STATISTICAL ANALYSIS PLAN

A Randomized, Sham-procedure-controlled, Blinded Study to Evaluate the Effectiveness and Acceptability of Right-sided Stellate Ganglion Block for Treatment of Posttraumatic Stress Disorder Symptoms

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ABBREVIATIONS

AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test Alcohol Consumption Questions
BHP	behavioral health provider
CAPS	Clinician-Administered PTSD Scale
CAPS-4	Clinician-Administered PTSD Scale for DSM-IV
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	complete blood count
CITI	Collaborative Institutional Training Initiative
CRF	Case Report Form(s)
CRO	Contract Research Organization
CRPS	complex regional pain syndrome
CS	Clinical Supervisor
DOD	Department of Defense
DRP	Distressed Respondent Protocol
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
DSMB	Data and Safety Monitoring Board
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition
ECG	electrocardiogram
ED	emergency department
EEG	electroencephalogram
FDA	(U.S.) Food and Drug Administration
GAD-7	Generalized Anxiety Disorder 7-item Scale
GCP	Good Clinical Practice (Guidelines)
HCT	hematocrit
HGB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HPA	Human Protections Administrator
HRB	Survey of Health Related Behaviors among Active Duty Service Members
HRPO	USAMRMC Office of Research Protections Human Research Protections Office
HSRRB	USAMRMC Office of Research Protections Human Subjects Research Review Board
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th edition
ICF	*International Classification of Functioning*, Disability and Health
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
ID	identification
IEC	Independent Ethics Committee
IND	investigational new drug
IOM	Institute of Medicine
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IUD	intrauterine device
IV	intravenous

JAMA	*Journal of the American Medical Association*
K6	Kessler Psychological Distress Scale
LEC	Life Events Checklist
LRMC	Landstuhl Regional Medical Center
mL	milliliter(s)
MP	Military Police
MRI	magnetic resonance imaging
NCS-R	National Comorbidity Survey Replication
NHIS	U.S. National Health Interview Survey
NSDUH	National Survey on Drug Use and Health
ORP	USAMRMC Office of Research Protections
PAPI	paper-and-pencil interviewing
PCL-5	PTSD Checklist for DSM-5
PCL-C	PTSD Checklist - Civilian
PCL-M	PTSD Checklist - Military
PE	physical examination
PHI	protected health information
PHQ	Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire - 9
PTSD	Posttraumatic Stress Disorder
PVN	paraventricular nucleus of the thalamus
RC	Research Coordinator
RCT	randomized, controlled trial
RSD	reflex sympathetic dystrophy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-12	Short Form (12) Health Survey
SF-36	Short Form (36) Health Survey
SG	stellate ganglion
SGB	stellate ganglion block
SOP	Standard Operating Procedure
SPN	sympathetic preganglionic neuron
TAMC	Tripler Army Medical Center
TBI	traumatic brain injury
TV	television
UCMJ	Uniform Code of Military Justice
ULN	upper limit of the normal range
USAMRAA	US Army Medical Research Acquisition Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USASOC	U.S. Army Special Operation Command
VA	Veterans Administration
WAMC	Womack Army Medical Center

BACKGROUND

Posttraumatic stress disorder (PTSD) is a reaction to a traumatic event in which an individual perceives threat of death or significant injury, resulting in acute fear that is experienced over an extended period of time following the event(s). Symptoms are generally categorized in terms of intrusive symptoms, avoidance, negative alterations in cognitions and mood and alterations in arousal and reactivity (American Psychiatric Association, 2013). PTSD will develop in up to a third of individuals who are exposed to a significant stressor (Committee on Treatment of Posttraumatic Stress Disorder, Institute of Medicine, 2008), and approximately 10% to 20% of those diagnosed with PTSD will become chronic (Fletcher, Creamer, & Forbes, 2010). According to the 2000 National Comorbidity Survey Replication (NCS-R), an estimated 6.8% of adults in the United States will experience PTSD during their lifetime (Dohrenwend et al., 2006). Certain subgroups (e.g., military service members) are at an increased risk because of their higher likelihood of trauma exposure (Jonas et al., 2013). PTSD prevalence among active duty service members ranges from approximately 5% to 15% (Tanielian & Jaycox, 2008). Hoge and colleagues (2004) reported an estimated 12.9% of service members returning from combat operations in Iraq fit diagnostic criteria for PTSD.

