Randomized Controlled Trial of Vitamin D to reduce racial disparity in chronic pain following Motor Vehicle Collision: The VENTURE Trial (Vitamin D to ENhance TraUma REcovery)

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Protocol Title:
Randomized Controlled Trial of Vitamin D to reduce racial disparity in chronic pain following Motor Vehicle Collision: The VENTURE Trial (**V**itamin D to **EN**hance **T**ra**U**ma **RE**covery)

Principal Investigators:

Matthew C. Mauck, MD PhD
Department of Anesthesiology
Campus Box 7010
Chapel Hill, NC 27599

Samuel McLean, MD, MPH
Professor of Emergency Medicine, Psychiatry, and Anesthesiology
101 Manning Drive
Chapel Hill, NC 27599

Funding Sponsor:

University of North Carolina
N2198 UNC Hospitals
Campus Box 7010
Chapel Hill, NC 27599

Study Product: *Ergocalciferol*

Protocol Number: 21-2589

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List of Abbreviations

AE: Adverse Events
cc: cubic centimeters
CRF: case report form
DASS: Depression, Anxiety, and Stress Scale
DCC: data coordinating center
DNA: deoxyribonucleic acid
EC: ethics committee
ELISA: enzyme linked immunosorbent assay
FDA: Food and Drug Administration
g: grams
GFR: glomerular filtration rate
IDS: investigational drug services
IRB: institutional review board
IU: international units
MAR: medication administration record
MCS: mental component score
MSP: severe musculoskeletal pain
MOS: medical outcomes survey
MVC: motor vehicle collision
NRS: numeric rating scale
OT: occupational therapy
PCS: physical component score
PT: physical therapy
PTSD: post-traumatic stress disorder
RCT: Randomized Controlled Trial
RNA: ribonucleic acid
RPS: regional pain scale
SAE: serious adverse events
SF-12: short form 12 item questionnaire
TBSA: total body surface area
UNC: University of North Carolina
UPLC/ESI/MS/MS: Ultraperformance Liquid Chromatography/Electrospray Ionization Mass Spectrometry

Study Summary

Title	Randomized Controlled Trial of Vitamin D to reduce racial disparity in chronic pain following Motor Vehicle Collision
Short Title	VENTURE
IRB Protocol Number	21-2589
Phase	2
Methodology	Double Blind, Randomized Controlled Trial using a parallel design
Study Duration	2 years
Study Center(s)	University of North Carolina-Data Coordinating Center Rhode Island Hospital University of Massachusetts Washington University Cooper University Hospital
Objectives	Assess the feasibility of administering a single dose of Vitamin D in the emergency department to Blacks and Whites presenting within 24 hours of MVC with moderate or severe musculoskeletal pain (MSP), along with the ability of this dose to achieve sustained increases in Vitamin D levels. Evaluate the potential efficacy of this intervention to improve MSP outcomes in Blacks and to reduce MSP disparities in Black vs. White MVC survivors.
Number of Subjects	90
Diagnosis and Main Inclusion Criteria	Presentation to emergency department (ED) within 24 hours of motor vehicle collision with an initial moderate/severe MSP severity (0-10 NRS of ≥4)
Study Product, Dose, Route, Regimen	Ergocalciferol (Vitamin D2), 300,000 IU (2-150,000 IU capsules) orally administered once as a single dose prior to discharge from emergency department
Duration of administration	One-time dose
Reference therapy	Matched placebo to Vitamin D preparation

Statistical Methodology	Assess the feasibility of the RCT protocol by (a) calculating recruitment rate and participant retention, and (b) measuring the ability of Vitamin D administration to generate sustained increases in whole-blood Vitamin D concentrations (assessed 3 months after MVC). Assess for preliminary efficacy that Vitamin D administration per protocol (a) decreases overall MSP severity in Black Americans during the 3 months following MVC, and (b) reduced MSP outcome disparities between Black vs. White Americans following MVC.

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

The main objective of this study is to determine whether administration of a single dose of Vitamin D in the Emergency Department following a motor vehicle collision reduces racial disparities in chronic pain following a traumatic event. This phase II, multicenter, randomized controlled trial is a pilot study to determine feasibility and potential efficacy (effect size, sample variation, response to study drug, ability to reduce racial disparity in pain outcomes) that can be used to adequately power a larger randomized controlled trial to fully assess efficacy.

1.1 Background

Motor vehicle collisions (MVCs) are one of the most common traumatic stress exposures in the US, and the most common for which individuals seek emergency department (ED) care. More than 1 million Black Americans (Blacks) come to the ED after MVC each year, and >90% of such ED MVC patients are discharged home with a diagnosis of acute musculoskeletal pain (MSP)/strain only. More than 80% of these individuals report acute moderate or severe (mod/sev) MSP in the ED, and >50% of those with acute mod/sev MSP transition to chronic MSP. MVCs, as well as pain after MVC, disproportionately affect Blacks vs. Whites. For example, in our previous cohort studies 67% of Blacks had mod/sev MSP six months after MVC, vs. only 40% of Whites. Interventions are urgently needed that prevent chronic MSP and reduce these MSP outcome disparities.

One safe, inexpensive, widely available, and well-tolerated intervention, with exciting potential to achieve these goals, is Vitamin D (Vitamin D). Vitamin D insufficiency is much more common in Blacks than Whites. In the investigators' previous observational study, 77% (103/133) of Black MVC survivors had Vitamin D insufficiency at the time of ED evaluation. Such low Vitamin D levels are associated with increased inflammation and worse pain outcomes. Vitamin D has anti-inflammatory, neuroprotective, and analgesic properties, and Vitamin D treatment improves pain outcomes in a range of conditions. Results of a recent Vitamin D intervention study in another trauma population (burn survivors) found that Vitamin D treatment after burn

injury disproportionately improved pain outcomes in Black vs. White burn survivors (67% vs. 33% pain improvement at 6 weeks). Results from a recent analysis suggest that Vitamin D administration in the ED after MVC could prevent at least 70,000 Blacks from developing chronic post-MVC MSP annually.

1.2 Investigational Agents

Some previous treatment trials of Vitamin D have elected to use Cholecalciferol (D3), rather than Ergocalciferol (D2), because of more favorable kinetics.[1] However, both have efficacy in raising serum concentration of 25-hydroxyvitamin D,[2] and only Ergocalciferol (D2) is available in an FDA-approved prescription formulation that is well-tolerated.[3,4] In addition, a major benefit of Ergocalciferol (D2) is that a single dose can result in Vitamin D sufficient levels for many weeks/months (Table 1). The dose of Ergocalciferol that we propose, 300,000 IU, has been shown to effectively raise Vitamin D concentration by ~9 ng/ml, and to raise serum 25 hydroxyvitamin D concentration above 30 ng/ml (Vitamin D sufficient *levels) for over 3 months*[5]. The ability of our single-dose protocol to raise Vitamin D will be a primary feasibility endpoint of this pilot study.

