SPLD-016-12F
RCT of Duloxetine & Pregabalin for the Treatment of Gulf War Illness in Veterans

NCT01846182

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1.0 INTRODUCTION

At least 1 in 4 of the 700,000 U.S. Veterans who served in the 1990-1991 Gulf War suffer from Gulf War Illness (GWI). Despite considerable research, effective treatments remain elusive. GWI refers to a complex of symptoms that typically include widespread chronic pain, persistent headache, memory and concentration problems, gastrointestinal difficulties, sleep disturbances and unexplained fatigue. This symptom profile is similar to that of fibromyalgia syndrome (FMS), another multi-symptom condition. Whereas, effective treatments for GWI have yet to be found, progress has been made in identifying medications to treat FMS. For example, the FDA has approved a number of medications including duloxetine and pregabalin for the treatment of FMS. Compared to placebo, duloxetine (a serotonin norepinephrine reuptake inhibitor) and pregabalin (an α-$_2\delta$-subunit calcium-channel ligand) significantly improved pain responses and fatigue. The capacity of duloxetine to increase central levels of serotonin and norepinephrine as well as the more complex alterations of neurotransmitters and CNS mediators of pain attributed to pregabalin are thought to be responsible for the medication's effects on pain, mood and sleep. The lack of progress in finding effective treatments for GWI, and the similarities between GWI and FMS, provides a rationale for determining if these FDA approved medications can provide symptomatic relief to Veterans who suffer from GWI.

Although both medications have been shown to provide significant benefit for FMS, some patients respond better than others. Studies have linked a number of genetic polymorphisms that are associated with significant differences in response to duloxetine and other serotonin norepinephrine uptake inhibitors. In some cases, these genotypes may also be associated with the risk for developing FMS. Although none of the genotypes of interest have been evaluated in GWI patients, they may have predictive value in identifying individuals who are most likely to benefit from these medications.

In a 1:1:1 randomized, double-blind, controlled trial, 162 veterans who meet defining criteria for GWI and whose symptom profile includes chronic widespread pain and sleep disturbances will be treated with one of the following medications; 1) duloxetine + placebo; 2) pregabalin + placebo or 3) placebo + placebo. All active treatments will titrate from a lower dose in 2-week increments to the full therapeutic doses (FDA-approved for FMS). The outcome of the double-dummy period will be compared statistically with 16 weeks of active treatment (weeks 3-18).

2.0 RATIONALE

Rationale for Selection of Doses.
All study staff will be blind to the medication that participants are taking until the study is completed. The therapeutic dose is 60 mg/day of duloxetine and 300 mg/evening of pregabalin taken on at least 80% of the treatment days.

Duloxetine: The dose of 60 mg/day of duloxetine was chosen based on safety, tolerability data from single and multiple-dose safety studies. Receptor occupancy data that suggest once-daily dosing is all that is necessary to maintain therapeutic plasma concentrations and receptor occupancy throughout the day. The 60-mg/day dose of duloxetine is also the recommended dose for treating symptoms of FMS.

Pregabalin: The dose of 300 mg/day of pregabalin taken before bed was chosen based on the effective dose for treating symptoms of FMS. The important issue for pregabalin in treating symptoms of FMS is the half-life of the receptor, which is long because of its high avidity, rather than its half-life in the serum. The avidity of pregabalin is substantial and the medication remains for a long time even when the plasma level declines. A significant problem with FMS, and GWI is the loss of sleep; slow-wave, restorative non-REM sleep. Pregabalin is known to facilitate this stage of sleep. A morning dosage of pregabalin is very sedating and can result in medication noncompliance because patients do not wish to be sleepy during

the day. Thus, the once daily evening dose of active medication was chosen because it helps with restoring the patient's sleep deficit and greatly improves compliance.

Rationale for Biomarker and Genetic Testing.

Biomarker and Genetic Testing: An important goal of the project and requirement of the funding agency is to begin to develop a collection of plasma and DNA samples that can be used to test future hypotheses as data emerges from this and future studies. Considering the large number of biological pathways that have been implicated in GWI, it will be important to obtain additional funding for further biomarker and genetic tests as new data emerges. The genes selected for study are those where there is a good rationale for potential association with drug response. Blood samples used for genotyping will not be retained once genotyping has been completed and the study has ended. Therefore, a tissue repository is not being established and the biological samples will not be stored indefinitely.

3.0 SPECIFIC AIMS

PRIMARY AIM 1: To evaluate the efficacy of duloxetine and pregabalin for the treatment of pain and overall physical functioning in veterans with GWI and to assess the safety and tolerability of these medications. It is anticipated that the active treatments will result in a significantly greater proportion of GWI participants achieving a 30% reduction in pain compared to placebo alone.

Primary Measures. Aim 1

1. 10-point Pain Visual Analog Scale (VAS); at least a 30% improvement in pain
2. Side effects checklist

Additional Measure Associated with Primary Aim

3. Beck Depression Inventory (Beck et al., 1961)

SECONDARY AIM 2: To evaluate the efficacy of duloxetine and pregabalin for the treatment of sleep disturbances, fatigue, mental health and physical functioning. It is anticipated that both active medication groups will experience significantly greater improvement on these measures than placebo.

1. SF-36 Veteran Version (Mental & Physical Component) (Kazis et al., 2004)
2. Jenkins Sleep Questionnaire (Jenkins et al., 1988)
3. Epworth Sleepiness Scale (MW Johns, 1990-1997)
4. Krupp Fatigue Severity Scale (Krupp et al., 1989)
5. Patient Global Impression of Improvement Score (Guy 1976)

EXPORATORY GENETIC AIM 3.1: To obtain pilot data on genes potentially associated with medication response that would begin the development of potential classification schemes to guide the choice of treatment.

1. Catechol-O-methyl transferase
2. Brain-derived neurotrophic factor
3. Serotonergic receptor and transporter genes
4. Dopaminergic receptor and transporter genotype
5. β_2-adrenergic receptor genotype

EXPLORATORY GENETIC AIM 3.2: To examine the effect of duloxetine and pregabalin on mood (Beck Depression Inventory) in a subset of depressed Veterans with GWI.

All data collected for AIMs 1, 2, and 3 will be used to examine this subset of Veterans with GWI who endorsed current depressive symptoms.