There is evidence that the prevalence of PTSD is increasing among service members. The 2008 Department of Defense Survey of Health Related Behaviors among Active Duty Service Members (HRB Survey) found that an estimated 11% met screening criteria for further evaluation of PTSD symptoms, up from 7% in 2005 (Bray et al., 2009). PTSD is also associated with certain mental health disorders, work impairment and decreased earnings, divorce, difficulties with child rearing (R. C. Kessler, 2000), depression and substance use disorders (Brady, Killeen, Brewerton, & Lucerini, 2000).

A. PTSD Treatment

Treatments for PTSD include both psychotherapeutic and pharmacologic modalities, with little existing systematic evidence for effectiveness (Institute of Medicine, 2008). Jonas et al. (2013) found similar results regarding the effectiveness of exposure therapy, and characterized a handful of pharmacologic modalities marginally effective when compared to exposure therapy.

Currently available treatments for PTSD have side effects and varying onset of action (the time required after administration for the treatment for the effect to be observed). Pharmacotherapies side effects include, but are not limited to, nausea, weight gain, headache, sexual dysfunction, and agitation. Symptom relief for this medication take between 6 to 8 weeks of regular use (Alexander, 2012), during which time side effects may develop and discontinuation of the medication(s) may occur. Psychotherapeutic modalities tend to take between 6 to 24 months before the patient experiences significant relief (Sharpless & Barber, 2011). Also, some of the most effective therapies involve exposure to traumatic stimuli which, if improperly applied, may risk further deterioration of the patient (Rauch, Eftekhari, & Ruzek, 2012).

Patient adherence to and acceptability of prescribed treatments also impact treatment effectiveness. Health beliefs (Spoont, Sayer, & Nelson, 2005); knowledge of PTSD and its potential therapies (Gray, Elhai, & Frueh, 2004); and comorbid substance abuse, depression, and other conditions (Kronish, Edmondson, Li, & Cohen, 2012) all play a role in adherence to prescribed treatment regimens.

Several studies demonstrated that stigma associated with receiving treatment is a significant concern for study participants (Rae Olmsted et al., 2011; Tarrier, Liversidge, & Gregg, 2006) and may result in higher likelihood of treatment failure or discontinuation (Fung, Tsang, & Chan, 2010; Kim, Britt, Klocko, Riviere, & Adler, 2011).

B. Stellate Ganglion Block

Sympathetic blockade, and stellate ganglion block (SGB) in particular, are PTSD treatments that are considered safe, effective, fast-acting, with few side effects, and with good patient acceptability and adherence. SGB is a procedure routinely performed since the 1920s to treat common conditions such as complex regional pain syndrome (CRPS), hot flashes, Raynaud's syndrome, hyperhidrosis, and other sympathetically mediated conditions. The stellate ganglion (SG) is a sympathetic ganglion located at the base of the cervical spine near the C7 transverse process. The SG thus is a major sympathetic switching and transit station for the "fight-or-flight" response; interrupting this complex circuitry with a local anesthetic could have observable effects on conditions mediated by similar responses, such as PTSD.

In SGB a local anesthetic is injected into the SG to "block" its function. To date, only a small number of studies have been published about the effectiveness of SGB in treating PTSD, but the findings are intriguing and warrant further scientific investigation (Lebovits, Yarmush, & Lefkowitz, 1990; Lipov, Joshi, Lipov, Sanders, & Siroko, 2008; Mulvaney, McLean, & De Leeuw, 2010) reported a patient with insufficient reduction in PTSD symptoms from pharmacotherapy who underwent SGB 55 days post-trauma. The individual reported immediate resolution of his symptoms (80% to 90% reduction) as well as improved appetite and sleep. The symptoms, however, returned 32 days later, at which time pulsed radiofrequency energy was applied to the SG. Three months later, the patient reported a continued 90% improvement in all symptoms of PTSD. Mulvaney and colleagues (2010), including two of the co-investigators of the current study (Mulvaney and McLean), described two patients diagnosed with PTSD and treated with SGB. In both, post-treatment PTSD Checklist (PCL) scores were sub-threshold for PTSD diagnosis. One of the patients requested retreatment 3 months later; their symptoms remained diminished for an additional 7 months of follow up. Hicky et al. (2012) described 9 military service members with chronic PTSD who were treated with SGB. Each of the participants had more than 1 year of unsuccessful treatment via pharmacotherapeutic and/or psychotherapeutic modalities. Following a single SGB, Clinician-Administered PTSD Scale (CAPS) assessments showed that 5 of the 9 patients experienced a clinically significant reduction in symptoms 1 week post-procedure. The effects of the procedure seemed to decrease

within 1 to 2 months, though symptoms that did return were not always as severe as they had been before the procedure. Of note, they also performed two repeat SGB treatments. One individual with no initial benefit also saw no improvement following a second block, whereas another who had seen the greatest reduction in symptoms experienced full remission after the second procedure.