Importantly, this dose is extremely well-tolerated: in previous trials, reports of side effects/adverse events is rare,[6] many studies administering single, high-dose regimens report no side effects[7-9], and the most common side effects have been mild GI complaints (e.g. nausea).[6] Vitamin D administration has also been demonstrated to be safe, even among individuals who are already Vitamin D sufficient. [10-12] Based on the Code of Federal Regulation (CFR), Ergocalciferol will be exempt from an investigational new drug (IND) application.[5,13-16]

Table 1. Studies demonstrating effectiveness of single-dose Vitamin D (Ergocalciferol, D2) to raise 25-hydroxyvitamin D levels

First author/year	Dose Used	Sample Size	Disease state	Magnitude increases of 25-OH Vitamin D @ timepoint
Martineau et al, 2007[13]	100,000 IU (PO)	N=192	Tuberculosis patients	↑ 13 ng/ml @ 6 weeks
Witham, et al, 2012[14]	100,000 IU (PO)	N=58	Stroke	↑ 6 ng/ml @ 8 weeks
Lanthan et al, 2003[5]	300,000 IU (PO)	N=243	Frail elderly	↑ 9 ng/ml @ 12 weeks
Alam, et al, 2017[15]	600,000 IU PO	N=143	Diabetic neuropathy	↑ 10 ng/ml @ 20 weeks
Cipriani et al, 2013 [16]	600,00 IU PO	N=6	Healthy Volunteers	↑ 6 ng/ml @ 4 weeks

1.3 Clinical Data to Date

Previous studies demonstrate that Vitamin D is a safe, and effective treatment option that has been used to treat a range of painful musculoskeletal disorders. Vitamin D has been shown to reduce chronic pain across a range of painful conditions. Clinical trial results demonstrate that Vitamin D supplementation improves symptoms experienced by patients suffering from fibromyalgia[17-21], a difficult to treat widespread pain condition. Vitamin D supplementation in a recent clinical trials also improved disability related to low back pain[22], osteoarthritis[23] and chronic pain related to migraine headache[24]. Not all studies are positive, for example a recent study demonstrated that Vitamin D supplementation did not change analgesic consumption, or improve pain outcomes among the general population[25]; however this study included the general population not those at high risk of chronic pain development as are the individuals we plan to recruit into this study. Taken together, the results of clinical trials of Vitamin D to address painful conditions are promising, and given the lack of available treatment options to prevent chronic pain.

1.4 Dose Rationale and Risk/Benefits

The dose of Ergocalciferol that we propose, 300,000 IU, has been shown to effectively raise Vitamin D concentration by ~9 ng/ml, and to raise serum 25 hydroxyvitamin D concentration above 30 ng/ml (Vitamin D sufficient levels) for over 3 months[5]. The ability of our single-dose protocol to raise Vitamin D will be a primary feasibility endpoint of this pilot study. Importantly, this dose is extremely well-tolerated: in previous trials, reports of side effects/adverse events is rare,[6] many studies administering single, high-dose regimens report no side effects[7-9], and the most common side effects have been mild GI complaints (e.g. nausea).[6] Vitamin D administration has also been demonstrated to be safe, even among individuals who are already Vitamin D sufficient. [10-12] Based on the Code of Federal Regulation (CFR), Ergocalciferol will be exempt from an investigational new drug (IND) application.[5,13-16]

Chronic pain is associated with reduced mental and physical health and interferes with essential activities of daily life. Currently there are limited treatment options to address chronic pain once it has become established and the overarching aim of this clinical trial is to prevent chronic pain development, therefore there is a critical unmet need of safe, non-addictive, non-invasive preventative treatment options that can be administered to MVC survivors in the aftermath of an injury. This study has the potential to benefit participants and future MVC survivors and improve pain and general health outcomes. The risks of taking Vitamin D are small. Side effects from Vitamin D are rare, however, it is possible that over supplementation of Vitamin D may be associated with headache, loss of appetite, dry mouth, metallic taste, and nausea/vomiting.

The risks to the subjects in experiencing these side effects are balanced against the potential for a new, safe, non-opioid preventative treatment option for chronic pain following MVC.

Study Objectives

2.1 Primary Objective:

1. Assess the feasibility of the RCT protocol by (a) calculating recruitment rate and participant retention, and (b) measuring the ability of Vitamin D administration to generate sustained increases in whole-blood Vitamin D concentrations (assessed 3 months after MVC).
2. To demonstrate the preliminary efficacy of Vitamin D administration per protocol on decreasing overall MSP severity during the 3 months following MVC, and reducing MSP outcome disparity between Blacks and Whites following MVC.

2.2 Secondary Objectives:

We will assess the effect of race and sex on treatment outcomes in secondary analyses. This will be accomplished using two analytic strategies. First, a sex X treatment interaction term (secondary analyses) will be entered into our statistical models to assess pain reduction in response to treatment. Second, a stratified analysis will be performed which will examine the influence of both sex and race on treatment effect on primary and secondary outcomes. Further, Secondary stratified analyses evaluate the influence of initial vitamin D level on treatment response. In addition, exploratory analyses on the relationship of vitamin D outcome and trajectory of pain as well as restricting analyses to participants with vitamin D deficiency at baseline will be performed. Secondary analyses will examine treatment effects adjusting for any baseline differences in psychosocial factors between treatment arms.

2.3 Long-Term Aims Beyond the Present Proposal

To use data collected to design and adequately power a larger-scale RCT assessing the efficacy of Vitamin D treatment in decreasing chronic pain in high-risk patients presenting for treatment in the aftermath of MVC and to reduce racial disparity in pain outcomes following MVC.

