Title: The Role of N-acetyl-l-cysteine (NAC) as an Adjuvant to Opioid Treatment in Patients With Chronic Neuropathic Pain

PI: Dace Svikis, PhD

NCT #: NCT01840345

Unique Protocol ID: HM14748

Document approval date: August 8, 2013

Document Type: Protocol and SAP

VCU RESEARCH PLAN TEMPLATE

Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor's protocol) exists, you may reference specific sections of that protocol. NOTE: **If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan. It is NOT acceptable to reference a research funding proposal**.

ALL Sections of the Human Subjects Instructions must be completed with the exception of the Section entitled "Special Consent Provisions." Complete that Section if applicable. When other Sections are not applicable, list the Section Heading and indicate "N/A."

NOTE: The Research Plan is required with ALL Expedited and Full review submissions and MUST follow the template, and include version number or date, and page numbers.

DO NOT DELETE SECTION HEADINGS OR THE INSTRUCTIONS.

I. TITLE

THE ROLE OF N-ACETYL-L-CYSTEINE (NAC) AS AN ADJUVANT TO OPIOID TREATMENT IN PATIENTS WITH CHRONIC NEUROPATHIC PAIN

II. RESEARCH PERSONNEL

A. PRINCIPAL INVESTIGATOR

List the name of the VCU Principal Investigator

Michael F. Weaver, MD

B. STUDY PERSONNEL

NOTE:

1. **Information pertaining to each project personnel, including their role, responsibilities, and qualifications, is to be submitted utilizing a *VCU IRB Study Personnel Information and Changes Form*. This form is available at http://www.research.vcu.edu/forms/vcuirb.htm.**
2. **A roster containing a list of project personnel is to be maintained as a separate study document which is retained with the Research Plan, and is to be updated as applicable. The roster is to include all VCU project personnel (including the principal investigator) who are *engaged* in this research protocol, as well as non-VCU personnel who are also *engaged* but do not have local IRB approval for this protocol from their own institution,. This template document, entitled *VCU IRB Study Personnel Roster*, is available at http://www.research.vcu.edu/forms/vcuirb.htm.**

C. Describe the process that you will use to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.

All research personnel will have successfully completed the CITI online training in human subjects' protection. In addition, Drs. Weaver and Svikis will conduct a variety of protocol-specific (e.g., participant recruitment, forms administration, standard operating procedures, emergency procedures, adverse event reporting procedures, etc), and intervention-specific training activities prior to study start and during the course of the study. The trainings include both didactic and hands-on/experiential learning activities. In addition to initial training activities, booster training will be conducted with research staff at regularly scheduled intervals.

III. CONFLICT OF INTEREST

Describe how the principal investigator and sub/co-investigators might benefit from the subject's participation in this project or completion of the project in general. Do not describe (1) academic recognition such as publications or (2) grant or contract based support of VCU salary commensurate with the professional effort required for the conduct of the project

Neither the principal investigator nor the sub-investigator will benefit from any subjects' participation in this study.

IV. RESOURCES

Briefly describe the resources committed to this project including: (1) time available to conduct and complete the research, (2) facilities where you will conduct the research, (3) availability of medical or psychological resources that participants might require as a consequence of the research (if applicable), and (4) financial support.

The investigators' chairs have committed to allowing the investigators to have sufficient time to complete the described research. Research expenses will be covered by funds from an AD Williams' grant. The clinical trial will be conducted in the VCUHS clinics and the VMI building located on the MCV campus. Individuals from the VCUHS clinics who are identified as in need of additional services (e.g., substance abuse treatment), will be provided with the appropriate referrals.

V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Neuropathic pain is a chronic debilitating condition affecting 3 – 4% of the global population. It results in profound decreases in patients' quality of life and is associated with a significant economic burden.

Despite the availability of numerous treatments for the condition, as many as three-fourths of patients continue to experience uncontrolled moderate to severe pain. N-acetyl-L-cysteine (NAC), an over-the-counter antioxidant and precursor to glutathione synthesis, is a free radical scavenger that affects pain by decreasing cellular levels of reactive oxygen species (ROS), and subsequently, decreasing levels of oxidative stress and pain. In a small clinical study, NAC decreased opioid use in patients undergoing knee ligamentoplasty, and in non-clinical research, NAC alleviated neuropathic pain in a rat model. These data suggest that NAC may be a promising adjunct to standard treatments for clinical neuropathic pain.

The specific aim of the current research is to conduct a small, pilot study to evaluate the effect of NAC, as an adjunct to opioid treatment, in patients with incompletely controlled neuropathic pain. Thirty-six men and women with non-cancer neuropathic pain will be treated with 2400 mg NAC daily for four weeks. Opioid use, pain, psychological assessments, adverse events, and medication compliance will be evaluated at Baseline, weekly throughout the four-week study period, and at the end of treatment. We hypothesize that 2400 mg of NAC added to standard opioid therapy for four weeks in patients with neuropathic pain will decrease opioid use, measured in morphine equivalents, compared to Baseline. Secondary analyses will evaluate the effect of NAC on pain, mood, and stress; assess the safety of NAC in neuropathic pain patients; and calculate patient compliance with medication dosing instructions.

This study will be the first to evaluate the potential benefits of NAC treatment as an adjunct to opioid therapy in patients with poorly controlled neuropathic pain. With positive outcomes from the addition of NAC therapy, the pilot data collected will be used for the calculation of effect and sample sizes for a large, randomized clinical trial (RCT) to further evaluate the use of NAC in neuropathic pain. If indeed NAC is effective in neuropathic pain, it will be an inexpensive and clinically significant addition to the armamentarium of therapies available to manage this chronic and disabling disease, ultimately improving the lives of the millions of patients affected by neuropathic pain.