4.0 STUDY DESIGN/INVESTIGATIVE PLAN

This is an intent-to-treat outpatient, randomized, double-blind, double-dummy trial of **129** completed participants identified as veterans with GWI. Study duration will be 22 weeks.

5.0 STUDY POPULATION (INCLUSION/EXCLUSION)

Inclusion Criteria

Participants are eligible to be included in the study if they meet **all** of the following criteria:

5.1 Served on active military duty and deployed to the Persian Gulf region for some period between August 1990 and July 1991

5.2 English speaking and able to understand the consent form and study questionnaires

5.3 Willing to complete study procedures and have the ability to consent and make medical decisions for self

5.4 Male or female

5.5 Ages 43 to 70 years old at the time of informed consent

5.6 Meet the Kansas GWI case definition for the diagnosis of GWI by endorsing at least 3 of 6 statistically-defined symptom domains including: 1) musculoskeletal pain, 2) neurocognitive/mood symptoms, 3) fatigue/sleep disturbances, 4) gastrointestinal symptoms, 5) respiratory symptoms, 6) skin abnormalities.

5.7 Report a baseline score $\geq$ 4 on a 10-point VAS assessing pain

5.8 Female participants of childbearing potential must test negative for pregnancy at the time of enrollment based on a urine pregnancy test and agree to use a reliable method of birth control (for example, oral contraceptives or Norplant; a reliable barrier method of birth control [diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam); intrauterine devices; partner with vasectomy; or abstinence) during the study and for 2 months following the last dose of the study drug. [Note that this inclusion criterion applies only to females of childbearing potential. Females of childbearing potential are defined as women not surgically sterilized and between menarche and 2 years post-menopause.]

Exclusion Criteria

5.9 Participants who do not meet the Kansas GWI definition *(*Note: The Kansas GWI case definition excludes veterans who have had chronic medical or psychiatric conditions that might explain their symptoms. Additional medical exclusions are required in relation to the medications and potential side effects of the medications under study, either for safety reasons or to minimize the potential for confounding of study results);

5.10 Unstable or poorly controlled chronic medical illness such as Diabetes type-II, HTN, heart disease, endocrine disorders, narrow angle glaucoma based on clinical interview and medical history;

5.11 Significant Central Nervous System disease including but not limited to, TIAs or stroke, Dementia, syncopal episodes, severe head trauma, multiple sclerosis based on medical history;

5.12 Serious or advanced heart disease or clinically relevant abnormal electrocardiogram (ECG), postural hypotension based on medical history;

5.13 Untreated sleep apnea based on self report and medical history;

5.14 A body mass index placing patients at risk for undiagnosed sleep apnea (BMI$\geq$ 35 kg/m2)

5.15 Diabetes type-I and Diabetes type-II associated with peripheral neuropathy based on medical history;

5.16 Acute liver injury (such as hepatitis) or severe cirrhosis (Child-Pugh Class C); >3 fold elevated serum alanine transaminase (ALT/SPGT) implying hepatitis; >3 fold elevated serum aspartate transaminase (AST) implying alcoholic hepatitis; or >2 fold elevated serum bilirubin indicating liver disease or other conditions such as biliary tract disease, based upon liver tests performed at screening;

5.17 End stage renal disease, renal dysfunction, and/or calculated creatinine clearance estimate <60 based on serum creatinine value;

5.18 History of hypersensitivity reaction to pregabalin, duloxetine, venlafaxine; active treatment with duloxetine or pregabalin; History of failure of duloxetine or pregabalin at therapeutic doses; history of angioedema reaction to pregabalin;
5.19 Active systemic infectious disease such as tuberculosis and HIV, shingles based on medical history;
5.20 Autoimmune mediated illnesses such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma based on medical history;
5.21 Lifetime history of mental illness requiring psychiatric hospitalization (depression, bipolar illness, post traumatic stress disorder, history of suicide attempts, psychosis, schizophrenia spectrum);
5.22 Current major depression or dysthymia according to DSM-IV-TR criteria;
5.23 Require the use of the following concomitant medications at any time during the study;
   a. Use of MAOIs within 2 weeks of evaluation.
   b. Active ongoing use of the following agents: desvenlafaxine, fenfluramine, linezolid, milnacipran, phentermine, tryptophan, tramadol, opiates.
5.24 Currently meets criterion within the last 6 months) for drug or alcohol dependence (except for nicotine and caffeine) according to the DSM-IV-TR criteria;
5.25 Cancer other than non-melanoma skin cancers based on medical history;
5.26 Women who are pregnant or desire to become pregnant, breastfeeding, who use unreliable contraception methods
5.27 Those with occupation;s requiring use and/or operation of hazardous heavy equipment or professional drivers;
5.28 Patients for whom the potential risk outweighs the potential benefit in the opinion of the treating psychiatrist and principal investigator;
5.29 Participants considered a high risk for suicidal acts – active suicidal ideation as determined by clinical interview OR any suicide attempt in 30 days prior to screening
5.30 Participants who demonstrate overtly aggressive behavior or who ar;e deemed to pose a substantial risk of danger in the principal investigator's opinion.

6.0 PARTICIPANT RECRUITMENT

We anticipate a total of **576** participants will be screened to randomize 162 adult Gulf War Veterans who meet Kansas GWI criteria and report a pain level of 4 or greater on the 10-point VAS to achieve a target sample of **129 study completers**. The sample will be identified from among Veterans who served in the military during 1990-1991 and currently reside in Central Texas.

Participants will be recruited in the following ways: 1) through the Gulf War Registry (prior to 2003, 2098 area Gulf War Veterans had participated in the Central Texas Registry), 2) through contact with local Veterans' Service Organizations, 3) through contact with national Gulf War Veteran Groups, 4) through CTVHCS referrals of symptomatic Gulf War Veterans who are registered with VA hospital in Central Texas 5) through direct contact with area Gulf War Veterans whose names are provided by the Department of Defense's Manpower Data Center, 6) through the community (e.g. shopping center and VFW bulletin boards, billboards), 7) through advertisements in local newspapers, local community-based advertisement sources, local Craigslist pages and other locally-based media platforms, on relevant VA and other Veteran-oriented websites and social media outlets (pending required approvals from VA public relations office). Contact information will be updated using VA and other professional locating services. Invitation letters will be mailed out allowing Veterans the opportunity to "opt in" to the study by calling study personnel. A few weeks after invitations are mailed, we will attempt to contact potential participants by telephone. If the Veteran is not interested, their name will be added to our do not call list on the w-drive.