Study Design

3.1 General Design

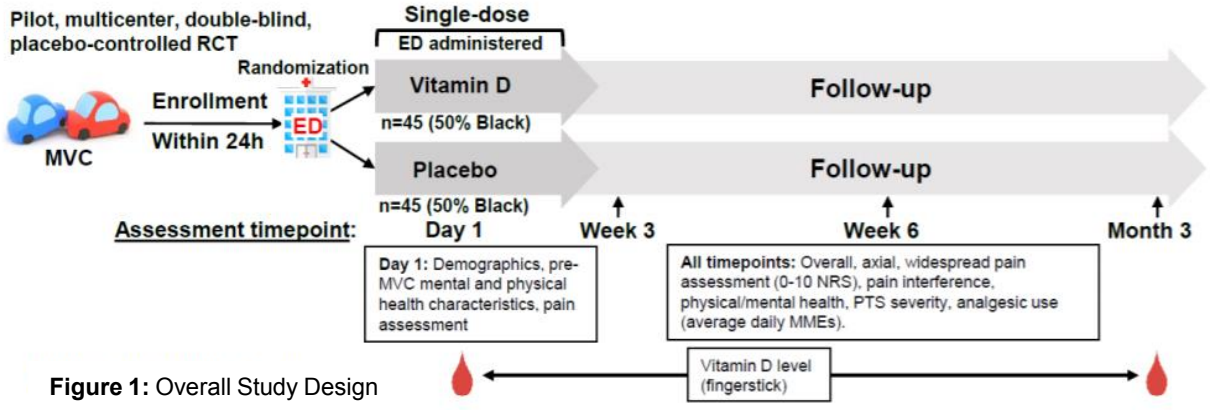

Figure 1: Overall Study Design

3.2 Study Overview

Described the sequence of events in recruiting 90 patients in a multi-center randomized controlled trial. To assess a key primary outcome, we will enroll 50% white and 50% black MVC into the study. Each participant will be screened in based on a point of care Vitamin D test. This will be performed at the time of screening. Individuals with a Vitamin D level <100 ng/ml will be enrolled. Patients will be randomized 1:1 to receive a single dose of 300,000 IU of ergocalciferol versus placebo and followed for 3 months. At 3 months, patients will send a blood sample easily collected at home on a blood spot card to assess Vitamin D level 3 months following injury which is a key feasibility primary outcome.

Patients presenting to the ED within 24 hours of MVC (n=90, 45 non-Hispanic Black, and 45 non-Hispanic White) will receive a single dose of study drug prior to ED discharge (1:1 allocation 300,000 IU ergocalciferol or placebo). Prior to study drug administration, a baseline assessment will be performed (see below), and a fingerstick blood sample will be obtained to evaluate 25-hydroxyvitamin D level. Online survey follow-ups assessing primary and secondary outcomes and potential adverse events will be performed 3 weeks, 6 weeks, and 3 months after ED enrollment by study RAs using web-based REDCap™ software. Participants will also complete brief “flash-surveys” at the 2-week, 4-week, and 5-week timepoints using REDCap survey links. At 3 months, participants will also perform a fingerstick blood collection at home and mail the sample in a prepaid envelope to a lab to be processed to enable assessment of 3 month 25-hydroxyvitamin D concentration by treatment group.

3.3 Posting on clinicaltrials.gov

The study protocol will be published to clinicaltrials.gov prior to commencement of the trial. Results will be posted on clinicaltrials.gov when available.

3.4 Primary Study Endpoints

The primary endpoint of this study will examine the feasibility and efficacy of Vitamin D to improve overall MSP severity outcomes following motor vehicle collision in Blacks and Whites, as well as to reduce MSP outcome disparity between Blacks vs. Whites following MVC.

Outcome to assess feasibility: 90 patients will be enrolled, randomized into one of 2 treatment arms in a 1:1 ratio, and treated with study drug as a single-dose following motor vehicle collision with moderate to severe MSP within a 15-month period. Feasibility will also be measured by the ability to retain >80% of participants through 3-month follow-up, and achieve Vitamin D levels >20 ng/ml in 90% of treatment group at 3-month follow-up. In addition, will determine whether Vitamin D administration per protocol can raise Vitamin D concentration in treatment group >10 ng/ml above baseline. The concentration of Vitamin

D will be calculated before and after the treatment in each treatment arm to assess the response.

Outcome to assess efficacy: Efficacy of Vitamin D will be measured by difference in pain severity in treatment arms versus control arms. Pain reduction between treatment groups will be assessed using patient-reported overall MSP scores (0-10 NRS) obtained at the ED, 3-week, 6-week, and 3-month assessments. Estimates of efficacy will be obtained via repeated measures analysis using mixed effects models. Secondary Study Endpoints

3.5 Primary Safety Endpoints

To assess safety, adverse events will be tracked using REDCap through emailed/text-messaged surveys during the drug treatment to assess side effects and safety profile of Vitamin D. Qualitative analysis of adverse events will be performed by investigative team.

3.6 Inclusion Criteria

1. ≥ 18 years and ≤ 65 years of age
2. Admitted to ED within 24 hours of motor vehicle collision
3. Plan to discharge to home from the emergency department
4. Stated willingness to comply with all study procedures and availability for the duration of the study (with the exception of the blood draw sample collected in the ED, which is optional)
5. Has a smartphone with continuous service ≥1 year
6. Able to speak and read English
7. Alert and oriented, and capable of engaging in informed consent
8. Willing to take on-time dose of study medication (2 capsules of Vitamin D or placebo)
9. Non-Hispanic white or non-Hispanic black
10. Point of care Vitamin D level <100 ng/ml
11. During ED admission pain severity must be at least 4/10 or higher

3.7 Exclusion Criteria

1. Substantial comorbid injury (e.g., long bone fracture)
2. Pregnancy/breastfeeding
3. Prisoner status
4. Chronic daily opioid use prior to MVC (>20 mg oral daily morphine equivalents)
5. Active psychosis, suicidal ideation, or homicidal ideation
6. Plans for hospital admission
7. Known chronic kidney disease, stage 4 or higher (GFR≤29)
8. Intubated and sedated at time of enrollment
9. Inability to provide informed consent (receipt of sedative, hypnotic agent making the patient non-decisional for consent)
10. Known hypercalcemia
11. Vitamin D supplements in excess of 800 IU daily

12. Any other history or condition that would, in the site investigator's judgement, indicate that the patient would very likely be non-compliant with the study or unsuitable for the study (e.g., might interfere with the study, confound interpretation, or endanger patient)

3.8 Subject Recruitment and Screening

Prior to approaching the participant, medical history data will be reviewed for information pertaining to inclusion/exclusion criteria in section 3.6 and 3.7. If the participant is determined to be ineligible, the review will stop. The purpose of assessing this information is to approach only those patients who are potentially eligible Record will be kept of patients who are screened but excluded and for what reason. A HIPAA waiver will be requested to permit the review of medical record data for evident exclusion criteria prior to approaching a participant (this will reduce study burden on the study population). In participants who otherwise appear to be eligible for the study, the attending physician/medical record will be consulted to determine if admission is planned (most of the time this can be determined through chart review). Reasons for exclusion will be recorded. To be eligible for the study, during ED admission pain severity must be at least 4/10 or higher). Participants will be approached by study personnel and will be offered participation. Participants will undergo informed consent with enrolling RAs in the ED. Participants will receive paper copies of their main study consent, HIPAA authorization, biospecimen collection and social security collection forms. Both the participant and consenter will open and review the documents. Because both the RA and the participant will have forms open, the participant will follow along on paper while the consenter explains each section. After reviewing the consent documents, if the potential participant is willing to participate, the consenter and participant both sign the consent forms and the RAs will enter their time and date of their signature in REDCap. Once all fields are complete, then a copy of the completed consents (Main Study Consent, HIPAA Authorization, Biospecimen Collection and SSN Form) are given to each the participant and the consenter. The consenter will then save a scanned copy of the forms to REDCap, the central and secure online study database.