Mulvaney et al. (2014) (including two other authors involved in this trial, Lynch and Kane) recently reported a case series of 166 patients, by far the largest in the literature. The PTSD Checklist – Military (PCL-M) was administered a day before treatment and repeated at 1 week and 1, 2, and 3-6 months post-SGB. An improvement in PCL-M scores of ≥10 was observed in 73.5% of the 132 patients evaluated at 3-6 months. 24 subjects who had a positive response for at least 3 months and then had the return of symptoms were treated with a second SGB; their PCL-M response trends were similar to those with their first SGB.

These findings support the need for a randomized, blinded, sham-procedure-controlled trial to rigorously study the effectiveness of SGB for treatment of PTSD symptoms.

1. PURPOSE OF THE ANALYSIS PLAN

This statistical analysis plan (SAP) contains detailed information about statistical analyses to be performed to evaluate the effectiveness of SGB applied at weeks 0 and 2 for treatment of PTSD symptoms. This study also includes an acceptability portion, which focuses on participants' perception of SGB in relation to other PTSD treatments. This SAP does not include statistical analysis for the acceptability portion of this study. Additional statistical analyses not included here may be done to support manuscript preparation but these will not require an update to the SAP.

2. STUDY OBJECTIVE AND OUTCOMES

2.1. STUDY OBJECTIVES

The primary study objective of the effectiveness study is to evaluate whether right-sided SGB performed at 0 and 2 weeks will reduce PTSD symptoms which will be reflected in the improvement of the CAPS-5 total symptom scores between baseline and 8 weeks. Data analysis will be performed according to the intent-to-treat principle. The primary outcome of this study (difference in CAPS-5 total syndrome score from baseline) will be tested for differences between arms.

Secondary objectives include:

1. to evaluate whether right-sided SGB performed at 0 and 2 weeks will improve PTSD symptoms as reflected by corresponding PCL-5 items across time
2. to explore the association between the main outcome and potential confounding variables (e.g., concomitant medications, duration of PTSD, post-block Horner's syndrome, etc.)

3. to evaluate whether right-sided SGB performed at 0 and 2 weeks will reduce distress (K6), suicidality (M.I.N.I.-Plus Suicidality), anxiety (GAD-7, PHQ-9) and pain (short pain scale) across time
4. to evaluate whether right-sided SGB performed at 0 and 2 weeks will improve physical and mental (SF-12) condition across time

2.2. PRIMARY OUTCOME MEASURES

The primary outcome of the study will be changes in the CAPS-5 total symptom scores between baseline and 8 weeks. The CAPS-5 is the gold standard in clinical PTSD assessment, and it is a 30-item structured interview that corresponds to the DSM-5 criteria for PTSD. For each item, standardized questions and probes are provided; total scores range from 0 to 80. CAPS-5 requires the identification of a single index trauma to serve as the basis of symptom inquiry.

2.3. SECONDARY OUTCOME MEASURES

2.3.1. PCL-5.

The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. Its purposes include screening for PTSD and/or provisional diagnosis, and monitoring symptom change before, during, and after treatment. A total symptom severity score ranging from 0 to 80 is possible (Weathers et al., 2013). The PCL-5 will be administered at baseline to establish a baseline score in support of secondary objective 1.

2.3.2. PCL-C (PTSD symptoms)

This standardized assessment comprised 17 items corresponding to the key symptoms of PTSD from the DSM-IV. The total symptom severity score ranges from 17 to 85. The PCL-C has been thoroughly validated and deemed reliable (Weathers, Litz, Herman, Huska, & Keane, 1994). The PCL-C will be administered at baseline in order to establish a baseline score in support of secondary objective 1.

2.3.3. MINI-INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (M.I.N.I.)-PLUS SUICIDALITY MODULE

The M.I.N.I.-Plus is a structured interview for diagnosing DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998). This assessment will be administered at each follow-up (weeks 2, 4, 6, and 8). Response options are dichotomous (yes/no) and questions ask about desire, thoughts, planning, taking steps toward, and attempting suicide as well as deliberate injury without intent to kill oneself. The set of 7 items employs a complex automated scoring algorithm, with each item representing a different point value. For example, an affirmative response to the question about wanting to harm oneself carries a value of 2 points, while a positive response to the question about taking active steps toward preparing to injure or kill oneself carries a value of 9 points. Individuals scoring nine points or greater will be asked to complete an additional 4 questions regarding any *current* desire to harm themselves, thoughts

about suicide, plans for suicide, and active steps they may be taking. These four items will be used only for clinical purposes by a behavioral health clinician on call, as discussed below.