7.0 CLINICAL ASSESSEMENTS AND PROCEDURES

Screening & Medication Washout Phase is a 14-day screening and washout period for excluded medication that begins at Visit 1 and concludes prior to randomization at Visit 2. Prior to Visit 1, the participant will be prescreened over the telephone by asking preliminary questions to determine eligibility such as age, general health status, and some questions related to the inclusion and exclusion criteria of the study. After informed consent has been obtained on Visit 1, the participant is considered entered into the study, a participant number is assigned and final baseline assessment and randomization will take place. Because 2-weeks is allowed for discontinuation and medication washout, the period between Visit 1 and Visit 2 may be 1 or 2 weeks and follow up may take place 22 to 23 weeks after week 19 downward titration.

Screening Measures
A telephone screen will collect basic demographic information (in order to compare eligible versus ineligible callers to evaluate the generalizability of the sample) and assess some inclusion/exclusion criteria prior to scheduling Visit 1. Assessment time: 15 min.

Visit 1: The study staff will:

- obtain informed consent;
- obtain demographics and contact information;
- assess for caseness;
- assess pain threshold criteria;
- obtain medical history;
- obtain a detailed list of current medications;
- record height, weight, temperature and vital signs, including assessment of orthostasis;
- obtain any history of previous treatment for the symptoms of GWI;
- assess heart functioning with a 12-lead ECG;
- obtain a blood sample for laboratory testing;
- obtain a urine sample for toxicology testing;
- record the use of concomitant medications (start and/or end date and dose).

Information obtained on Visit 1 will be shared with the study physician who will perform a physical examination. The examination will include assessment of tender points to assess fibromyalgia caseness and evaluate the veteran's general health status.

Visit 2 (Baseline/Randomization): Visit 2 will take place 1-2 weeks after Visit 1. The participant will be randomized to one of three treatment arms and receive their first container of study medication. Participants will also participate in their first Medical Management visit (described below) conducted by the study staff who will explain how and when the medications should be taken and what to expect while on medication. Participants will complete the primary and secondary assessments (see below), and provide a blood sample for DNA.

Visits 3-11 (Medical Management Visits): During these bi-weekly visits medications will be titrated up to the therapeutic dose and then maintained at the therapeutic dose for 16 weeks. Study medication containers will be returned for a tally of any remaining capsules and so study staff can assess and discuss medication compliance and issue a new container of medication. Assessments obtained at this time are displayed in Table 1, below. Liver functions, creatinine, urine toxicology and urine pregnancy testing will be performed every four weeks during active treatment. The side effects checklist, start/stop of concomitant medications, and the VAS pain assessment will take place at every visit. The remaining primary and secondary outcome measures will be assessed every four weeks.

Visit 11 & 12 (End of Study Visits): Visit 11 ends the treatment phase. The assessments, laboratory tests and the physical examination that are conducted during Visit 11 will also be performed for Early Termination visits.

Visit 12 (Follow-Up Visit): Visit 12 assessments will be collected over the telephone 3 weeks after Visit 11. Alternatively, to increase retention, participants will be given the choice to take home self-report measures with them at visit 11 to fill out and mail back. If measures are mailed back, study staff will still call and follow-up with the participant regarding side effects and adverse events.

Medical Back-up Plan
If the study physician and nurse practitioner are not available at a study visit and a patient has a medical complaint and/or exam findings that warrant further evaluation, study staff activate the medical back-up plan. Study staff will take the patient to the primary care walk-in clinics at the Waco and Temple VA campuses, dependent upon where the participant is being evaluated.

IN PERSON SCREENING MEASURES

- **Demographic Questionnaires**: Assesses demographic and veteran-specific characteristics (e.g. years of military service), whether or not the caller is experiencing pain and sleep disruption.

- **Kansas Case Definition (symptoms/exposure).** This questionnaire (Steele 2000) will be used at screening to identify GWI case status, including symptom scores in each of six domains; 1) musculoskeletal pain; 2) neurocognitive/mood symptoms; 3) fatigue/sleep disturbances; 4) gastrointestinal symptoms; 5) respiratory symptoms; 6) skin abnormalities.

- **10-point VAS for Pain:** This is a simple 10-point likert scale that will be assessed at screening to insure study candidates score at 4 or higher. This scale is also a primary outcome measure and will be administered at every study visit.

- **Mini International Neuropsychiatric Interview (MINI)**: The MINI (Sheehan et al., 1998) is a state-of-the-art instrument for assessing and diagnosing Axis I disorders. The MINI will be used to screen out participants with severe psychiatric disorders (as required for caseness), such as schizophrenia, schizoaffective disorder, bipolar disorder, major depression, dysthymia, risk of suicide and PTSD.

- **Semi-Structured Clinical Interview for the DSM IV, alcohol and drug dependence modules (SCID)**: The SCID (First et al., 1996) will be used to exclude dependence on alcohol and other substances with the exception of caffeine and nicotine. Alcohol and drug use is not typically common in veterans suffering from GWI.

- **Standardized Medical History form**: Assesses past and current medical problems as well as medication use.

- **Standardized Concomitant Medication Log**: This log is used to record newly started or stopped medications throughout the trial including the start and stop dates and dose.

- **Fibromyalgia Case Assessment Questionnaire**: There are two current approaches to making the diagnosis of FMS, whether it exists alone in a patient or is comorbid with another medical condition such as GWI. The 1990 America College of Rheumatology Research Classification Criteria (1990 ARC RCC) (Wolfe 1990) is the current gold standard approach. That approach has been consistently used in the research studies that have established pathogenesis and efficacy of treatment, including the clinical trials of pregabalin and duloxetine that led to FDA approvals. The 1990 ACR RCC approach requires a medical history of widespread body pain for at least 3

months and the examination finding of at least 11 of 18 tender points in response to 4 kg of digital pressure. Both components in the 1990 ACR RCC focus on pain or pain sensitivity.

- **Widespread Pain Index**: This 2010 update from ACR RCC involves a checklist of 19 areas of the body and will be given in conjunction with the Fibromyalgia case ascertainment with tenderpoints.

Total time to complete the in person screening measure is ~3.5 hours.
PRIMARY AND SECONDARY MEASURES

- **10-point VAS for Pain:** This is a simple 10-point likert scale assessed at Screening and as a primary outcome measure at every study visit.