If participant refuses consent, data collected to that point will be retained to describe the proportion of MVC patients who were screened but refused to participate (we will maintain demographic information for audit purposes). Reason to refuse participation will be also documented and retained.

If the participant is after 10 days following their last menstrual period, and is not on birth control, a urine pregnancy test will be performed prior to randomization. If the participant is found to be pregnant, they will be excluded from the study. Once participants are determined to meet full inclusion criteria and have no reason for exclusion, consented participants will be randomized and study drug will commence on enrollment in the study. Participants who are initially intubated may be eligible for the study, as long as they are extubated, alert, and oriented at the time of consent, enrollment and other eligibility criteria are met.

3.9 Early Withdrawal of Subjects

3.9.1 When and How to Withdraw Subjects

Participants may withdraw from the study at any point in time if they no longer wish to participate in the study.

3.9.2 Data Collection and Follow-up for Withdrawn Subjects

If the patient voluntarily withdraws from the study, outcome measures from completed timepoints will be collected and included in intention to treat analysis. If the patient is lost to follow-up and is unresponsive to more than 3 phone calls and 3 secure e-mails, the next of kin listed in the medical record will be contacted once to attempt to reach the participant. If this is not successful, then 1 final email will be sent to attempt to contact the consented participant.

Study Drug

4.1 Description

The study drug is Vitamin D_2 (ergocalciferol) 300,000 IU administered orally as 2 capsules comprising approximately 150,000 IU each.

4.2 Treatment Regimen

Within 24 hours of presenting to the ED for a MVC, and immediately following enrollment in this study, participants will be provided with study drug or placebo. The study drug and placebo will be manufactured and encapsulated by a 503b compounding pharmacy (i.e., Pharmacy Innovations), and will ship the study drug to the investigational pharmacy at each study site. Immediately following randomization, the IDS pharmacy will receive an email with the unblinded treatment allocation for the participant. The IDS at each site will dispense the appropriate study drug once they receive a prescription from the clinician at enrollment. Study medications (placebo or active) will be administered orally via a one-time dose that will be observed by the research personnel in the ER.

4.3 Method for Assigning Subjects to Treatment Groups

Once a potential subject has been successfully screened, does not meet any exclusion criteria, is willing to participate in the study, and signs informed consent, the participant will be randomized by the study site using a minimization algorithm stratified on race, sex, and pain score. Randomization of participants using minimization will be accomplished using a centralized, web-based, validated (compliant with FDA 21 CFR Part 11) service (randomize.net). In this algorithm, a new participant is sequentially assigned to a particular treatment group by taking into account the covariates of the current and previously randomized participants. To further optimize power in this small, pilot study to examine the effect of race, and achieve a main goal of this study, a 1:1 ratio of non-Hispanic Black and White Americans will be enrolled. Once enrollment reaches 45 in a given race strata (e.g., non-Hispanic Black), enrollment for that race will cease. All participants, investigators, study

personnel, and follow-up team members will be blinded to allocation and concealment will be maintained throughout the study. Only the investigational pharmacy and study statistician will be unblinded to the drug the participant is receiving. They will not reveal this to the patient care team, investigative team, or to the participant. Dosing schedule, route of administration, number of pills in each dose, and the appearance of the capsules will be identical among each group.

4.4 Preparation and Administration of Study Drug

Study medication Vitamin D_2 and comparator, will be ordered and manufactured directly by a 503b compounding pharmacy (i.e., Pharmacy Innovations) and shipped to each site's investigational drug pharmacy (IDS). All medication will be stored in a climate-controlled storage area. The containers will be labeled by the manufacturer and each IDS will receive 2 bottles (active and placebo). The IDS will store and administer each dose, depending on the arm the participant is randomized into. Each participant will receive 2 capsules of indistinguishable active study drug or placebo.

4.5 Subject Compliance Monitoring

Administration of the study drug will be completed by ED nursing staff and will be documented in the medication administration record (MAR). Reasons for refusal will be documented in the MAR. If the participant does not receive study drug but is randomized, they will be excluded from subsequent analysis.

4.6 Prior and Concomitant Therapy

Prior and concomitant analgesic and anti-inflammatory treatments will be collected on enrollment, discharge from the hospital through data extraction, and at each REDCap survey follow-up assessment. Analgesic medications as would be normally prescribed are permitted throughout this study including anti-inflammatory agents. Consumption of medication will be tracked and addressed in secondary analyses.

4.7 Packaging

Study drug and inert placebo will be shipped from supplier in bulk containers and stored in the investigational drug pharmacy.

4.8 Blinding of Study Drug (if applicable)

Only the investigational drug services and unaffiliated staff will know the contents of the capsules. The study drugs and comparator will be packaged in identical capsules and will be indistinguishable. Each participant will be assigned to a treatment arm using randomize.net. Randomization will be accomplished via randomize.net. A Randomization ID will be generated that corresponds to the treatment. Only the IDS will dispense the study drug maintaining strict blinding.

4.9 Receiving, Storage, Dispensing and Return

4.9.1 Receipt of Drug Supplies

The drug supplier will ship the study drug and comparator to the Investigation Drug Pharmacy. Once the study drug arrives, receipt of the study drug will be performed. A drug receipt log will be completed and signed by the person accepting the shipment. Each site will develop their own process for maintaining a log of drug administration. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory supplied at the time of shipment. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.

4.9.2 Storage

Drug will be stored at 77 degrees Fahrenheit with excursions permitted from 59-86 degrees Fahrenheit at the investigational drug pharmacy. At each site, it will be kept in a climate-controlled room. The drug will not be frozen. There is no requirement for the drug to be shielded from light or any other special requirements.