The suicidal ideation items from the M.I.N.I.-Plus serves to monitor participant safety during the course of their participation in the study, particularly since the 4-, 6-, and 8-week follow-up assessments will be administered online and completed by participants on their own (i.e., not in the study RC's office). If an individual should score 9 or greater on the M.I.N.I.-Plus items, they will be asked an additional 4 questions regarding *current* suicidal ideation or plans.

2.3.4. AUDIT-C/AUDIT.

The Alcohol Use Disorders Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001) will be used to assess potential alcohol abuse symptoms. The instrument was developed as a means of brief assessment and screening for excessive drinking. This 10-item scale is widely used and has been shown to be consistent with ICD-10 definitions for alcohol dependence and harmful alcohol use (Allen, Litten, Fertig, & Babor, 1997; Saunders, Aasland, Amundsen, & Grant, 1993). Scores range from 0 to 40, with scores between 8 and 15 (inclusive) suggest a medium level of alcohol problems, scores ranging from 16 to 19 represent a high risk of alcohol problems, and scores of 20 or greater warrant further diagnostic evaluation for alcohol dependence.

The AUDIT-C (AUDIT alcohol consumption questions) consists of the first 3 items of the full AUDIT and assess frequency of drinking, typical quantity, and frequency of heavy drinking. Based on a scale of 0 to 12, a score of 4 or greater is considered positive in males, while a score of 3 or more is positive among females.

2.3.5. K6

The K6 was developed for use in the U.S. National Health Interview Survey (NHIS) as a means of assessing nonspecific psychological distress. Scores range from 0 to 24 resulting from 6 items administered on a scale of 0 to 4, with a score of 13 or greater are indicative of serious psychological distress in the U.S. general population (Kessler et al., 2003).

2.3.6. PHQ-9

Depression symptoms will be assessed using the validated PHQ-9 (Kroenke, Spitzer, & Williams, 2001) in support of secondary objective 2. The PHQ-9 was developed as a short form of the full Patient Health Questionnaire (which was a self-administered version of the PRIME-MD instrument). Severity scores range from 0 to 27, with a score of 5 to 9 representing mild depression, a score of 10 to 14 representing moderate depression, and a score of 15 or greater representing a severe level of depression. Scores of 10 or greater are considered a "yellow flag" indicating possibly clinically significant depression (Kroenke et al., 2001; Löwe, Unützer, Callahan, Perkins, & Kroenke, 2004).

2.3.7. GAD-7

Generalized anxiety symptoms will be assessed via the GAD-7 (Spitzer, Kroenke, Williams, & Löwe, 2006) in support of secondary objective 2. Scores range from 0 to 21, with a score of 5 to 9 representing mild anxiety, a score of 10 to 14 representing moderate anxiety, and a score of 15 or greater representing a severe level of anxiety. Scores of 10 or greater are considered a "yellow flag" indicating possibly clinically significant anxiety (http://www.phqscreeners.com/instructions/instructions.pdf)

2.3.8. SF-12 (Version 2.0)

The SF-12 is a shortened version of the SF-36, which was designed as a general health utility index. The twelve items provide an estimate for eight domains of functional health and well-being: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Together, the first four domains constitute a Physical Health summary measure, and the second 4 constitute a Mental Health summary measure (Ware, Kosinski, & Keller, 1996). This assessment will be used as a measure of general functioning in support of secondary objective 2.

2.3.9. Short pain scale

Because pain frequently presents with PTSD and may play a confounding role in treatment effectiveness (Asmundson, Coons, Taylor, & Katz, 2002; McGeary, Moore, Vriend, Peterson, & Gatchel, 2011), a 0-10 Likert-type numeric pain scale where 0 represents "No pain," 5 represents "Moderate pain," and 10 represents "Worst possible pain" will be administered. The pain scale will be administered in support of secondary objective 2.

Other information that will be collected include:

2.3.10. Current Medications

In order to assess the potential impact of medication use concurrent with study participation, information on prescription psychotropics (including stimulants, anxiolytics, and antidepressants), anticonvulsants, antipsychotics, anticholinergic drugs, opioids, nicotine, sleeping medications, antihypertensives, and sympathomimetics/sympatholytics will be collected.