- **Side Effects Checklist**: This generic side effect checklist will be used to assess safety and tolerability. It queries patients on side effects that are commonly reported in drug trials. The SL 21 also asks open-ended questions to assess for any unusual side effects that might be unique to each medication alone or to the combined effect of taking both medications. Twenty-one items are rated on a 5-point scale based on the degree of distress related to known duloxetine and pregabalin side effects. The scale has been shown to be sensitive to change across treatment.

- **Beck Depression Inventory**: This measures subjective wellbeing and distress and at higher scores, clinical depression. Because both medications have been shown to increase the risk of suicidality and depression, this 21-item scale will be used to track changes in mood during the study.

- **SF 36 (veteran's version):** This 36-item instrument widely used in veteran populations, provides measures for health-related quality of life/functional status in eight domains, as well as overall summary measures of physical and mental health. Primary outcome: at least a 5-point improvement in the Physical Component Score. This degree of improvement is considered clinically meaningful for most medical conditions (Kazis et al., 2004).

- **Jenkins Sleep Questionnaire**: The Jenkins Sleep Questionnaire (Jenkins et al 1988) is an 11-item scale that assesses individual sleep profiles and subjective effects of sleep disruption.

- **Epworth Sleepiness Scale:** The Epworth Sleepiness Scale is an 8-item scale that measures a person's general level of daytime sleepiness.

- **Krupp Fatigue Severity Scale**: The Krupp Fatigue Severity Scale (Krupp et al, 1989) is a 7-item scale that measures the severity of fatigue and its effect on a person's activities and lifestyle.

- **Patient Global Impression of Improvement Score**: This scale is a single-item scale often used to rate the response of a condition to a treatment. It has become a standard metric for assessing overall response to medications in studies evaluating treatments for fibromyalgia and other chronic pain conditions. Patients are asked to rate their response to medication using a 7-point scale with the options "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", and "very much worse".

- **Time Line Follow-Back Interview (TLFB)**: The TLFB is a reliable and valid instrument for determining patterns of daily drinking and drug use (Sobell et al., 1979). TLFB data collected over the 90 days prior to randomization will be used to characterize the participants drinking and drug use history according to: 1) percentage days abstinent; 2) percentage of heavy drinking or using

day days; and 3) drinks per drinking days. Alcohol or drug use will be assessed by TLFB between all study visits.

Total time to complete the primary and secondary measures is ~1 hour.

Table 1: Assessments & Timeline for Study Visits

	Screening	Baseline Randomization	Active Treatment								End Treatment/ Early Termination	Taper	Follow up
Weeks	0	1	2	4	6	8	10	12	14	16	18	19	22-23
ASSESSMENT & PROCEDURES **Visits**	1	2	3	4	5	6	7	8	9	10	11		12
Brief Telephone Screen *Includes Kansas for caseness*													
SCREENING													
Informed Consent	x												
Demographics/Contact Information	x												
MINI (30-60 min)	x												
SCID	x												
10-pt VAS for Pain	x												
Medical/Medication History Form	x												
Concomitant Medications log	x												
Physical Exam & 12-lead ECG	x										x		
Laboratory Tests (blood & urine)	x			x		x		x		x	x		
Total Maximum Time for Screening	~3.5												
PRIMARY OUTCOME MEASURES													
10-pt VAS for Pain				x		x		x		x	x		x
Side Effects Checklist		x	x	x	x	x	x	x	x	x	x		
Beck Depression Scale		x									x		x
Total Time	~25 min												
SECONDARY OUTCOME MEASURES													
SF-36 for Veterans		x		x		x		x		x	x		x
Jenkins Sleep Questionnaire		x		x		x		x		x	x		x
Epworth Sleepiness Scale		x		x		x		x		x	x		x
Krupp Fatigue Severity Scale		x		x		x		x		x	x		x
Patient Global Impression of Improvement											x		x
Total Time	~45 min												
CORROBORATIVE OUTCOMES													
GWI symptoms/exposure (self report)		x				x				x	x		x
Gulf War Military Questionnaire		x											
FMS case ascertainment w/tenderpoints		x									x		x
Widespread Pain Index		x									x		
Medical Management (concomitant medications)		x	x	x	x	x	x	x	x	x	x		
Pill Count			x	x	x	x	x	x	x	x	x		
Time Line Followback Interview		x		x		x		x		x	x		x
DNA blood sample - Biomarkers		x									x		
Remuneration ($135 max)		$25		$20		$20					$35		$35

v February 12, 2016

Medical Management
The research staff will deliver the brief Medical Management therapy to participants throughout the treatment phase following the NIAAA Medical Management model (NIAAA, 1998). Medical Management was designed as a minimal clinical intervention with demonstrated efficacy in enhancing participant retention and medication compliance. Medical Management has been adapted to provide support and education related to symptoms of GWI and the known side effects of the study medications administered in this protocol. Medical Management will enhance medication compliance by; 1) instructing participants to return any remaining capsules for pill count/missed doses so that results can be discussed with the participants; 2) collecting information on a side effects questionnaire so that questions and concerns about the medication and possible side effects that might threaten medication compliance can be addressed; 3) working on establishing routines to help participants remember to take their medication should it be discovered that they are frequently missing doses (e.g. PM medication can be taken before a nighttime ritual. AM medication can be taken with morning breakfast; a wristwatch or mobile phone alarm may also be helpful); 4) provide education and answer any questions about how medication should be helping, concerns about taking medication in general or concerns that they may have been assigned to the placebo arm.

PARTICIPANT RETENTION
Retention is arguably the most essential element of a study because without good retention, the human and financial resources invested are wasted. Every effort will be made by study staff to establish personal relationships with participants to help them feel connected and invested in the study. At each assessment point, study staff will verify that the veteran's contact information has not changed.

PARTICIPANT PAYMENTS
Because of the importance of the study visits for patient safety and assessment of treatment efficacy, participants will receive remuneration. Monetary remuneration should reduce participant burden related to their time spent, travel costs and other expenses (e.g. childcare). Participants will receive $25 for the Baseline/Randomization visit and $20 for Visits 4 and 6. They will also receive $35 for the End of Study (visit 18)/Early Termination visit and for participating in the telephone follow-up visit (visit 12). Thus total reimbursement for completing all study visits is $135.