VI. SPECIFIC AIMS

The specific aim of the current research is to conduct a small, pilot study to evaluate the effect of NAC, as an adjunct

to opioid treatment, in patients with incompletely controlled neuropathic pain. Thirty-six men and women with non-cancer neuropathic pain will be treated with 2400 mg NAC daily for four weeks. Opioid use, pain, psychological assessments, adverse events, and medication compliance will be evaluated at Baseline, weekly throughout the four-week study period, and at the end of treatment. We hypothesize that 2400 mg of NAC added to standard opioid therapy for four weeks in patients with neuropathic pain will decrease opioid use, measured in morphine equivalents, compared to Baseline. Secondary analyses will evaluate the effect of NAC on pain, mood, and stress; assess the safety of NAC in neuropathic pain patients; and calculate patient compliance with medication dosing instructions.

This study will be the first to evaluate the potential benefits of NAC treatment as an adjunct to opioid therapy in patients with poorly controlled neuropathic pain. With positive outcomes from the addition of NAC therapy, the pilot data collected will be used for the calculation of effect and sample sizes for a large, randomized clinical trial (RCT) to further evaluate the use of NAC in neuropathic pain. If indeed NAC is effective in neuropathic pain, it will be an inexpensive and clinically significant addition to the armamentarium of therapies available to manage this chronic and disabling disease, ultimately improving the lives of the millions of patients affected by neuropathic pain.

VII. BACKGROUND AND SIGNIFICANCE

Include information regarding pre-clinical and early human studies. Attach appropriate citations.

Neuropathic pain is a chronic debilitating condition arising from damage to or dysfunction of the nervous system resulting in symptoms like burning and tingling sensations, numbness, and itching. It affects approximately 3.8 million patients in the United States (Bennett, 1997) and 3 –4% of the population worldwide (Global Industry Analysts, Inc. Report, 2011).

Persistent neuropathic pain has a significant impact on quality of life as well as a substantial burden on society. Patients report decreased overall physical and mental health, decreased mobility, increased mood disorders, and increased sleep disturbances and fatigue (Jensen, 2007). In fact, Bouhassira and colleagues (2008) reported that neuropathic pain is associated with greater psychological stress and increased intensity compared to nociceptive pain. Further, neuropathic pain has tremendous economic costs in terms of direct medical expenses, lost productivity, and caregiver burden (O'Connor 2009).

The causes of neuropathic pain are heterogeneous and include such etiologies as diabetes mellitus, spinal cord injury, multiple sclerosis, herpes zoster, and HIV-related neuropathies. Initial treatment includes addressing the underlying cause of the pathology; however, the pain often remains, and its treatment is especially challenging. A recent report by the International Association for the Study of Pain's Neuropathic Pain Special Interest Group described evidence-based guidelines for the treatment of neuropathic pain (O'Connor, 2009). According to the report, tricyclic antidepressants, selective serotonin norepinephrine reuptake inhibitors, calcium channel α_2-δ ligands, topical lidocaine, and in some cases, opioid analgesics are first-line therapies for neuropathic pain. Often, multiple medications are used in an attempt to control neuropathic pain. However, even with treatment, as many as 50-75% of patients still have persistent moderate to severe neuropathic pain (McDermott, 2006).

Clearly, additional therapeutic options are needed to improve outcomes in patients with neuropathic pain. One particular agent that has shown promise in non-clinical studies of neuropathy is N-acetyl-L-cysteine (NAC), a derivative of the amino acid cysteine and an antioxidant, which appears to affect neuropathic pain by acting as a free radical scavenger. It acts by directly scavenging free radicals as well as by increasing glutathione synthesis, resulting in increased cellular clearance of reactive oxygen species (ROS), decreased oxidative stress, and subsequently, decreased pain. In a rat spinal nerve ligation model (SNL) of neuropathic pain, Kim and colleagues (2004) implicated ROS in the pathology of neuropathic pain. They showed that ROS scavengers ameliorated SNL-induced mechanical allodynia and prevented the development of neuropathic pain in these rats. Gao, et al. further detailed the role of ROS in neuropathic pain with experiments that showed that elevated levels of ROS were associated with increased phosphorylation of N-methyl-D-aspartate (NMDA) receptors, central sensitization, and hyperalgesia in a rat SNL model of neuropathic pain. Naik, et al. (2005) showed that NAC in particular significantly reduced the increased sensitivity to mechanical, thermal, and cold allodynia tests in a peripheral neuropathy model (chronic constriction injury of sciatic nerve) in rats. Further, the Investigators noted that glutathione levels were decreased following injury.

In a clinical research study, Orban, et al (2006) theorized that NAC decreased ROS, resulting in decreased pain intensity, as measured by decreased morphine use, in patients undergoing knee ligamentoplasty. Patients treated with 1200 mg NAC prior to and 600 mg NAC post procedure used less morphine (0.22 mg/kg vs 0.47 mg/kg, $p<0.05$) in the first 48

hours post-surgery compared to a control group that did not receive NAC. In the study, NAC was well-tolerated with no difference in the occurrence of adverse events between the treatment groups.

While studies in pain are limited, a growing body of literature supports the use of NAC in a variety of psychiatric illness, including substance abuse where data suggest that oxidative stress plays a role in the pathophysiology of drug addiction. A number of small clinical trials have shown decreased self-reported use in marijuana (Gray, 2010) and tobacco (Knackstedt, 2009) users and decreased use and cravings in cocaine addicts (LaRowe, 2006; LaRowe, 2007; Mardikian, 2007). Especially relevant to the proposed research, the doses of NAC used in these studies, generally 2400 mg/day for four weeks, were well-tolerated. No patients experienced serious adverse events, and no patients were discontinued from the studies due to adverse events.