3. STUDY METHOD

This is a multisite, randomized, blinded, sham-procedure-controlled study to evaluate the effectiveness of unilateral right-sided stellate ganglion block (SGB) on the acute symptomatology of PTSD, evaluated by the CAPS-5 pre-treatment and at 8 weeks. Participants

will be centrally randomized to 2:1 active:sham SGB and will be evaluated at Womack Army Medical Center in North Carolina, Tripler Army Medical Center in Hawaii, and Landstuhl Regional Medical Center in Germany. A total of up to 240 participants will be enrolled at the three sites (up to 80 per site). No single site will enroll more than half the participants and each will have a 2:1 active:sham ratio.

Study intervention will be administered at week 0 and at week 2. Participants will be evaluated for PTSD symptomatology at 0 weeks (pre-treatment) and at 8 weeks using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). They will complete the PTSD Checklist for DSM-5 (PCL-5) and the M.I.N.I.-Plus Suicidality Module at 0, 2, 4, 6, and 8 weeks; they also will complete the M.I.N.I.-Plus module at screening. The SF-12, GAD-7, PHQ-9, K6, AUDIT-C/AUDIT, and a short pain scale will be completed at weeks 0, 4, and 8.

4. STUDY POPULATION AND INCLUSION CRITERIA

Participants will be active duty service members who meet inclusion criteria (as described below):

- Active duty status

- Personal access to Internet

- Anticipated stable assignment to installation for at least 2 months

- Stable dosing for ≥3 months, if receiving psychotropic medications

- Prior to enrollment, offered PTSD treatment using A-level modality (as defined by MEDCOM policy 14-094; 18 Dec 2014)

- PCL-C score of 32 or greater at screening

- Acceptable clinically indicated preoperative laboratory studies, per standard site-specific protocols

EXCLUSION CRITERIA

Enrolled subjects must not meet any of the following criteria:

- Prior SGB

- Allergy to amide local anesthetics (e.g., ropivacaine, bupivacaine)

- Pre-existing Horner's syndrome

- Pregnancy

- Current anticoagulant use

- History of a bleeding disorder

- Infection or mass at injection site

- Myocardial infarction within 6 months of procedure

- Phrenic or laryngeal nerve palsy (hoarseness)

- History of glaucoma

- History of schizophrenia, other psychotic disorder, bipolar disorder, or personality disorder (axis 2), as verified by medical record review by an Army Co-Investigator with access to medical records

- Moderate or severe traumatic brain injury as verified by medical record review by an Army Co-Investigator with access to medical records

- Symptoms of moderate to severe substance use disorder in past 30 days

- Suicidal ideation in the past 2 months, documented by the M.I.N.I.-Plus Suicidality Module

- Any ongoing other major life stressor or condition not listed here that the site Investigator believes clearly would place the participant at risk for injury or a poor outcome (including anniversary of the inciting event, pending divorce, undergoing medical board/retirement, undergoing UCMJ or pending legal administrative actions, recent significant illness in participant or family)

5. RECRUITMENT

For recruitment, behavioral health providers (BHP) or family or other physicians within the medical center referral area will identify potential participants and obtain their permission to pass contact information on to the site Research Coordinator (RC). The RC will contact by telephone those who have expressed interest in the study, to explain the study and invite them to participate. The RC will provide a study overview and answer any questions that individuals may have about participation. Once individuals have agreed to take part in the study, they will be asked a few pre-screening questions over the telephone to determine eligibility. Those who pre-screen as eligible will be asked to come to the RC's office to complete the consenting process in person and to complete a computer-based screening, which will assess the study inclusion and exclusion criteria.

6. DISCONTINUATION OF INTERVENTION

Study intervention may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.

- Unacceptable toxicity that compromises the ability to continue study-specific procedures, or is considered to not be in the participant's best interest.

- Participant request to discontinue for any reason.

- Participant non-compliance.

- Pregnancy during the first two weeks of the study, when study-related treatment procedures (either active or sham) are being conducted.

- Discontinuation of the study at the request of the relevant IRB.

7. DATA LOCK AND UNMASKING

Data lock and unmasking will occur after enrollment is completed. The study is designed as intention-to-treat (ITT), and therefore participants will not be excluded after randomization. If a participant discontinues further treatment or participation in the study, for example as a result of an adverse event, every attempt should be made to continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the participant or Investigator, the participant may be withdrawn from the study.

8. STATISTICAL / ANALYTICAL ISSUES

8.1 Analysis Populations

This study will have two analysis populations, and intention-to-treat (ITT) population and a per protocol (PP) population.