Participants may be reimbursed for travel expenses, not to exceed the VA rate, to and from the study visits relating to this study protocol. Reimbursement will be based upon the following guidelines:

- Travel exceeds 20 or more miles (one-way) from 4800 Memorial Dr. – Waco VA campus or 1901 Veterans Memorial Dr. – Temple VA campus.
- The participant is not receiving travel pay for another VA medical appointment on that day.
- Travel reimbursement is subject to availability of funds for this project. Therefore, reimbursement cannot be guaranteed.
- Google Maps will be used to calculate reimbursement. (Home address to/from Waco VA or Temple VA)
- Shortest calculated distance x 2 x Standard VA rate of $.415 = Reimbursement to Participant

Final Follow up. Visit 12 will take place between 2-3 weeks after all treatments are terminated. Study staff will follow-up on and document AEs and/or side effects reported at the previous visit 11. If AEs and/or side effects are reported at this visit, the nurse practitioner or study physician will follow up with the participant to determine if they need additional medical care. Data from the follow up period will be used to ascertain the reversibility of the efficacy measures and to identify any potential adverse effects of study drug discontinuation.

8.0 SAFETY ASSESSMENTS AND PROCEDURES

Vital Signs: Vital signs will be taken at every study visit with the exception of visit 12, as that visit is conducted over the phone. Blood pressure, heart rate, and temperature will be taken in a seated position or supine position after a rest period of five minutes.

Medical History: The subject's lifetime medical history will be taken during the screening period. Medical history includes previous and current diseases.

Physical Examination: A physical examination including a neurological examination, an assessment for breast tenderness and gynecomastia, thrombosis (e.g., calf tenderness, shortness of breath) and sexual dysfunction. Tender points will also be assessed.

Electrocardiograph (ECG): A supine, 12 lead ECG will be performed according to Table 1 above. Potentially clinically significant ECG abnormalities will be interpreted by a local cardiologist at the discretion of the principal investigator.

9.0 LABORATORY ASSESSMENTS

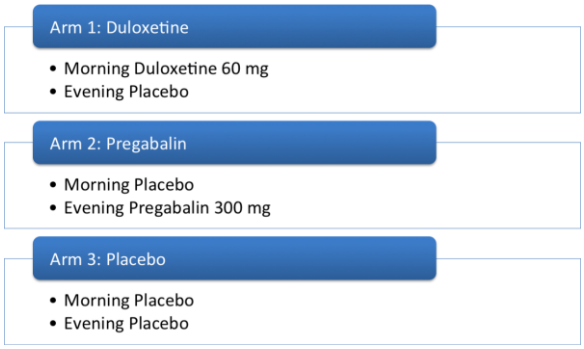
Study associated laboratory assessments (blood and urine) will be collected at time points specified in Table 1 above and analyzed by a local laboratory with the exception of the urine dipstick assessments which will be collected and analyzed onsite. A total of 6 mL of blood will be collected at each time point indicated in Table 1 above with the exception of Visit 2 where an additional 6 mL of blood will be collected and stored for genotyping.

Laboratory assessments to be completed:

Liver tests
Urine pregnancy test
Urine toxicology

10.0 STUDY MEDICATIONS

Figure 1: Medication groups



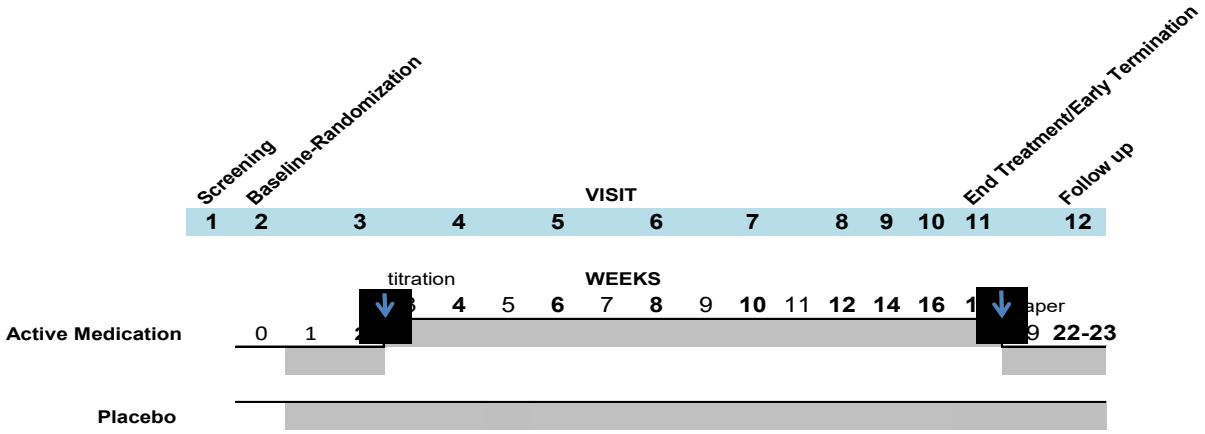
Duloxetine Arm; Group 1 (AM duloxetine + PM placebo): In the morning, **Group 1** will begin dose escalation of duloxetine starting with 30 mg of duloxetine for 2 weeks (weeks 1 & 2) followed by 60 mg of duloxetine for 16 weeks (weeks 3 to 18). They will also take a placebo pill at night for 18 weeks.

Pregabalin Arm; Group 2 (AM placebo + PM pregabalin): In the morning, **Group 2** will take a placebo pill for 18 weeks. At night **Group 2** will begin dose escalation of pregabalin starting with 150 mg for 2 weeks (week 1 & 2) followed by 300 mg of pregabalin for 16 weeks (weeks 3 to 18).

Placebo Arm: Group 3 (AM placebo + PM placebo): In the morning, **Group 3** will take one placebo pill in the morning and one placebo pill at night for 18 weeks.

After the treatment phase, all groups will taper off and stop their coded medication over a 1-week period (week 19). A final follow up telephone assessment will take place 3 weeks after the participants have taken their last dose of medication. The dosing schedule is illustrated Figure 2 below.

Figure 2: Study Medication Dosing Schedule



Randomization: A computer generated randomization master list will be generated by a CoE investigator using a free web-based application "www.randomizer.org". The program will generate an equal number of participants in the 3 study arms. Group assignment will take place at the CTVHCS pharmacy. Emergency unblinding process will be in place in case of emergency. A copy of the randomization will be kept in a sealed envelope in the offices of Dr.Bartlett, the Chief of Pharmacy. Participants will receive a wallet-size card that contains the date and time of their next study visit and a 24-hour telephone number for study staff.