These data suggest that additional research with NAC in pain is warranted. To our knowledge, there have been no studies that have evaluated NAC as an adjunct to opioid treatment in patients with chronic neuropathic pain. Therefore the proposed research will be the first to prospectively study the effect of NAC on pain medication use (as measured by morphine equivalents) in this population.

VIII. PRELIMINARY PROGRESS/DATA REPORT

If available.

N/A

IX. RESEARCH METHOD AND DESIGN

Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.

Despite numerous evidence-based approaches to the treatment of neuropathic pain, only about half of patients achieve even partial relief. NAC is a potential adjuvant to standard treatment that may improve overall treatment effectiveness. The proposed research will examine the effect of NAC use in patients whose neuropathic pain is not controlled with opioids. Specifically, we will enroll 36 patients who have been diagnosed with neuropathic pain, and despite stable doses of opioids, still have pain. Study participants will be treated with 1200 mg NAC twice daily for four weeks, and efficacy, safety, and compliance data will be collected weekly. Statistical analysis will be performed with the primary outcome variable being amount of breakthrough medication, measured in morphine equivalents, required daily.

Study Participants. Study participants will be N=36 men and women who 1) are 18 to 65 years old; 2) have been diagnosed with non-cancer neuropathic pain; 3) are currently taking a stable (same dose and dosing schedule for at least 6 months) dose of opioids for the pain; 4) require short-acting opioid medication on an "as-needed" basis to control breakthrough pain; and 5) report a score of 5 or higher on the 10-point visual analogue scale. Patients will be excluded from the study if they 1) are pregnant or nursing; 2) have a serious, unstable medical or psychiatric illness that in the opinion of the Investigator would preclude them from safely participating in the study; 3) have an active stomach ulcer or a history of seizures or asthma; 4) use breakthrough medications other than opioids to control their neuropathic pain; or 5) are using illicit drugs. Potential study participants will be recruited from the VCU Primary Care and Neurology Clinics. The clinics serve approximately 1,500 patients with a diagnosis of neuropathic pain, and approximately 600 of these patients are being treated with opioid pain medication. These patients are equally men and women, predominately African-American (65%) and of low socioeconomic status.

Recruitment and Informed Consent. Dr. Weaver receives referrals for pain management from both the VCU Primary Care and Neurology Clinics. As such, he works closely with practitioners from both clinics. Prior to the start of the study, Dr. Weaver will meet with these clinicians to describe the study, its eligibility criteria, and outcome measures. As described below, these clinicians will be asked to refer patients to this study. A Research Assistant (RA) will help recruit potential participants for this study. With appropriate IRB approval (already obtained), the trained RA will utilize the i2b2 Cohort Identification Program to identify potential study participants based on their diagnosis of neuropathic pain, use of opioid medications, and attendance at the Primary Care or Neurology Clinic. The RA will work with clinic staff to

determine when these patients have visits scheduled and will coordinate with the clinicians to be available to tell appropriate patients about the study if they are interested. With a potential participant pool of approximately 600 patients, many of whom will have appointments on a regular basis due to the uncontrolled nature of their pain, we expect that the RA will identify about 8-10 unique patients/week to approach about participation in this research study.

For patients who are interested in the study, the RA will tell them that their decisions to participate in the study are entirely voluntary. Also, the RA will assure potential participants that their study data is confidential, will not be shared with anyone outside the research team, and if published or presented, will only be done as aggregate data. For patients who are interested in participating in the study and who meet the eligibility criteria, the RA will answer any questions they have about the study and then obtain informed consent for study participation.

Study Procedures. This will be an open-label pilot study to evaluate the efficacy and safety of NAC in patients with neuropathic pain. Patients who meet all study eligibility criteria and who have signed an informed consent form will be enrolled in the study. Study participants will be treated with 2400 mg NAC (1200 mg twice daily).

Screening

At Screening, basic demographic and medical information will be collected.

1) Demographics. Age, race, ethnicity, and gender data will be collected.
2) Medicalhistory. A complete medical history will be done.
3) Medicationuse. A medication inventory form, including questions about prescription, non-prescription, and medical/nutritional supplement use will be completed.
4) Pregnancytest. Women of childbearing potential will have a urine pregnancy test.
5) Urinedrugtest. A urine sample will be analyzed for five classes of drugs [cocaine, amphetamines, marijuana (THC), methadone, and sedative hypnotics].
6) Opioidmedicationuseassessment. Participants will be asked to record their scheduled and breakthrough pain medication use in a medication diary. The RA will provide directions to the participants regarding the proper completion of the diaries. Participants will also be asked to bring their medicine bottles with them to each visit, and use will be confirmed by pill counts.

Baseline Period

Immediately following Screening, study participants will enter the study Baseline Period, which lasts two weeks. The patients will come in for a visit at the end of each week. At the first Baseline Period Visit, pain medication use will be assessed.

1) Opioidmedicationuseassessmentasdescribedabove.

Study participants will come in for a second Baseline Visit approximately one week after the first visit. At the second Baseline Period Visit, pain medication use will be assessed and baseline assessments will be completed.