4.9.3 Dispensing of Study Drug

The study drug will be dispensed by ED nursing staff. Study drug reconciliation will be performed at the conclusion of the study. This reconciliation will be logged on the drug accountability form and signed and dated by the study team. This log will be kept by the site investigational drug pharmacy and via the REDCap data collection software being used in this study.

4.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

Study Procedures

5.1 Enrollment Procedures

This first visit will take place upon admission to the hospital following MVC within 24 hours of the collision. Patients who meet inclusion criteria/exclusion criteria based on a review of the electronic medical record by research assistants, participants will be approached for participation. If the patient is interested in participating, they will then undergo informed consent. At this point in time, the participants will undergo baseline assessments (administered through REDCap) and collections of point of care Vitamin D levels with blood spot card. The participants will also have the option to consent to collect additional blood during a standard of care procedure while in the ED. The study would collect an EDTA tube,

a sodium heparin tube, and PAX gene RNA and DNA tubes. Patients with a Vitamin D level <100 ng/ml, will then take the baseline questionnaire. After all baseline data is collected, participants will be randomized and then administered appropriate study medication (Vitamin D or placebo). This administration will be documented in the MAR. Patients will be given a paper copy of their consent. Upon discharge of the patient, the patient will be given supplies to perform a home fingerstick blood draw (similar to one collected in the ED for baseline) and blotting on a blood spot card, which will occur at the 3-month timepoint.

Medical record information abstracted at time of admission will include information related to patient past medical history and initial motor vehicle collision care, and medication use prior to admission and prior to enrollment. Laboratory values relevant to patient renal and hepatic function will also be recorded (if obtained) along with any toxicology labs obtained by the primary treating team.

Demographic and phenotypic data will be collected at this time. Patients will be asked to report demographic information including age, sex, ethnicity, education level, income level, and marital status. In addition, patients will be administered an enrollment survey which will collect domains important to the pain experience. These are listed in table 2. All patient information will be recorded by a trained research assistant or the patient via direct entry. We will assess treatment expectation using a modified survey that uses Likert scales prior randomization. In addition, we will administer weekly surveys of pain severity and to assess whether adverse events are experienced weekly through 6 weeks (these brief surveys will be sent at 2 weeks, 4 weeks and 5 weeks). Adverse events will also be monitored at 3 weeks, 6 weeks, and 3 months following administration of study drug.

Table 2. Assessments by domain at each timepoint

Domain	Measure	D1	3W	6W	3M
Demographic information	Age, sex, gender, race/ethnicity, education, income, marital status	●			
Pre-MVC	Pain catastrophizing scale[26], PROMIS Item Bank v1.0 - Emotional Distress – Anxiety[27], PROMIS Item Bank v1.0 - Emotional Distress - Depression[27], Anxiety Sensitivity Index[51]	●	●	●	●
Traumatic Event	Details of Traumatic Event, Concussion, Traumatic Brain Injury, Life events checklist[28]	●			
MVC Injury Severity	Abbreviated injury scale[29]	●			
Pain	Numeric Rating Scale, †RPS[30], PROMIS Short Form v1.0 - Pain Interference 4a[31], PROMIS Scale v2.0 - Neuropathic Pain Quality 5a[32], PROMIS Scale v2.0-Nociceptive Pain Quality 5a	●	●	●	●
Somatic Symptoms	Pennebaker Inventory of Limbic Languidness[52]	●	●	●	●
Global Mental and Physical Health	PROMIS Scale v1.2 - Global Mental 2a[33], PROMIS Scale v1.2 - Global Physical 2a[33,34]	●	●	●	●

Anxiety/Depressive Symptoms	PROMIS Item Bank v1.0 - Emotional Distress – Anxiety[27], PROMIS Item Bank v1.0 - Emotional Distress - Depression[27]	●	●	●	●
Posttraumatic stress symptoms	PTSD Symptom Severity index-interview for DSM-5[35], Peritraumatic Distress Inventory items (PDI)[53]	●	●	●	●
Dissociative Symptoms	Michigan Critical Events Perception Scale[36]	●			
Analgesic Medication Use	Daily milligram morphine equivalents, non-opioid analgesic use, Date of opioid cessation (first day in three consecutive where patient took no opioids)[37].	●	●	●	●
Substance abuse	PROMIS Short Form v1.0 - Severity of Substance Use (Past 30 days) 7a[38]	●	●	●	●
Patient satisfaction with treatment	Patient Global Impression of Change[39]		●	●	●

At the time of enrollment, blood for DNA will be collected using a PAXgene DNA storage tube (8.5cc). These samples will be stored at -70 °C or below for future testing. Blood for RNA will be collected using a PAXgene RNA storage tube (2.5cc). These samples will be stored at -70 °C or below for future testing. Blood for immune profiling will be collected in sodium heparin tubes (16cc). Whole blood collected from sodium heparin tubes will be aliquoted into SmartTubes which allow storage for later processing by mass cytometric methods. Additional aliquots from these tubes will used to assess adaptive and innate immune function in vitro. Blood for lipidomics, vitamin D level and protein expression analysis will be obtained via EDTA tubes containing K_2EDTA for sample anticoagulation (8cc). Plasma will be separated from the cells by centrifuging the collection tube for 10 minutes at 2000 rpm at 25 °C, within two to 48 hours of collection. Plasma will be stored in 100-250 µL aliquots in plastic microcentrifuge tubes at -70 °C or below for future testing. Total amount of blood collected via venipuncture will be 35-36cc. A drop of blood will be applied to a dried blood spot cards for Vitamin D testing.

5.2 Emergency Department Medication Administration

The single dose administration will be provided in an observed fashion in the emergency department. This administration will be recorded in the patient's electronic medical record in the medication administration record (MAR).

5.3 Data Extraction

Medical record information abstracted after discharge will include information on the patient's health status and care during hospitalization and at the time of discharge. This information will include MVC characteristics, medications taken during emergency department admission, and discharge medications. All data extraction will be stored in REDCap.

5.4 Text messaged or e-mailed outpatient Weekly Pain and Compliance Assessments

Brief, weekly assessments of pain severity (0-10 NRS), and review of any AEs over the past week will occur via e-mailed surveys administered through our secure study database REDCap. Patients will receive text messages from the Data Coordinating Center based on a predetermined schedule based on progress, using the secure study phone number. If

patients are not able to respond via text messaging or e-mail, they will be called by investigative team. This brief survey will be administered at 2 weeks, 4 weeks, and 5 weeks.