Study medication will be taken by mouth twice daily. Active medications and matched placebo will be over encapsulated by the pharmacy so that placebo capsules will look like the active medication, with matching shape, taste and color. All study medication supplies will be labeled, stored, reconciled, and destroyed according to applicable regulatory requirements.

Tolerability to the medications will be assessed by the side effects checklist and evaluation by the study physician who will remain blind to the participants' treatment condition.

Adjustments and Maintaining the Blind
All participants will receive a container identical encapsulated pills; the pack will indicate which pills are the "morning medication" and which are the "night time medication." Aside from AM and PM dosing indicators, the containers will only be labeled with the Investigational Study Name (REGIONS), medication lot number and expiration date. Only the dispensing pharmacists will know the contents of the capsules.

Unit Dose Packaging
Medication compliance will be monitored using blister packaging. The blister packs are sealed and will protect the medication's integrity as well as prevent any accidental spills. Because the study is using twice daily dosing, the blister pack will indicated which pills are to be taken in the morning and which pills are to be taken at night. This will act as a visual aid to help participants take their study medication at the prescribed times and avoid missed doses. Used blister packs will be returned at each visit.

11.0 DNA/RNA TESTING

After veterans are accepted into the study, each participant will be asked to provide approximately 20 mL. These tubes will be coded and will not contain any personal information. Blood will be processed to provide aliquots for DNA extraction, RNA and other blood products in the VA laboratory. Two EDTA tubes and one Tempus Tube for RNA will be collected and stored at ~80. DNA extraction will be performed in Dr. Young's laboratory using DNA extraction kits (Amplicon). Coded DNA samples will be

stored in a limited access facility at -80 and in liquid nitrogen until genotyping. Length variant and SNP genotypes are performed as standard procedures in Dr. Young's laboratory.

12.0 CONCOMITANT MEDICATION

The standardized concomitant medication log will be used to record newly started or stopped medications throughout the trial including the start and stop dates and dose.

Exclusionary concomitant medications include the following at any time during the active treatment phase of the study:

- Use of MAOIs
- Active ongoing use of the following agents: desvenlafaxine, fenfluramine, linezolid, milnacipran, phentermine, tryptophan, tramadol, opiates

Acetaminophen (<4 g/day) will be the only rescue pain medication that is allowed during the trial.

13.0 DISCONTINUATION CRITERIA-ADVERSE EVENTS

Study staff will meet weekly so that the study physician and principle investigator can review the participant's progress in the trial (concomitant medications, side effects checklist, scores on the Beck Depression scale, laboratory tests and medical concerns).

Participants will be discontinued from the study for the following reasons:

- Participants with clinically significant abnormalities in vital signs (e.g., significant postural hypotension with syncope at baseline or systolic blood pressure >150 mm Hg or diastolic blood pressure >100 mm Hg), physical exams, or laboratories at baseline or for two consecutive evaluations will be discontinued from the treatment phase of the study.
- Participants who develop significant adverse side effects or destabilization of a chronic medical illness will be discontinued from the treatment phase of the study.
- Participants who develop significant depression or suicidal ideation will be discontinued from the treatment phase.
- Study Physician Discretion: Participants demonstrates significant clinical deterioration.
- Liver enzyme's greater than 3 times normal, on 3 consecutive laboratory tests.
- Participant Lost to Follow-up: If a participant has missed 2 consecutive study visits and the study staff are unable to contact the participant via telephone or mail, the participant will be considered "Lost to Full-up"
- Noncompliance: If the participant misses more than 2 weeks of study medication or 2 consecutive study visits.
- SAE's documented in the package inserts for duloxetine and pregabalin are listed in the Study Medication section of this document and are indicated with a "*" will result in immediate removal from the protocol (SAE's marked with a "**") will indicated close monitoring until resolution (see SAEs below.
- Termination of the study

Anticipated SAE's for Duloxetine:
Serotonin syndrome*, GI bleeding* (depending on severity, may only require monitoring), confusion*, hallucinations *, seizures *, SIADH* (syndrome of inappropriate antidiuretic hormone secretion), hypersensitivity* (including Steven's Johnson syndrome), elevated liver tests**, hypertensive crisis**, supraventricular arrhythmia**, orthostatic hypotension and syncope**, increased risk for suicide ideation**, hyponatremia**, urinary hesitation and retention**, and slow gastric empting**.

SAE's with pregabalin are rare because pregabalin is not bound to blood proteins and exhibits almost no drug-drug interaction. The most common side effects reported in clinical trials with pregabalin include CNS disturbances such as dizziness (8—45%) and somnolence/ (drowsiness) (4—28%). The majority (85%) of these side effects in were considered mild to moderate in intensity and dose dependent.

Anticipated SAE's for Pregabalin:
Angioedema*, increased risk or onset of suicidal ideation**, peripheral edema**, increases in creatinine phosphokinase**, dizziness and somnolence**, delirium*, increased intracranial pressure*, new onset movement disorders**, heart failure*, ventricular fibrillation*, renal failure* and syncope and hypotension**.

Discontinuation Procedure
All Participants who are randomized and then discontinued from medication will undergo a visit 11 early termination procedure (see Table 1), and a visit 12 follow-up. If a participant withdraws from the study of their own volition, they will not undergo visit 12 procedures, as they no longer wish to be followed.

Participants excluded from treatment (e.g. clinically significant abnormalities) will be referred for clinical care to the appropriate clinic and a clinic staff member will be identified with whom the participant will check in with. If the study withdrawal is due to threat of suicide, the participant will be walked over to the clinic in a warm hand off. Medically withdrawn participants will be followed until study termination. This information will be reported to the IRB, the FDA, and the funding agency's (CSRD) Data Monitoring Committee.

Medical Monitoring and Safety: Oversight of the internal monitoring of the participant's day-to-day safety will be conducted by the principal investigator, study staff, nurse practitioner and physician. In particular, monitoring for side effects and adverse events will occur on a regular basis. All participants in the study will be given a 24-hour telephone number to call in case of an emergency such as a serious adverse event. All emergencies will be reported to the principal investigator who, in addition to completing appropriate mandatory reports and referrals for services, will report these as adverse events to the appropriate oversight agencies including the VA IRB and the funding agency's (Clinical Science Research and Development) Data Monitoring Committee. The VA's Office of Research Development's CSR&D prepared a Data Monitoring Committee Charter on November 15, 2014 that the Principle Investigator agreed to and signed. The DMC serves as an independent oversight group. The DMC created a protocol specific Charter outlining the timeline for reviewing the clinical trial to maximize patient safety and minimize risk, assesses recruitment milestones and conducts periodic assessments of the data quality and timeliness. Reviews will take place quarterly throughout the trial. Issues concerning participant safety are reported to the Acting Director of CSR&D and the study and the principle investigator.