The primary analysis will be based on the intention-to-treat principle. All participants who were enrolled and randomly allocated to a treatment arm will be included in the analysis in the group to which they were randomized (not to which treatment they actually received). This approach ignores noncompliance, protocol deviations, withdrawal and lost-to-follow-ups. Analysis of the ITT population avoids overoptimistic estimates of the efficacy of an intervention resulting from the removal of non-compliers, accepting that protocol deviations occur in actual clinical practice (Heritier, Gebski, & Keech, 2003).

Analyses will be replicated on the per-protocol population. The per-protocol population will consist of those participants who strictly adhered to the protocol (i.e., will exclude participants that withdrew or were lost-to-follow-up prior to completion of the study, received treatment they were not randomized to, completed visits outside of the prespecified window, participants known to the intervening anesthesiologist, baseline CAPS < 10, screening to baseline interval >32 days, or any other protocol deviation). The per-protocol analysis provides an estimate of the true efficacy of an intervention (i.e., among those who completed the treatment as planned) (Ranganathan, Pramesh, & Aggarwal, 2016).

A sensitivity analysis also will be performed, excluding subjects with final CAPS scores obtained more than 12 weeks post initial intervention and assigning discordant interventions to the one actually delivered.

8.2 General Considerations
Data will be summarized by treatment group. For summaries of study data, categorical measures will be summarized in tables listing the frequency and the percentage of subjects in each treatment; continuous data will be summarized by presenting mean, standard deviation, median and range; and ordinal data will be summarized by only presenting median and range.

Most statistical computations will be performed and data summaries will be created using SAS 9.4. If additional statistical software is required, this will be discussed in the study report. All statistical analyses will be conducted using the intent to treat principle, unless explicitly specified otherwise (e.g., the per-protocol protocol, or for certain secondary and/or post-hoc analyses).

Demographic and all baseline characteristics will be compared between treatment groups. If analyses of these characteristics suggest that substantial differences exist for some of these characteristics between treatments at baseline, their use as covariates will be explored in the model-based secondary analyses.

8.3 Missing Data Approaches
The primary analysis will be conducted using the available data without any statistical imputation for missing data for data lost to follow up or otherwise unavailable. Accordingly, it is assumed for the primary analyses that missing primary outcomes are missing completely at random. We will examine the proportion of missing primary outcome data to ensure that the missing rate is comparable across the two treatments.

Analysis of the secondary objectives will generally include available data such that no data obtained within the study assessments windows will be discarded and no imputation for missing data will be done.

8.4 Other Analysis

All other analyses of outcomes not described in the primary or secondary outcomes are exploratory in nature; therefore, resulting p-values and confidence intervals will generally be provided for descriptive purposes only. All p-values provided for any baseline and demographic characteristics will be for descriptive purposes only. As such, unless otherwise specified, p-values presented will be on a per analysis basis, with no further control for multiple tests.

For model building activities, p-values will be used to identify the best fitting model as well as covariates to be included in the final models. For these model building activities, p-values <0.05 will generally determine significance. However, due to the exploratory nature of these models, less rigid standards may be considered and would be described fully in the final clinical study report and study manuscript.

8.5 Primary Analysis

Data analysis for the primary outcome will be performed according to the intent-to-treat principle with an analogous secondary analysis conducted with the per-protocol population. The primary outcome of this study (difference in CAPS-5 total syndrome score from baseline) will be tested for differences between arms. The primary outcome will be analyzed using a linear model for continuous variable that accounts for treatment assignment, site and baseline CAPs score (see proposed initial model below). 95% confidence intervals will be produced for each of the arms.

$$Y_i = \beta_0 + \beta_1 Treatment_i + \beta_2 Site_i + \beta_3 Baseline\ CAPs_i + \epsilon_i$$

Where Y_i is the primary outcome measure (Week 8 CAPs score minus the Baseline CAPs score), β_0 is the intercept, β_1 through β_3 are coefficients, and ϵ_i is the error term which is assumed normally distributed.

