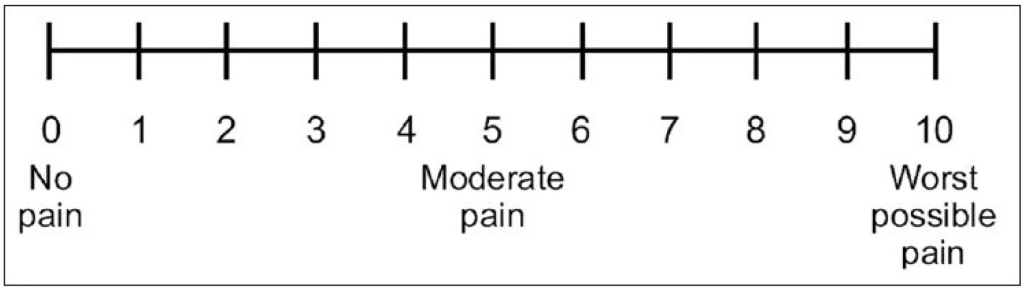
Visit: ☐ Treatment Titration Visit
☐ Week 8
Most recent home VCU temperature setting (°F): _____
Most recent home VCU compression setting (mmHg): _____

Treatment Side: ☐ Right
☐ Left

	Time	VCU Temperature Setting (°F)	VCU Compression Setting (mmHg)	Visual Analog Scale (0 – 10)	Notes (e.g. adverse events and modifications of treatment settings)
Start of Treatment					
10-minutes post treatment start					
20-minutes post treatment start					
End of Treatment (30-minutes post treatment start)					

		Surface Skin Temperature (°F)			
	Time	**Right Hand**	**Left Hand**	**Right Foot**	**Left Foot**
Pre-treatment					
Post-treatment					

Visual Analog Scale



Appendix N – Adverse Events Log

OnCore PID: __ __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

WFBCCC Adverse Event (AE) Log

*Due to the observational nature of this study, adverse events of interest are limited to those that occur in the immediate duration of the cyrocompression procedure. Should an AE related to cyrocompression occur, the investigators will notify study staff for logging in this form.

Adverse Event CTC Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**End Date**	**Attribution** DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxitity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP=Supportive VSUP=Vigorous supportive	**Reportable?** IRB-IRB STRC-STRC FDA-FDA SPON-Sponsor (Mark all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R=Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died	**Treating MD Initials/ Date**

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

STRC- Safety and Toxicity Review Committee | Version 1/10/18

Appendix O – Home Cryocompression Treatment Log

OnCore PID: __ __ __ __ __ __ __ __ __
PI: Roy Strowd MD **Study Number:** WFBCCC01119

Treatment Side: ☐ Right
☐ Left

Treatment Date	Temperature Setting (°F)	Compression Setting (mmHg)	Treatment Duration (minutes)	Notes (e.g. side effects or additional treatments)
_ _ / _ _ / _ _				
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		

Treatment Date	Temperature Setting (°F)	Compression Setting (mmHg)	Treatment Duration (minutes)	Notes (e.g. side effects or additional treatments)
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		

Treatment Date	Temperature Setting (°F)	Compression Setting (mmHg)	Treatment Duration (minutes)	Notes (e.g. side effects or additional treatments)
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		

Treatment Date	Temperature Setting (°F)	Compression Setting (mmHg)	Treatment Duration (minutes)	Notes (e.g. side effects or additional treatments)
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
_ _ / _ _ / _ _	☐ Same as above	☐ Same as above		
Final cryocompression treatment to be completed in clinic during 8-week follow up visit.				

Appendix P – CTCAE Neuropathy Grading Form

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Instructions: To be completed by medical staff.

Visit: ☐ Baseline
☐ Week 4
☐ Week 8

Treatment Side: ☐ Right
☐ Left
Date of Visit (mm/dd/yy): __ __/__ __/__ __

Please select the appropriate grade of the patient's neuropathy based on your assessment today.