1) Physicalexamination. A complete physical examination including evaluation of general appearance, review of body systems, and assessment of vital signs will be done.
2) Pregnancytest. For women of childbearing potential as described above.
3) Urinedrugtestasdescribedabove.
4) Painintensityassessment. Pain intensity will be measured by using the 10-point Visual Analogue Scale, a 10-mm horizontal line with anchors of "no pain at all" and "worst pain imaginable" on which patients' pain intensities are measured (Katz, 1999)
5) Painqualityevaluation. Pain quality will be evaluated by using the Pain Quality Assessment Scale (PQAS), a 20-question measure that assesses the type of pain experienced (Jensen, in press).
6) "Painproblem"assessment. The degree to which participants have a chronic "pain problem" will be evaluated by using the15-item Profile of Chronic Pain: Screening (PCP:S; Ruehlman, 2005).
7) Painimpactassessment. The impact of pain on the patients' lives will be assessed by using the Pain Disability Index (Chibnall and Tait, 1994)
8) Moodassessment. Mood will be assessed by using the Patient Health Questionnaire (PHQ-9), a validated 9-question assessment of depression (Kroenke, 2001).
9) Stressevaluation. Stress will be measured by the Perceived Stress Scale ((PSS), a 10-item instrument for measuring the perception of stress (Cohen et al, 1983).

10) Opioidmedicationuseassessmentasdescribedabove.

Treatment Period

At the end of the Baseline Period, the participants will start the four-week, study Treatment Period. Participants will come to the clinic weekly during the Treatment Period.

1) Pain,mood,andstressassessmentsasdescribedabove. The PCP:S will only be repeated at the end of the study.
2) Pregnancytest. For women of child-bearing potential as described above. Women who become pregnant during the Treatment Period will be withdrawn from the study.
3) Adverseeventassessment. Adverse events will be assessed at each visit.
4) Medicationcomplianceassessment. Medication compliance will be assessed by using eCAP technology. A special eCAP will be placed on each prescription vial at the time of dispensing. A card in the cap records the date and time each time that the vial is opened and transmits the data wirelessly to a computer.
5) Opioidmedicationuseassessmentasdescribedabove.
6) Dispensemedication. At each visit, participants will be given a one-week supply (+/- two days) of study medication and scheduled for their next visit.

NAC will be provided as 600-mg capsules, and study participants will be instructed to take two, 600-mg capsules twice daily in the morning and evening. If patients miss a dose of study medication, they will be instructed to take the dose if it is more than six hours before their next scheduled dose. If it is six hours or less until their next dose, participants will be instructed to skip the dose of NAC.

X. PLAN FOR CONTROL OF INVESTIGATIONAL DRUGS, BIOLOGICS, AND DEVICES.

Investigational drugs and biologics: IF Investigational Drug Pharmacy Service (IDS) is not being used, attach the IDS confirmation of receipt of the management plan.

Investigational and humanitarian use devices (HUDs): Describe your plans for the control of investigational devices and HUDs including:
(1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s);
(2) plan for storing the investigational product(s)/ HUD as specified by the sponsor (if any) and in accordance with applicable regulatory requirements;
(3) plan for ensuring that the investigational product(s)/HUDs are used only in accordance with the approved protocol; and
(4) how you will ensure that each subject understands the correct use of the investigational product(s)/HUDs (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

NAC is a compound that is available without a prescription. For this research, study participants will be seen and medication will be dispensed from the research assistant's (RA's) office on the 4th floor of the VMI building. Study medication will be stored in a locked cabinet in a locked office in the research coordinator's office on the 4th floor of the VMI building. Only the RA and the study investigators (Drs. Michael Weaver, Dace Svikis, and Pamela Dillon) will have access to the cabinet in which the drug will be stored. The cabinet will contain a thermometer that is checked on a weekly basis and the medication storage temperature will be recorded on a temperature log.

Study medication receipt, dispensing, return and disposition records will be maintained and stored in the Regulatory Binder. All study medication order forms, packing slips, and invoices will be filed in the Regulatory Binder. In addition, subject-specific dispensing/use/return logs will be maintained. Finally, records detailing the destruction of unused study medication will be filed in the Regulatory Binder. An electronic monitoring system (e.g., MEMS) will be used to track subject medication compliance. In addition, the RA will reconcile all study medication dispensed and returned during each scheduled study participant visit. The RA will also reconcile all unused study medication on a monthly basis.

Study participants will be given written instructions regarding the dosing schedule and use of the study medication. In addition, the study Investigator or the RA will verbally review the proper use of the study medication with the participants at the study visit. Medication compliance will be assessed by using eCAP technology. A special eCAP will be placed on

each prescription vial at the time of dispensing. A card in the cap records the date and time each time that the vial is opened and transmits the data wirelessly to a computer. The Investigator or RA will discuss any instances of non-compliance with the study participants at the scheduled visits.

The Investigator or RA will package the NAC in vials; a one-week supply (+/- 2 days) will be supplied to each participant at each scheduled visit. The vials will be labeled with the name of the study medication, strength, quantity, dosing instructions, the study participants' initials and subject numbers, and the date dispensed.

XI. DATA ANALYSIS PLAN

For investigator–initiated studies.

The primary outcome of interest in this research is the amount of breakthrough medication, converted to morphine equivalents, used by the patients during the study. The amount of breakthrough medication used by subjects on a weekly basis will be converted to morphine equivalents and analyzed using a repeated measures analysis implemented through a mixed linear model (MLM) to see if there is a significant within subjects Time (Baseline, Week 1, Week 2, Week 3 and Week 4) factor. If there is a significant Time factor, a post-hoc test assessing the significance of the change in Week 4 morphine use from the Baseline morphine use will be done. Additional post-hoc tests will be conducted comparing Week 1, Week 2 and Week 3 morphine use to the Baseline morphine use; these subsequent tests will be adjusted using a Bonferroni adjustment to accommodate the multiple comparisons.