Statistical analysis modeling will be carried out utilizing SAS/STAT PROC GLM (SAS Institute Inc., 2009) with the general structure of the SAS code for this model shown below. Adjusted estimates of the difference in the change between the two arms and within each treatment arm and corresponding 95% confidence intervals will be produced.

```
proc glm data=Primanaly_sgb;
     class Treat site;
     model CAPS5_Differ = Treat site BL_CAPS/ solution clparm;
          estimate 'Stellate Ganglion Block (SGB)' intercept 1 Treat
          1 0 site 1 0 0 BL_CAPS 38.56;
          estimate 'Placebo' intercept 1 Treat 0 1 site 1 0 0 BL_CAPS
          38.11;
          estimate 'Intervention Effect of SGB' Treat 1 -1;
          lsmeans Treat / cl; /*Confirm est. means for Tx group*/
ods output Estimates = SGB_Estimates ParameterEstimates =
SGB_overallEstimates FitStatistics = SGB_fitstats;
run;
```

As of February 2017, new psychometric data have become available regarding the CAPS-5. Although initial psychometric properties are still being analyzed (Weathers et al., 2017), consultants from the National Center for PTSD have suggested that 8-10 points are indicative of clinically significant or meaningful change. We have recently communicated with Frank Weathers, co-author of the CAPS, and he conveyed the following:

> *"There isn't a well-validated change score, but most people are using somewhere around 8 to 10 points for the CAPS-5. They also use loss of diagnosis or moving into a lower severity range as alternative indicators. In case you don't have them, here are the rationally derived CAPS-5 severity score ranges."*

Additionally, Paula Schnurr at the National Center for PTSD told us:

> *"We have not finalized a number but I am suggesting somewhere between 8 and 10. I think 10 is probably better given the larger number of sxs in the criteria, despite the 0-4 scoring on the CAPS. In our prior work with the CAPS-IV, we had defined 10 points as response…"*

Given this "new" information, we are establishing a 10-point change in CAPS score from baseline to follow-up eight weeks after stellate ganglion block as a clinically meaningful change. Consequently, as a part of the primary outcome analyses, point and interval estimates of the change will be generated for each treatment arm to evaluate whether one or both arms reach the level of clinically meaningful change.

8.6 Secondary Analyses

All secondary analyses will be performed according to both the intent-to-treat and per-protocol principle.

8.6.1 Explore the Association between the Main Outcome and Other Potential Confounding Variables

An analogous model to the one described in section 8.5 will be run as a sensitivity analysis; however, additional covariates (e.g. effect modification or confounder) may be included in the model. Covariates to be examined will include:

- Taking specific concomitant mediations (stimulant, sleeping medication, anticonvulsant, antidepressant, anxiolytic, nicotine, antihypertensive, antipsychotic, and opioid),
- Concurrent behavioral health therapy (defined as an affirmative response to PTSDTx30DCONT),
- Participant self-assessment of intervention (SGB vs. Sham),
- Post-block Horner's (HRNRSCOR_POST), and

- Duration of PTSD (derived from DxMonth and DxYear for formal diagnoses or SxMonth and SxYear for symptom presence)

Other additional covariates may be considered for inclusion into the model based on a univariate analysis to investigate if any other measures are significantly associated with change in baseline to week 8 CAPs (where the p-value is less than 0.05). The study team will identify the list of potential covariates to include in the base model.

Each covariate will be included in the 'full' model as a confounder or effect modifier (an interaction term of the covariate with treatment arm will be included in the model). To simplify the full model, non-significant (p > 0.05) covariates will be removed and reduced models will be run and compared against the full model. A final parsimonious model will be selected via two model fit indices: Akaike information criterion (AIC) and Bayesian information criterion (BIC).

8.6.2 Evaluate Treatment Effects on PTSD symptoms (via PCL-5 score) Across Time

The treatment effect on the clinical criteria of PTSD as measured by the PCL-5 over time will be assessed at weeks 2, 4, 6 and 8 using a generalized-linear mixed model to account for temporal correlation between weekly measures and the clustering of the data; this model will control for treatment, week, site, baseline PCL-5 score and the two way interaction between treatment and time (see below for proposed model). The outcome variable will be the continuous PCL-5 score obtained at each visit. A sensitivity analysis will also be run by treating the outcome variable as a binary indicator of positive PTSD diagnosis (score of 33 or greater suggests positive screening for PTSD) (National Center for PTSD, 2017).

$$Y_{ij}=\alpha+\beta_1 Time_{ij}+\beta_2 Site_{ij}+\beta_3 Treatment_{ij}+\beta_4 BaselinePCL5_{ij}i+\beta_5(TimeXTreatment)_i+ s_i + \varepsilon_{ij}$$