Serious adverse events (SAEs, defined as any unanticipated event that requires medical attention that is at least "possibly" attributable to participation in the study) will be reported immediately by telephone and by written report within 24 hours of our receipt of information regarding the event.

Adverse Events: Defined as "any untoward occurrence (physical psychological, social or economic) in a human subject participating in research (ORO Handbook 1058.01).

All adverse events, whether known to be causally related to pregabalin and/or duloxetine treatment or not, will be documented. Adverse events are defined by the ICH for Clinical Safety Data Management definition as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmacological product which does not necessarily have to have a causal relationship with this treatment."

Serious adverse events (SAE) will be defined as any adverse event that is life-threatening, requires inpatient hospitalization or results in death. Study staff will receive training from the principal investigator on how to conduct an adverse event AE assessment and when an AE should be categorized as a SAE or an Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO). Participants will be queried at each study visit regarding the presence of adverse effects associated with the study medication (review of medical history, physical examination, and vital signs). Participants will have 24-hour contact information for someone within the research team. They may be seen between scheduled appointments for any concerns about emergence of possible adverse side effects or clinical deterioration. Participants with clinically significant abnormalities in vital signs (e.g. significant postural hypotension with syncope at baseline or systolic blood pressure >150 mm Hg or diastolic blood pressure >100 mm Hg), physical exams or laboratories at baseline for two consecutive evaluations will be excluded from the treatment phase of the study. Participants who develop significant adverse side effects or destabilization of a chronic medical illness will be excluded from the treatment phase of the study. The Beck Depression Inventory will be used to track for suicidality and depression. Participants who develop significant depression or suicidal ideation will be withdrawn from the treatment.

14.0 DATA SAFETY MONITORING BOARD

The protocol funding agency, VA CSR&D provides a Service Centralized Data Monitoring Committee for Psychiatric, Behavioral Health and Neurologic Disorders. The DMC expects quarterly reports on AE and SAE data, although frequency may be adjusted at the discretion of the DMC. All protocol changes must be submitted to and approved by the CSR&D-CO through the DMS in addition to the CTVHCS IRB. The DMC also wants to be notified of the data of first enrollment of a participant as well as quarterly reports on enrollment. The CSR&D DMC also expect an interim and annual progress report. The DMC will review the report to evaluate the continuing validity and scientific merit of the study as well as determining if the trial should be stopped for efficacy or futility.

The study statistician will prepare a blinded report on the primary outcomes for the study that will be submitted quarterly to the CSR&D, DMC.

15.0 STATISTICAL METHODS

Primary Outcomes

Note that most of the outcome variables are measured repeatedly over time. For the primary outcome of the 10-point Pain Visual Analog Scale (VAS), we will define a binary outcome which takes on one or zero accordingly as a subject reports a pain level of at least 3 out of 10. We will then analyze this outcome data using a mixed effects logistic regression model (McCulloch and Searle, 2001). Subject-specific effects will be accounted for through a subject-specific random intercept. The predictor variables include treatment (duloxetine, pregabalin, or placebo), week of treatment, and treatment by week interaction, along with covariates of comorbid psychiatric disorders, alcohol use, sex, age and pain level at intake.

Safety and tolerability effects, also a primary outcome, are studied via the side effects checklist, in which side effects are recorded as “Yes” or “No.” We will study the effects of the treatments on these factors by fitting a mixed effects logistic regression model for each side effect, similar to the model for the 10-point VAS.

The final primary outcome is the Beck Depression Inventory, and this will be analyzed using a generalized linear model (Stroup, 2013). Note that this measure is only taken twice during the

study and once at follow up, so there will be fewer weeks in the study, but a model with similar predictor variables, main effects, and covariates will be used.

For the two primary outcomes of the 10-point VAS and the Beck Depression Inventory, post-hoc power analyses will be conducted in order to determine the observed power. Post-hoc power analyses assume that the effect sizes seen in the data are the true effect sizes, and determine the probability that a new sample with a similar number of participants would obtain statistically significant results. Due to the complicated nature of these mixed effects models, simulation is the most feasible way to approach the post-hoc power analyses.

Secondary Outcomes
Secondary outcomes measured repeatedly throughout the study include the SF-36, the Jenkins Sleep Scale, the Epworth Sleepiness Scale, and the Krupp Fatigue Severity Scale. The analysis of the SF-36 Physical component summary score will be analyzed by defining a binary outcome following at least 5-point pain reduction criteria. The Jenkins Sleep Scale, the Epworth Sleepiness Scale, and the Krupp Fatigue Severity Scale will be analyzed as continuous outcomes. Finally, the Patient Global Impression of Improvement Scale is a single 7-point item that will be analyzed as an ordinal outcome. A mixed effects logistic regression model will be used to analyze the SF-36. A linear mixed effects model (Stroup, 2013) will be used to analyze the three continuous variables. Each of these models will include subject-specific random intercepts, treatment effect, and the effects of baseline covariates such as age, sex, comorbid psychiatric disorder, alcohol use, and pain level at intake.

One secondary outcome is only measured once during the study, the Patient Global Impression of Improvement Score. This analysis will not require a mixed effects model, as there are no repeated measures. This analysis will be an ordinal logistic regression, as the outcome is measured on an ordinal 7-point scale. The predictor will be treatment, and covariates will include comorbid psychiatric disorders, alcohol use, sex, age and pain level at intake.

Exploratory Genetic Analysis
For the exploratory genetic analysis we will use t-test, ANCOVA to study the effect of each variants on the treatment response and the side-effect profiles. We will also include gene x environment interaction terms in the model. The environmental variables include alcohol drinking and drug use.

Early Dropouts
Not all participants remained active in the study for the entirety of the planned treatment. Due to the nature of repeated measures analysis through mixed effects models, no data imputation is required or desirable for these participants; the analysis does not require that all participants have the same number of repeated measures, and we can retain the weeks in which they did participate.