Secondary analyses will examine total amount of pain medication used (in morphine equivalents), pain (by using the VAS), mood (by using the PHQ-9) and stress (by using the PSS), and Baseline values will be compared to end of study values by using paired t-tests. All statistical efficacy analyses will be done only in those subjects who complete the entire Treatment Period and will be calculated at the alpha=0.05 significance level.

Safety data will be examined quantitatively and qualitatively for all participants who take at least one dose of NAC. Adverse events will be tabulated by body system and examined for trends. Medication compliance will be evaluated using the eCAP data, and percent of doses taken will be calculated.

XII. DATA AND SAFETY MONITORING

- **If the research involves greater than minimal risk and there is no provision made for data and safety monitoring by any sponsor, include a data and safety-monitoring plan that is suitable for the level of risk to be faced by subjects and the nature of the research involved.**
- **If the research involves greater than minimal risk, and there is a provision made for data and safety monitoring by any sponsor, describe the sponsor's plan.**
- **If you are serving as a Sponsor-Investigator, identify the Contract Research Organization (CRO) that you will be using and describe the provisions made for data and safety monitoring by the CRO. Guidance on additional requirements for Sponsor-Investigators is available at http://www.research.vcu.edu/irb/wpp/flash/X-2.htm**

The principal investigator, Dr. Weaver, will be responsible for overall data safety and monitoring during the study. All research staff who regularly come in contact with study participants, (e.g., Research Assistants) will be instructed on procedures for managing and reporting adverse events (AEs). All adverse events will be documented, and records regarding the events will be retained in the study binder for review by the study team. Dr. Weaver will be informed immediately, in person or by telephone, of any potential or actual serious adverse event (SAE), and he will report all SAEs to the IRB within 24 hours.

The Research Assistant (RA) will generate a quarterly report of aggregate data for Dr. Weaver. The report will summarize rates of recruitment, participants' demographic characteristics, AEs, SAEs (as defined the FDA), and rates of follow-up. Dr. Weaver will review the report and decide whether recruitment will continue as planned. If he decides that the study protocol should be amended for patient safety reasons or that recruitment should be discontinued for safety reasons, he will inform the IRB of such in a written report. Finally, a copy of the aggregate data report will be provided annually to the IRB.

Data safety will be insured as follows. To protect confidentiality, each participant will be assigned a subject ID number

that will be used to identify all biological specimens and paper data collection forms. This unique subject ID number will also appear on the computer-directed assessment module (for baseline screening and assessment). Participant names will appear only on the consent form (signature), and the participant tracking form that contains information about the participant and others in his/her family or social network who are likely to know the participant's whereabouts (for contact purposes).

All patient identifying information will be kept in a locked, limited-access file cabinet separate from other study data. Hard copies of all other study data will be kept in a separate, locked, limited-access file cabinet. A RA will double enter all study data into a web-based database (REDCap).

All data collected during this study that is presented in reports and publications will be presented in aggregate form, and it will not be possible to identify any individual participants in such documents that result from this research. Specifically, data collected as part of this research will not be shared with members of the clinical staff except in aggregate when the study has been completed.

XIII. MULTI-CENTER STUDIES

If VCU is the lead site in a multi-center project or the VCU PI is the lead investigator in a multi-center project, describe the plan for management of information that may be relevant to the protection of subjects, such as reporting of unexpected problems, project modifications, and interim results.

N/A

XIV. INVOLVEMENT OF NON-VCU INSTITUTIONS/SITES (DOMESTIC AND FOREIGN)

1. **Provide the following information for each non-VCU institution/site (domestic and foreign) that has agreed to participate (all non-VCU institutions/sites are to be listed, including those who obtain local IRB approval from their own institution and those who request deferral to the VCU IRB):**
   - **Name of institution/site**
   - **Contact information for institution/site**
   - **Engaged in Research or not (if YES AND the research involves a DIRECT FEDERAL AWARD made to VCU, include FWA #). See OHRP's guidance on "Engagement of Institutions in Research" at http://www.hhs.gov/ohrp/policy/engage08.html.**
   - **Request for the VCU IRB to review on behalf of the Non-VCU institution?** Submit either the template Authorization Agreement or Individual Investigator Agreement with this application. See additional requirements found at http://www.research.vcu.edu/irb/wpp/flash/XVII-6.htm.
   - See VCU WPPs:
     http://www.research.vcu.edu/irb/wpp/flash/XVII-6.htm and
     http://www.research.vcu.edu/irb/wpp/flash/XVII-11.htm.

Name of Institution	Contact Information for Site	Engaged (Y/N) and FWA # if applicable	Request for VCU IRB to review on behalf of the non-VCU institution (Y/N)*
N/A			

*NOTE: If a Non-VCU site is engaged in the research, the site is obligated to obtain IRB review or request that the VCU IRB review on its behalf.

2. **Provide a description of each institution's role (whether engaged or not) in the research, adequacy of the facility (in order to ensure participant safety in the case of an unanticipated emergency), responsibilities of its**

agents/employees, and oversight that you will be providing in order to ensure adequate and ongoing protection of the human subjects. You should only identify institutions that have agreed to participate. If additional institutions agree to participate at a later time, they must be added by amendment to the protocol.

XV. HUMAN SUBJECTS INSTRUCTIONS

ALL sections of the Human Subjects Instructions must be completed with the exception of the section entitled "Special Consent Provisions." Complete that section if applicable.

A. DESCRIPTION

Provide a detailed description of the proposed involvement of human subjects or their private identifiable data.