CTCAE Grade of neuropathy	Description of CTCAE grade	Question you may consider asking:	Check the box that corresponds to neuropathy grade	
			Right	Left
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Do you have any numbness or tingling in your hands, fingers, feet or toes?		
Grade 2	Moderate symptoms; limiting instrumental ADL	Because of your neuropathy, are you not able to clean your home, cook meals, shop for groceries, or use your telephone?		
Grade 3	Severe symptoms; limiting self-care ADL; assistive device indicated	Because of your neuropathy, are you not able to dress yourself, button your shirt or pants, bath or shower, cut your food or eat?		
Grade 4	Life-threatening consequences; urgent intervention indicated			
Grade 5	Death			

Appendix Q – Cohort 1 Chemotherapy Form

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Instructions: To be completed at the Week 8 visit for patients enrolled in Cohort 1. Use this form to summarize regimen type and changes in regimen during the study.

Total chemotherapy cycles completed: ☐1 ☐2 ☐3 ☐4

Was the chemotherapy regimen changed during treatment? ☐Yes ☐No

If yes, was it due to CIPN? ☐Yes ☐No

Chemotherapy Received During Study					
Name	**Chemotherapy Dose**	**Start Date (mm/dd/yy)**	**End Date (mm/dd/yy)**	**No. of cycles completed**	**No. of weeks completed**
☐					
☐					
☐					
☐					
☐					
☐					

*If standard dose was not given during all cycles, complete the table below for all cycles/weeks of regimen given:

Dose Reductions During Chemotherapy Treatment				
Regimen (use abbreviation above)	**Cycle**	**Week**	**Chemotherapy Dose (mg/m^2)**	**Reduction due to CIPN?**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**

** If other, please explain: _____

_____

_____

Person filling out form: _____

Date (mm/dd/yy): ___ ___/___ ___/___

Appendix R – Cohort 2 Chemotherapy Form

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Instructions: To be completed at the Week 8 visit for patients enrolled in Cohort 2. Use this form to summarize regimen type and changes in regimen during the study.

Total chemotherapy cycles completed: ☐1 ☐2 ☐3 ☐4

Weeks completed (bortezomib):

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8

Was the chemotherapy regimen changed during treatment? ☐Yes ☐No

If yes, was it due to CIPN? ☐Yes ☐No

Chemotherapy Regimens Received During Study						
Name	**Bortezomib Dose**	**Start Date (mm/dd/yy)**	**End Date (mm/dd/yy)**	**No. of cycles completed**	**No. of weeks completed**	**Standard bortezomib dose during all cycles?**
☐						Yes No*
☐						Yes No*
☐						Yes No*
☐						Yes No*
☐						Yes No*
☐ Oth Other (specify):						Yes No*

*If standard dose was not given during all cycles, complete the table below for all cycles/weeks of regimen given:

Dose Reductions During Chemotherapy Treatment				
Regimen (use abbreviation above)	**Cycle**	**Week**	**Bortezomib Dose (mg/m^2)**	**Reduction due to CIPN?**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**

** If other, please explain: _____

_____

_____

Person filling out form: _____

Date (mm/dd/yy): ___ ___/___ ___/___

Appendix S – 30-day Treatment Follow-up Form

OnCore PID: __ __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Instructions: Complete this form to follow-up with patients for adverse events.

Name of Person Competing form_____

Did the subject have any adverse events in the last 30 days? Yes ☐ No ☐

If yes, please describe nature and grade of AE (Note*: If an SAE occurs in this period, report the event as required in Appendix D):

_____
_____
_____
_____
_____
_____

Was the subject removed from the study by the PI? Yes ☐ No ☐

Did the subject withdraw from the study? Yes ☐ No ☐

Did the subject complete the study? Yes ☐ No ☐

Was there any change in the subject's neuropathy? Yes ☐ No ☐

Appendix T — Life Expectancy Confirmation

Instructions: To be filled out by principal investigator or co-investigator for eligibility confirmation.

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Is the life expectancy of this participant ≥ 6 months? Yes ☐ No ☐

Person filling out form: _____

Date (mm/dd/yy): ___ ___/___ ___/___

Appendix U – VCU Data Confirmation

OnCore PID: __ __ __ __ __ __ __ __	**Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Roy Strowd MD	**Study Number:** WFBCCC01119

Instructions: Complete this form to confirm receipt of VCU data.

Visit: ☐ Week 4
☐ Week 8

Was the VCU data received? Yes ☐ No ☐