5.5 3- and 6-week assessment

The goal of this assessment is to perform a comprehensive phenotypic follow-up and a questionnaire assessing domains listed in table 2 will be assessed. Outcome assessments will be performed via structured survey either via a web-based Redcap survey emailed to their on-file email address or via telephone. Multiple methods of contacting participants are involved to best meet the needs of each individual participant. Patients will receive automated REDCap email reminders. Participants will also receive text reminders based on a predetermined schedule based on progress. If patients are not able to respond via text messaging or e-mail, they will be called by investigative team.

5.6 3-month assessment

The goal of this assessment is to perform a comprehensive phenotypic follow-up and a questionnaire assessing domains listed in table 2 will be assessed. Outcome assessments will be performed via structured survey either via a web-based Redcap survey emailed to their on-file email address or via telephone. Multiple methods of contacting participants are involved to best meet the needs of each individual participant. Patients will receive automated REDCap email reminders, and text message reminders sent on a predetermined schedule based on progress. If patients are not able to respond via text messaging or e-mail, they will be called by investigative team. In addition, the patient will obtain a blood sample blotted onto a blood spot care acquired via a fingerstick at the 3-month mark of their study participation (achieved with a sterile lancet mailed to the participant at the 2-month timepoint of study participation). The completed sample card will be mailed via a self-addressed envelope to the central processing laboratory. All materials and education to conduct this blood draw will be mailed to participants and patients will be reminded this procedure at the 3-month follow-up. If the participant loses the materials, they will be re-shipped to the participant from the data coordinating center.

Statistical Plan

6.1 Outcome definitions/Analysis plan/Power calculation

Assess the **feasibility** of the RCT protocol by (a) calculating recruitment rate and participant retention, and (b) measuring the ability of Vitamin D administration to generate sustained increases in whole-blood Vitamin D concentrations (assessed 3 months after MVC).

Outcome definitions for Feasibility will be determined by the ability of the study team to: recruit 90 patients into the trial over the 15-month recruitment period, retain >80% of participants through 3-month follow-up, and achieve Vitamin D levels >20 ng/ml in 90% of treatment group at 3-month follow-up. In addition, will determine whether Vitamin D

administration per protocol can raise Vitamin D concentration in treatment group > 10ng/ml above baseline.

Analyses: Feasibility analyses will be performed using descriptive statistics. To assess Vitamin D increase according to treatment group, paired t-test will used.

Power: Based on our previous Vitamin D trial and other work,[40-45] we estimate that observed follow-up will be ~80%. With n=90 sample, this will permit follow-up rates estimates at 3 months with 95% CI ± 8.3%. This will permit assessment of follow-up feasibility and necessary sample size for an R01 RCT, if pilot results warrant. In addition, based on our previous Vitamin D trial, assuming 80% retention and Vitamin D concentration standard deviation of 4ng/ml, we will have >99% power to detect a change of 10 ng/ml in Vitamin D level in the treatment group.

Assess **preliminary efficacy** of Vitamin D administration per protocol to (a) decrease overall MSP severity during the 3 months following MVC, and (b) reduce MSP outcome disparity between Blacks vs. Whites following MVC.

Outcome Definitions for Pain Reduction between treatment groups will be assessed using patient-reported overall MSP scores (0-10 NRS) obtained at the ED, 3-week, 6-week, and 3-month assessments. NRS scores are valid measures of pain assessment.[46,47]

Analysis plan Overall efficacy (a) will be addressed by evaluating for evidence that Vitamin D administration per protocol vs. placebo decreases overall MSP scores across study timepoints. The effect of the intervention on overall pain over time will be assessed by evaluating the coefficient for treatment group (β_1) in the model: $P_{ij} = \beta_0 + \alpha_{0i} + \beta_1 \text{Treatment}_i + \beta_2 \text{Race}_i + \beta_3(\text{Treatment} \times \text{Race}) + \varepsilon_{ij}$, where P_{ij} is the pain score for the ith individual at time point j, β's denotes fixed effects, α_{0i} is the random intercept for the ith individual and ε corresponds to random errors. Narrowing of racial disparity will be addressed by evaluating the interaction between race and treatment (β_3 in model above). Specifically, as described above we will assess whether Vitamin D has greater effect on pain outcomes over time in Blacks than Whites. All analyses will be evaluated on the basis of intention to treat. Prior to

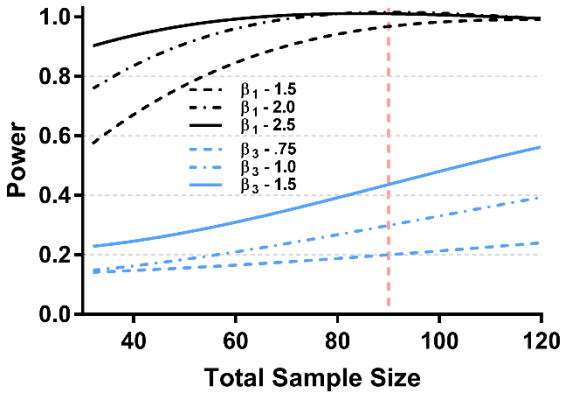

Figure 2. Plot demonstrating power to detect a main effect (β_1, black lines) and interaction (β_3, blue lines) across a range of sample sizes, at three effect sizes estimated using simulation data generated from previous studies. Vertical red line indicates sample size proposed here (n=90). This demonstrates the power to assess Aim 2a (black) and 2b (blue).

data un-blinding, the study statistician will perform a blind review of the data in which statistical models will be developed and tested using dummy (computer-generated) treatment assignments. This is to ensure important covariates are added to the model prior to un-blinding to eliminate any bias of model covariate selection on results. After un-blinding the data, we will use appropriately specified linear contrasts of model parameters to estimate mean differences between participants treated with Vitamin D and placebo and 95% confidence intervals.

Power Estimates of power were derived using a Monte Carlo simulation based on parameter estimates from our observational data of MVC survivors using R (*v*. 4.0.2[48]); and the *simr* package (*v*. 1.0.5[49]). The power across a range of effect sizes for the main effect (a) is shown in Figure 2. These data and analysis must be seen as general estimates given that we lack intervention data for this population/condition.

Secondary Analyses:
Similar models as for the primary outcome will be fit for both the Brief Pain Inventory and the SF-12 Mental and Physical Component Scale Scores.

Sex as a biological variable (SABV) will be examined in treatment response including sex-by treatment interaction terms in the mixed effect model specified above and exploring sex differences in therapeutic response to Vitamin D and n-3 PUFAs.