Eligible participants will provide demographic, medical history, and medication use information and will complete a number of Baseline assessments including a physical examination, pregnancy and drug screen, pain assessment, mood assessment, and stress evaluation. Participants will take 2400 mg NAC (1200 mg BID) daily for four weeks. Weekly throughout the four-week study period, participants will provide information about their opioid medication use; complete pain, mood, and stress assessments; provide urine for a pregnancy test; and report information about adverse events. All data will be labeled only with subject ID numbers and patient initials and no identifiers (names, medical records numbers) will be linked to computer data files. Other records that contain personal identifying information will be kept separate and all records will be stored in locked file cabinets accessible only by members of the research team.

B. SUBJECT POPULATION

Describe the subject population in terms of sex, race, ethnicity, age, etc., and your access to the population that will allow recruitment of the necessary number of participants. Identify the criteria for inclusion or exclusion of all targeted populations and include a justification for any exclusions. Explain the rationale for the involvement of special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. If you plan to allow for the enrollment of Wards of the State (or any other agency, institution, or entity), you must specifically request their inclusion and follow guidance in VCU IRB WPP XV-3: Wards and Emancipated Minors available at http://www.research.vcu.edu/irb/wpp/flash/XV-3.htm.

Study participants will be N=36 men and women who 1) are 18 to 65 years old; 2) have been diagnosed with non-cancer neuropathic pain; 3) are currently taking a stable (same dose and dosing schedule for at least 6 months) dose of opioids for the pain; 4) require short-acting opioid medication on an "as-needed" to control breakthrough pain; and 5) report a score of 5 or higher on the 10-point visual analogue scale. Patients will be excluded from the study if they 1) are pregnant or nursing; 2) have a serious, unstable medical or psychiatric illness that in the opinion of the Investigator would preclude them from safely participating in the study; 3) have an active stomach ulcer or a history of seizures or asthma; 4) use breakthrough medications other than opioids to control their neuropathic pain; or 5) are using illicit drugs. Potential study participants will be recruited from the VCU Primary Care and Neurology Clinics. The clinics serve approximately 1,500 patients with a diagnosis of neuropathic pain, and approximately 600 of these patients are being treated with opioid pain medication. These patients are equally men and women, predominately African-American (65%) and of low socioeconomic status.

C. RESEARCH MATERIAL

Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

Data used in this study will be obtained strictly for research purposes. Multiple methods of data collection will be used,

including direct computer entry by research participants, interview data, and pencil and paper survey data.

D. RECRUITMENT PLAN

Describe <u>in detail</u> your plans for the recruitment of subjects including:
(1) how potential subjects will be identified (e.g., school personnel, health care professionals, etc),
(2) how you will get the names and contact information for potential subjects, and
(3) who will make initial contact with these individuals (if relevant) and how that contact will be done.
If you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable, describe any special recruitment procedures for these populations.

Dr. Weaver receives referrals for pain management from both the VCU Primary Care and Neurology Clinics. As such, he works closely with practitioners from both clinics. Prior to the start of the study, Dr. Weaver will meet with these clinicians to describe the study, its eligibility criteria, and outcome measures. As described below, these clinicians will be asked to refer patients to this study. A Research Assistant (RA) will help recruit potential participants for this study. With appropriate IRB approval (already obtained), the trained RA will utilize the i2b2 Cohort Identification Program to identify potential study participants based on their diagnosis of neuropathic pain, use of opioid medications, and attendance at the Primary Care or Neurology Clinic. The RA will work with clinic staff to determine when these patients have visits scheduled and will coordinate with the clinicians to be available to tell appropriate patients about the study if they are interested. With a potential participant pool of approximately 600 patients, many of whom will have appointments on a regular basis due to the uncontrolled nature of their pain, we expect that the RA will identify about 8-10 unique patients/week to approach about participation in this research study.

For patients who are interested in the study, the RA will tell them that their decisions to participate in the study are entirely voluntary. Also, the RA will assure potential participants that their study data is confidential, will not be shared with anyone outside the research team, and if published or presented, will only be done as aggregate data. For patients who are interested in participating in the study and who meet the eligibility criteria, the RA will answer any questions they have about the study and then obtain informed consent for study participation.

E. PRIVACY OF PARTICIPANTS

NOTE: Privacy refers to individuals and their interests in controlling access to their identities, their physical person, and how and what kind of information is obtained about them. Privacy also encompasses the interests of defined communities (e.g. those with a certain diagnosis or social circumstance) in controlling access to the group identity and information about the group or individuals as part of the group.

Describe how the privacy interests of subjects (and communities, if appropriate) will be protected including:
(1) in the research setting (e.g., in the identification, recruitment, and intervention settings) and
(2) with the information being sought and the way it is sought. For example, providing drapes or barriers, interviewing in a private room, and collecting only the amount of sensitive information needed for identification, recruitment, or the conduct of the study.

Consent, assessments, and other study activities will be conducted by trained members of the research staff in private areas in or near the clinics. Participant information will be kept in a locked filing cabinet in a locked room and will be accessible only to the study team.

F. CONFIDENTIALITY OF DATA

NOTE: Confidentiality refers to the way private, identifiable information about a subject or defined community is maintained and shared.