However, it is important to compare the characteristics of the early dropouts to those of the study completers, in order to determine whether there are systematic differences between these two groups of participants. Baseline characteristics, including variables such as age, sex, comorbid psychiatric disorder, alcohol use, and pain level at intake, will be compared between the two groups. Continuous variables will be compared using independent t-tests or nonparametric sign tests, depending on the distribution of the variables; categorical variables will be compared using chi-square tests. Additionally, chi-square tests will be used to compare

the assigned treatment arm of the early dropouts to the study completers, to determine whether participants in one arm of the study are more likely to drop out early.

The analyses of the primary outcomes, including the 10-point VAS scale, side effects, and the Beck Depression Inventory, will additionally be repeated with a variable that accounts for whether or not a participant dropped out of the study early. This will allow for the examination of any trends in outcomes that may be related to an early dropout.

Missing Data

Data from an active participant may be missing in one of two ways: a participant may miss an entire visit, or a participant may be missing one measure from a visit while retaining others. If a participant misses an entire visit, no imputation will occur; the visits for which they have recorded information will be included in the model. If a participant is missing an entire outcome measure for a visit, no imputation will occur for that measure; per Vin Hippel (2007)[i], when dependent variables can be assumed to be missing at random, there is no benefit to imputation with respect to the model estimation.

If any individuals are missing responses to items within a scale, but most information required to calculate a score is present, the responses to missing items will be imputed unless this is in direct conflict with directions provided by the authors of the instruments. If missing data is common for one or more instruments, multiple imputation will be used for this purpose. More likely, missing data of this type will be rare, and simpler methods (such as mean imputation or mode imputation, depending on the nature of the item) will be used instead, as this will have little influence on the conclusions made in the analysis.

Reconsented Participants

Due to an error in enrollment protocol, some individuals who were not eligible for the study due to a baseline diagnosis of depression were consented and participated. A number of those participants will be reconsented and their data will remain available for analysis. We will not include these participants in the primary and secondary analyses described in earlier sections of this statistical analysis plan. These participants will be analyzed separately, using repeated measures analyses similar to those used for the main sample. Due to a potentially small sample size, the number of baseline covariates that can be incorporated into the analysis of these reconsented patients will be limited; however, every effort will be made to include covariates that are determined to be significant at the 0.05 level for the main sample.

These analyses will also be likely to have low statistical power, due to a small number of reconsented participants; therefore, the emphasis when discussing these analyses will be on the sizes of the effects, rather than the statistical significance (although this will be reported). The sizes of these effects will then be compared in a narrative format to those found in the analyses of the main sample. Again, because of low statistical power, a lack of significance in a combined statistical analysis comparing these individuals to the main sample would have very little meaning; this would not necessarily imply the two groups of individuals are similar, and could simply be due to a lack of ability to detect differences.

16.0 PRIVACY AND CONFIDENTIALITY ISSUES

Confidentiality will be protected by ensuring all research staff have been properly trained in confidentiality and human subject research procedures, coding all subject information when possible, and by securing subject files in a locked filing cabinet or on secured databases with access available only to the principal investigator and research staff. All staff will complete the privacy trainings and data security trainings required by the CTVHCS. Furthermore, data entered into a computer database will only use subject codes on secured computers that will be password protected with access available only to the principal investigator and research staff. Any screening information obtained from potential research subjects who subsequently do not participate in the research study will be destroyed.

In accordance with VA Handbook 6500.2 (Management of Security and Privacy Incidents), Information Security Program, incidents, i.e. theft or loss of data or storage media, authorized access of sensitive data or storage devices or non-compliance with security controls will be reported immediately as noted below:

i) VA Handbook 6500.2 (Management of Security and Privacy Incidents) requires that theft of VA issued computer equipment, electronic devise (cell phone, PIV badges, thumb drives) or software be reported to the VA Police and Security Service: the Information Security Officer (ISO), and the Privacy Officer (PO). Incidents are to be reported within one hour of being discovered or noticed to have occurred.
ii) The ISO or Privacy Officer will be notified expeditiously so he/she may report this incident to VA management in a timely manner. If the ISO or Privacy Officer is not available, a telephone message and/or email message will be left so the ISO/PO can follow-up with when he/she returns to the office. In situations where the ISO or PO cannot be contacted in a timely manner, the incident will be reported to the VANSOC@va.gov via email or by telephone at (800) 877-4328.
iii) Removal of access to research study data will be accomplished by the Project Coordinator with oversight of the PI for study personnel who leave the study.

17.0 RECORD RETENTION AND SOURCE DOCUMENTATION

Source Documentation. The data sources for this study are clinical interviews, self-report questionnaires and laboratory test results. Clinical interviews, self-report questionnaires and laboratory test results will be coded and stored in a secure locked filing cabinet in building 91, 1A-117 and accessible to study staff only. Signed consent forms will be kept in the PI's office in building 91, 1A-107 separate from the raw data. The data will be protected as mandated by the VA IRB and national HIPAA guidelines.

Only study personnel will have access to the de-coded data once it is entered and stored on VINCI. Once entered in the database with assigned subject numbers with the IRB approval, CDs will be obtained from our local IT Service so a de-identified CD of the data can be made. The CD(s) will be sent to the study statistician at Texas A&M University Department of Statistics for data analyses, following review and approval of the privacy officer. The CDs will be shipped quarterly via United Parcel Service with signature required/proof of delivery. Once the data analyses are complete, the CDs will be returned to the Principal Investigator in the same manner. The CDs will be stored in the secure locked filing cabinet in building 93, 1A137.

Destruction of data. Any and all paper and electronic documentation containing PHI will be disposed/destroyed according to current VA regulations at the time of disposal/destruction of documentation. The required records, including the investigator's research records and all data, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1).

In addition to interviews and self-report questionnaires, blood samples will be collected from participants. Blood samples will be used strictly for research purposes. Blood samples will be obtained by venipuncture from trained phlebotomists at the VA laboratory. Blood samples for liver function and creatinine levels will not be retained once they are processed. For the biomarker and genetic testing, samples will be frozen at -80 C and periodically transported by laboratory courier to Dr. Young's laboratory, which is on the Temple VA campus for DNA extraction and storage. Blood samples used for genotyping will not be retained once genotyping has been completed and the study ended. Therefore, a tissue repository is not being established and the biological samples will not be store indefinitely.