General mental and physical health will be assessed using SF-12 physical and mental component scores (PCS and MCS) and the impact on physical and mental functioning will be determined in each of the treatment groups. A clinically important reduction in SF-12 PCS and MCS ranges between 2.5-4.5[50]; therefore, a reduction of ≥ 4.5 will be considered a clinically significant improvement MCS/PCS.

Brief Pain Inventory: We will also use multivariable analysis to determine the role of n-3 PUFA/Vitamin D supplementation in pain interference using composite and individual measures of the Brief Pain Inventory.

6.2 Subject Population(s) for Analysis

We will examine effect of Vitamin D on pain outcomes using an intention to treat paradigm. Participants will be analyzed in the group in which they are randomized.

Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.).
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).
- Serious (as defined below) "***Serious" is different than "severe" as reported in the CTC criteria that applies a grade to the AE.***

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment

follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled survey, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate

adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

(See definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.3.1 Investigator reporting

7.3.1.1 Unanticipated Problems, Severe Adverse Events

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study data coordinating center by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed/emailed to the data coordinating center within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other

diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the data coordinating center.

7.3.1.2 Other Reportable Events

For clinical drug trials, the following events are also reportable to the UNC IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.
- For reportable deaths, the initial submission to the UNC IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

7.3.1.3 External Site Reporting

Investigators who are not UNC faculty or affiliated with a UNC research site are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

7.4 Unblinding Procedures

Unblinding the group in which the patient is randomized will only occur in exceptional circumstances when the knowledge of treatment is essential for the management of an individual patient. In emergency situations (e.g., anaphylaxis) the principal investigator may contact IDS to have the identity of the patient's treatment drug revealed to help manage the patient more effectively. If this occurs, the unblinding procedure will be documented in the patient's source documents.

7.5 Stopping Rules

The entire trial will stop if 3 or more patients have severe adverse events of grade 3 (severe) or higher severity per the CTCAE scale that is related or possibly related to study participation, or any investigator judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, or good clinical practice. Patients who decline further participation and patients experiencing adverse effects that in the opinion of study investigators indicate that study drug should be stopped will be discontinued from study medication. Criteria for stopping the study trial among individual participants for review are shown in Appendix 1.

7.6 Medical Monitoring

Safety Monitoring Plan: Overall safety oversight will be the responsibility of the data coordinating center PIs Mauck and McLean (DCC PIs). The DCC PIs will monitor study and will communicate with the independent medical monitor with study status if adverse events occur.

Data Safety Monitoring Board (DSMB):

The NC TraCS DSMB Monitoring board will serve as the independent monitoring board for this trial. They will review and approve the study protocol, and will meet quarterly to review study progress (reports of enrollment, adverse events listed by type and severity will be generated by the study statistician and will be reported by treatment type (Vitamin D or placebo) once greater than 4 patients are enrolled in the study, and will again review the data at study conclusion. They will also review serious adverse events as they occur, and determine whether the adverse events change the risk of the study. Monitoring the study (across one or more study sites) is considerably facilitated by the use of a single electronic database which can be reviewed by the network PI,

Serious AE	Death, Life threatening reaction Inpatient hospitalization prolonged, or rehospitalization. Persistent or significant disability/incapacity Congenital anomaly/birth defect Represents other significant hazards or potentially serious harm to research subjects (similar to "important medical event")
Expected AE	Known potential effect of the drug (based on drug description information from manufacturer) or disease process

study site PI(s), and other investigators. The DCC PI will monitor for adverse events that change study risk level and this will be communicated with the independent medical monitor if needed. Adverse events at individual study sites will also be monitored by the site PI. If an adverse event occurs which changes the study risk level, the DCC PI will immediately report this event to the DCC IRB (UNC IRB), inform the site PI(s), and oversee the process of modifying the study at the study site(s) as appropriate to address the change in risk. The DCC PI will also provide annual reports summarizing AE data to the data coordinating center IRB (UNC IRB) and any other requesting IRB. The site PI(s) will oversee patient safety at their site, with delegation of responsibilities to other investigators and designated study personnel as appropriate. The DCC PI, together with their study site teams, will ensure that all entry criteria are met prior to the initiation of the protocol, and that all study procedures and reporting of adverse events are performed according to the protocol. Serious adverse events (SAE's) will be monitored by the study site investigative teams in real time throughout the trial.

Patient monitoring: An adverse event is any physical or clinical change experienced by the patient. This includes the onset of new symptoms and the exacerbation of pre-existing conditions. Adverse event assessments will be performed according to the following schedule:

Adverse event monitoring after discharge from ED: Adverse events will be assessed at each patient contact (telephone or text-messaged/emailed survey), which will occur weekly for 6 weeks, then again at 3 months.

Additional reporting: In addition to receiving these regular side effect assessments, patients will be given contact information to reach the study team at the DCC, as well as telephone and pager numbers for individuals at the study site, and will be instructed to call these numbers if they experience any changes in their health status or if they have questions regarding the study medication.

Category definitions for adverse events are shown in Table 3. An electronic adverse event form will be completed for all unanticipated AEs. The severity of the AE will be assessed a CTCAE grade will be recorded for each. An investigator will also assess the relationship of any adverse event to study medication or procedures. Severity assessments will be performed using the Common Toxicity Criteria (http://ctep.cancer.gov/). The time table for reporting serious and other adverse events is shown in Appendix 1.

Table 3. Time table for reporting unanticipated adverse events.

	Unanticipated
Serious AE	One week
Not Serious AE/other	Two weeks

Unanticipated problems involving risks to participants or others, defined as any incident, experience or outcome that is both unexpected and related or possibly related to the research, will be reported to the IRB. Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event. Any other

unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem. The study team will report all serious unanticipated adverse events to the DCC PI immediately, and will review all non-serious unanticipated adverse events with the PI within 24 hours.

Patients with adverse events will be monitored with relevant clinical assessments (and laboratory tests if necessary) as determined by an investigator in collaboration with the patient's care team. All adverse events will be followed to satisfactory resolution or stabilization of the event(s). Any actions taken and follow-up results will be recorded on the appropriate AE form and given a CTCAE grade.

Appendix 1 describes the adverse event grading scale and management guidelines for potential adverse events related to the study drugs. This chart covers a number of common adverse effects, but will not be comprehensive. As other situations are encountered and managed by the study team, this decision rule chart will be updated and expanded so that it remains current and inclusive.

Summary information regarding adverse events will be provided to the IRB at the time of annual IRB renewal. As described below, medical monitor reports from both DCC and Independent Medical Monitor will also be submitted to the UNC IRB on a quarterly basis. Criteria for stopping the study trial among all participants for review are shown in Appendix 1.