Check all of the following precautions that will be used to maintain the confidentiality of identifiable information:

☒ Paper-based records will be kept in secure location and only accessed by authorized study personnel
☒ Electronic records will be made available only to those personnel in the study through the use of access controls and encryption
☒ Identifiers will be removed from study-related data (data is coded with a key stored in a separate secure location)
☐ For research involving web-based surveys, data is secured via passwords and encryption
☐ Audio or video recordings of subjects will be transcribed and then destroyed to prevent audio or visual identification. Note the date of destruction (e.g., 3 months from close of study; after transcription is determined to be error free).
☐ Obtaining a Certificate of Confidentiality
☐ Other precautions: ☐

G. Potential Risks

Describe potential risks (physical, psychological, social, legal, or other) and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

NAC is contraindicated in patients who are hypersensitive to it. NAC should be used with caution in patients with asthma or severe respiratory insufficiency as NAC may worsen these conditions. It should also be used with caution in patients with conditions predisposing to gastrointestinal hemorrhage (e.g., esophageal varices and peptic ulceration) because drug-induced nausea and vomiting may increase the risk of such hemorrhage in patients predisposed to the condition and because of the theoretical risk that mucolytics may disrupt the gastric mucosal barrier.

The most common side effects of oral NAC are nausea, vomiting and diarrhea, or constipation. Rarely, it causes rashes with or without mild fever or drowsiness.

A rare side effect of NAC is hypersensitivity/anaphylactoid reaction, which may manifest as a bronchospastic allergic reaction, allergic dermatitis or facial edema.

Adequate and well-controlled studies in pregnant and breastfeeding women have not been done. Therefore, pregnant women will not be allowed to participate in this study. If a woman becomes pregnant while she is in the study, she will be discontinued from treatment immediately.

There have not been any drug-drug interaction studies, and there are no well-documented drug interactions with NAC.

H. Risk Reduction

Describe procedures for protecting against or minimizing potential risk. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events to the subjects. Describe the provisions for monitoring the data collected to ensure the safety of subjects, if any.

To minimize the risk of harm to participants in this study, patients with unstable medical or psychiatric illnesses will not be enrolled in the study. Patients with a history of sensitivity to NAC, those with asthma or severe respiratory insufficiency, and those with active peptic ulcer disease also will not be enrolled in the study. To optimize the safety of subjects enrolled in the study, all participants will be asked about side effects and adverse events on a weekly basis, and any adverse events reported by the patients will be evaluated by study staff.

I. Additional Safeguards for Vulnerable Participants

Describe any additional safeguards to protect the rights and welfare of participants if you plan to involve special cases of subjects such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable.

Safeguards to protect the rights and welfare of participants might relate to Inclusion/Exclusion Criteria: ("Adults with moderate to severe cognitive impairment will be excluded." "Children must have diabetes. No normal controls who are children will be used.") Consent: ("Participants must have an adult care giver who agrees to the participant taking part in the research and will make sure the participant complies with research procedures." "Adults must be able to assent. Any dissent by the participant will end the research procedures.") Benefit: ("Individuals who have not shown benefit to this type of drug in the past will be excluded.").

N/A

J. RISK/BENEFIT

Discuss why the risks to participants are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If a test article (investigational new drug, device, or biologic) is involved, name the test article and supply the FDA approval letter.

While there are risks associated with the use of NAC, these risks will be minimized as described above. Further, NAC has been used safely in a number of conditions, and the formulation to be used in this study is available without a prescription. The benefit of the research may be significant. Despite the availability of numerous treatments for chronic neuropathic pain, as many as three-fourths of patients continue to experience uncontrolled moderate to severe pain. With positive outcomes from the addition of NAC therapy to opioid therapy in this study, the pilot data collected will be used for the calculation of effect and sample sizes for a large, randomized clinical trial (RCT) to further evaluate the use of NAC in neuropathic pain. If indeed NAC is effective in neuropathic pain, it will be an inexpensive and clinically significant addition to the armamentarium of therapies available to manage this chronic and disabling disease, ultimately improving the lives of the millions of patients affected by neuropathic pain.

K. COMPENSATION PLAN

Compensation for participants (if applicable) should be described, including possible total compensation, pro-rating, any proposed bonus, and any proposed reductions or penalties for not completing the project.

Participants will be compensated for the time and effort that they spend participating in this research study. They will receive $25 for completing the Screening Visit, $15 for completing each of the two Baseline Visits, $25 for completing each of the first three, weekly Treatment Period Visits, and $50 for completing the last study visit. At the end of the study, participants will receive an additional $20 if they have attended each of their study visits. Thus, the potential maximum compensation for this study is $200. Compensation will be prorated based on the visits attended for those participants who miss study visits or discontinue from the study.

L. CONSENT ISSUES

1. CONSENT PROCESS

Indicate who will be asked to provide consent/assent, who will obtain consent/assent, what language (e.g., English, Spanish) will be used by those obtaining consent/assent, where and when will consent/assent be obtained, what steps will be taken to minimize the possibility of coercion or undue influence, and how much time will subjects be afforded to make a decision to participate.

For patients who are interested in the study, the RA will tell them that their decisions to participate in the study are entirely voluntary. Also, the RA will assure potential participants that their study data is confidential, will not be shared with anyone outside the research team, and if published or presented, will only be done as aggregate data. For patients who are interested in participating in the study and who meet the eligibility criteria, the RA will answer any questions they have about the study and then obtain informed consent for study participation. The informed consent process will be conducted by the RA in English (as only English-speaking participants will be recruited) in private areas in or near the clinics. Potential participants who want additional time to decide about study participation will be allowed to take a blank consent form home with them and may go through the consent process at a subsequent clinic visit.

2. SPECIAL CONSENT PROVISIONS

If some or all subjects will be cognitively impaired, or have language/hearing difficulties, describe how capacity for consent will be determined. Consider using the VCU Informed Consent Evaluation Instrument available at http://www.research.vcu.edu/irb/guidance.htm. If you anticipate the need to obtain informed consent from legally authorized representatives (LARs), please describe how you will identify an appropriate representative and ensure that their consent is obtained. Guidance on LAR is available at http://www.research.vcu.edu/irb/wpp/flash/XI-3.htm.

N/A

3. ASSENT PROCESS

If applicable, explain the Assent Process for children or decisionally impaired subjects. Describe the procedures, if any, for re-consenting children upon attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm and http://www.research.vcu.edu/irb/wpp/flash/XVII-7.htm.

N/A

4. REQUESTS FOR WAIVERS OF CONSENT (COMPLETE IF REQUESTING ANY TYPE OF WAIVER OF CONSENT OR ASSENT)

4-A. REQUEST TO WAIVE SOME OR ALL ELEMENTS OF INFORMED CONSENT FROM SUBJECTS OR PERMISSION FROM PARENTS: A waiver of informed consent means that the IRB is not requiring the investigator to obtain informed consent OR the IRB approves a consent form that does not include or alters some/all of the required elements of consent. **Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XI-1.htm. NOTE: Waiver is not allowed for FDA-regulated research unless it meets FDA requirements for Waiver of Consent for Emergency Research (see below).**

4-A.1. Explain why a waiver or alteration of informed consent is being requested.

4-A.2. Describe how this study meets ALL FOUR of the following conditions for a waiver or alteration:

- The research involves no more than minimal risk to the participants. → Explain how your study meets this criteria:
- The waiver or alteration will not adversely affect the rights and welfare of participants. → Explain how your study meets this criteria:
- The research could not practicably be carried out without the waiver or alteration. → Explain how your study meets this criteria:
- Will participants be provided with additional pertinent information after participation?
  - ☐ Yes
  - ☐ No → Explain why not:

4-B. REQUEST TO WAIVE DOCUMENTATION OF CONSENT: A waiver of documentation occurs when the consent process occurs but participants are not required to sign the consent form. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XI-2.htm **. One of the following two conditions must be met to allow for consenting without signed documentation. Choose which condition is applicable and explain why (explanation required)**:

☐ The only record linking the participant and the research would be the informed consent form. The principal risk to the

participant is the potential harm resulting from a breach of confidentiality. Each participant will be asked whether he/she wants documentation linking the participant with the research and the participants wishes will govern. → Explain how your study fits into the category: ☐

☐ The research presents no more than minimal risk of harm to participants & involves no procedures for which signed consent is normally required outside of the research context. → Explain how your study fits into the category: ☐

4-C. REQUEST TO WAIVE SOME OR ALL ELEMENTS OF ASSENT FROM CHILDREN ≥ AGE 7 OR FROM DECISIONALLY IMPAIRED INDIVIDUALS: A waiver of assent means that the IRB is not requiring the investigator to obtain assent OR the IRB approves an assent form that does not include some/all of the required elements. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm.

4-C.1. Explain why a waiver or alteration of informed consent is being requested.
☐

In order for the IRB to approve a request for waiver of assent, the conditions for 4-C.2, 4-C.3, OR 4-C.4 must be met. Check which ONE applies and explain all required justifications.

4-C.2. ☐ **Some or all of the individuals age 7 or higher will not be capable of providing assent based on their developmental status or impact of illness**. → Explain how your study meets this criteria: ☐

4-C.3. ☐ **The research holds out a prospect of direct benefit not available outside of the research**. → Explain how your study meets this criteria: ☐

4-C.4. ☐ **Describe how this study meets ALL FOUR of the following conditions**:

- The research involves no more than minimal risk to the participants. → Explain how your study meets this criteria: ☐
- The waiver or alteration will not adversely affect the rights and welfare of participants. → Explain how your study meets this criteria: ☐
- The research could not practicably be carried out without the waiver or alteration. → Explain how your study meets this criteria: ☐
- Will participants be provided with additional pertinent information after participation?
  - ☐ Yes
  - ☐ No → Explain why not: ☐

4-D. REQUEST TO WAIVE CONSENT FOR EMERGENCY RESEARCH: Describe how the study meets the criteria for emergency research and the process for obtaining LAR consent is appropriate. See guidance at http://www.research.vcu.edu/irb/wpp/flash/XVII-16.htm.

5. GENETIC TESTING
If applicable, address the following issues related to Genetic Testing.

5-A. FUTURE CONTACT CONCERNING FURTHER GENETIC TESTING RESEARCH
Describe the circumstances under which the subject might be contacted in the future concerning further participation in this or related genetic testing research.

N/A

5-B. FUTURE CONTACT CONCERNING GENETIC TESTING RESULTS
If planned or possible future genetic testing results are unlikely to have clinical implications, then a statement that the results will not be made available to subjects may be appropriate. If results might be of clinical significance, then describe the circumstances and procedures by which subjects would receive results. Describe how subjects might access genetic counseling for assistance in understanding the implications of genetic testing results, and whether this might involve costs to subjects. Investigators should be aware that federal regulations, in general, require that testing results used in clinical management must have been obtained in a CLIA-certified laboratory.

N/A

5-C. WITHDRAWAL OF GENETIC TESTING CONSENT
Describe whether and how subjects might, in the future, request to have test results and/or samples withdrawn in order to prevent further analysis, reporting, and/or testing.

N/A

5-D. GENETIC TESTING INVOLVING CHILDREN OR DECISIONALLY IMPAIRED PARTICIPANTS
Describe procedures, if any, for consenting children upon the attainment of adulthood. Describe procedures, if any, for consenting participants who are no longer decisionally impaired.

N/A

5-E. CONFIDENTIALITY OF GENETIC INFORMATION
Describe the extent to which genetic testing results will remain confidential and special precautions, if any, to protect confidentiality.

N/A