Patients experiencing adverse effects that in the opinion of the investigators merit drug dosage adjustment will have their dosage advanced more slowly, or the next dose reduced or held as appropriate. If necessary, patients will be maintained on a lower dose, or their dose will be re-advanced depending on the nature of the side effect(s). Patients who decline further participation and patients experiencing adverse effects that in the opinion of study investigators indicate that study drug should be stopped will be discontinued from study medication.

Independent Medical Monitor: To handle individual problems that may require communication directly with physician caring for the patient, an independent Medical Monitor will become involved. This is to avoid any conflicts of interest that may arise with data Handling and record keeping.

7.7 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

7.8 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

7.9 Case Report Forms (as applicable)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded in REDCap. All missing data will be noted. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be entered electronically in REDCap database. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. For clarification of illegible or uncertain entries, the clarification above the item will be printed initialed and dated.

7.10 Records Retention

Essential study documents (consents, paper questionnaires, screening forms) will be maintained for the duration of the IND. Data will not be de-identified/unlinked from original dataset to preserve the ability to contact patients should any unknown adverse events become known following the study. This data will be stored on a password encrypted server (REDCap at UNC).

Study Monitoring, Auditing, and Inspecting

8.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan described above. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer

is given access to all the above noted study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

8.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.). Risk based monitoring plan will include study site visits (may be virtual via secure video conferencing link) from study DCC after 2 and 10 enrolled patients at sites once they become active.

Participation as an investigator in this study implies acceptance of potential inspection by regulatory authorities and applicable University compliance and quality assurance offices.

Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See attached copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Study Finances

10.1 Funding Source

This study is funded by the National Institute of Health (NIMHD) and the UNC Department of Anesthesiology, and the Institute for Trauma Recovery.

10.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All UNC investigators will follow the University conflict of interest policy.

10.3 Subject Stipends or Payments

To compensate participants for their time for completing follow-up interviews, we will offer patients $40 for the enrollment interview and $10 for patients who consent to the optional blood draw. Participants will be contacted at week 2, week 4 and 5 for brief surveys and will be compensated $20 for each week's survey completion (for a total of 60 dollars for these assessments). At 3 weeks, participants will be compensated $50 for survey completion, at 6 weeks they will receive $55 for survey completion, and at the 3 months visit they will be compensated $60 for survey completion and $40 for returning a blood spot card collected at home and mailed to the laboratory processing facility. The maximum total compensation for completing all study tasks will be $315. All payments will be made via electronic gift card(s) sent to the patient's email within the week after a study activity is completed.

Publication Plan

Principal investigator, in coordination with investigative team will determine the publication plan as appropriate on an ongoing basis. We will make every effort to publish study results within 1 year of database completion. The results will be published on ClinicalTrials.gov website within 1 year of study completion per regulation.

Data Management Plan

REDCap will be used as our research database and is a secure, widely-used system for recording study information. Access to enter data and view patient information will be password protected and accessed only by study personnel. At the time of enrollment or subsequent follow-up interview, data will be directly entered into REDCap. A codebook for the dataset will be compiled and saved along with the completed dataset. Our laboratory data manager will be responsible for assembling the final de-identified dataset and distribution to the study statistician for analysis. Completeness of the dataset will be determined as a percentage of non-missing data. When possible, reasons for missing values will be recorded (e.g., not applicable, refused to answer). Each research assistant that enters data in the system will be trained on mock patients and coding of patient responses will be checked. Data will be recorded by study sites directly into REDCap. Any discrepancies in coding will be handled by direct communication with study personnel at each study site.

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Appendices

14.1 Appendix 1: Adverse Event Monitoring and Stopping Rules Table

AE	Relatedness	CTCAE Grade				
		1	2	3	4	5
Back Pain		Mild Pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL		
	Possible	O	O	O		
	Probable	O	O	SI		
	Definite	O	SI	SI		
Gastrointestinal pain		Mild Pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL		
	Possible	O	O	O		
	Probable	O	O	SI		
	Definite	O	SI	SI		
Belching (or Flatulence)		Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae			
	Possible	O	O			
	Probable	O	O			
	Definite	O	SI			
Rash (maculo-papular?)		Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL		
	Possible	O	O	O		
	Probable	O	O	SI		
	Definite	O	SI	SI		
Dysgeusia		Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste			
	Possible	O	O			
	Probable	O	SI			
	Definite	O	SI			
Bruising		Localized or in a dependent area	Generalized			
	Possible	O	O			
	Probable	O	O			
	Definite	O	SI			
Hematoma		Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	Possible	O	O	SI	SI	
	Probable	O	SI	SI	SI	
	Definite	O	SI	SI	SI	

Atrial fibrillation		Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
	Possible	O	SI	SI	SI	
	Probable	O	SI	SI	SI	
	Definite	O	SI	SI	SI	
Atrial flutter		Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
	Possible	O	SI	SI	SI	
	Probable	O	SI	SI	SI	
	Definite	O	SI	SI	SI	
Alanine aminotransferase (ALT) increased		>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	
	Possible	O	SI	SI	SI	
	Probable	O	SI	SI	SI	
	Definite	O	SI	SI	SI	
Aspartate aminotransferase increased		>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	
	Possible	O	SI	SI	SI	
	Probable	O	SI	SI	SI	
	Definite	O	SI	SI	SI	
Cholesterol high		>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
	Possible	O	O	O	SI	
	Probable	O	O	SI	SI	
	Definite	O	O	SI	SI	
Chills		Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics		
	Possible	O	RD	SI		
	Probable	O	SI	SI		
	Definite	O	SI	SI		
Fever		38-39ºC	>39-40ºC	>40ºC for ≤24 hours	>40ºC for >24 hours	Death
	Possible	O	O	SI	SI	
	Probable	SI	SI	SI	SI	
	Definite	SI	SI	SI	SI	

Criteria for stopping entire trial for review: The entire trial will stop if any investigator judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, or good clinical practice.

Possible = The AE **may be related** to the intervention
Probable = The AE **is likely related** to the intervention
Definite = The AE **is clearly related** to the intervention

*O = observe; SI = stop individual; ST = stop trial

*Grades defined by NCI CTCAEv5.0

*This chart covers many common adverse effects, but will not be comprehensive. This chart is intended to provide guidelines for handling adverse events but ultimate judgment will be the responsibility of the investigator. In addition, as other situations are encountered and managed by the study team, this decision guideline chart will be updated and expanded so that it remains current and fully inclusive.