Where Y_{ij} is the jth measure of PCL-5 in subject i, α is the intercept, β_1 through β_5 are coefficients, s_i is a random subject effect and ε_{ij} is the residual error term. Statistical analysis modeling will be carried out utilizing SAS/STAT PROC MIXED (Littell, Milliken, Stroup, Wolfinger, & Schabenberger, 2006) with the general structure of the SAS code for this model shown below. Adjusted estimates of the PCL-5 scores at each visit between the two arms and corresponding 95% confidence intervals will be produced.

```
proc mixed data = Secanaly_sgb;
class Unique_ID timepointN Treat site;
model PCL5_TotalScore = timepointN Treat BL_Score timepointN*Treat/s;
    random int / subject= Unique_ID;
    repeated timepointN / type=cs subject=Unique_ID;
    estimate 'Intervention Effect of SGB' Treat 1 -1;
    lsmeans timepointN* Treat;
run;
```

8.6.3 Evaluate Treatment Effects on Suicidal Thoughts (via M.I.N.I.-Plus Suicidality), Psychological Distress (via the K6), Anxiety Disorders (via GAD-7), Depression (via PHQ-9), Physical and Mental Composite Measures (via SF-12), and Pain (via Short Pain Scale) Across Time

Treatment effect in the improvement or reduction of relevant health and psychological status information such as suicidal thoughts (M.I.N.I.-Plus Suicidality), psychological distress (K6), anxiety disorders (GAD-7), depression (PHQ-9), physical and mental composite measures (SF-12), and pain (short pain scale) will be analyzed using similar modeling techniques as mentioned in section 8.6.2. Modeling techniques with either linear mixed models or generalized mixed models will account for the structure of the outcome measure (continuous, binary, ordinal, nominal). Each model will incorporate treatment, baseline measure, site, time (as categorical variable) and two-way interactions between treatment and time. Other potential covariates or effect modification variables may be included in the model based on a univariate analysis of baseline measures with the specific outcome measure of interest.

Another secondary analysis of interest is to determine the effectiveness of the SGB among the participants for whom the stellate ganglion was anesthetized effectively. The population that will be utilized for this analysis will be defined as the "Horner's responder population." This population will be defined as those participants who showed a maximum density of Horner's syndrome, reflected by scleral injection, meiosis, and ptosis, following the procedure. For analytic purposes, this will include all participants with a Post-Horner's total score of 12. The analytic approach will mirror that for the primary analysis but will utilize only Horner's responders from the active treatment arm, with propensity scores based on baseline demographic and clinical characteristics used to define a comparator control population.

9. SUBJECT CHARACTERIZATION

9.1 Subject Disposition

Subject eligibility status will be summarized and listed by treatment group. The number of subjects screened; eligible; randomized; completing or discontinuing treatment; and completing follow up will be summarized by treatment group as well. Study withdrawals and reasons thereof will also be listed in a similar manner.

9.2 Protocol Deviations

Protocol deviations are identified by site staff and via automated checks of the database. Protocol deviations will be listed by site with information such as type of deviation, time of occurrence, and reason. Incidence rate of protocol deviations will also be summarized overall and for each protocol deviation category by site.

10. ADVERSE EVENTS

Reports of adverse events will be collected during the trial, and the Research Monitor is required to review all unanticipated problems involving risk to volunteers or others, Serious Adverse Events (SAE) and all volunteer deaths associated with the protocol and provide an unbiased written report of the event to the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO).

An adverse event (AE) is any untoward medical occurrence in a clinical investigation participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g. invasive procedures such as venipuncture, biopsy, etc.). Pre-existing events, which increase in severity or change in nature during or as a consequence of use of a medicinal product in human clinical trials, will also be considered AEs.

An AE does not include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected prior to the screening visit, that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the participant is hospitalized for observation.

10.1 Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded on the appropriate CRF page, including the date of onset and resolution, severity, relationship to study drug or study procedures, outcome and action taken with study medication.

The relationship to study drug therapy or study procedures should be assessed using the following definitions:

- Definitely Not Related: The participant did not receive the study drug and/or study procedure, the temporal sequence of the AE/SAE onset relative to administration of the study drug or performance of the procedure is not reasonable, or there is another obvious cause of the AE/SAE.
- Possibly Related: There is evidence of exposure to the study drug and/or study procedure, the temporal sequence of the AE/SAE onset relative to administration of the study drug or performance of the procedure is reasonable, but the AE/SAE could have been due to another cause.
- Definitely Related: There is evidence of exposure to the study drug and/or study procedure, the temporal sequence of the AE/SAE onset relative to administration of the study drug and/or study procedure is reasonable, the AE/SAE is more likely explained by the study drug and/or study procedure than by any other cause, and the AE/SAE shows a pattern

consistent with previous knowledge of the study drug or study drug class and/or the study procedure.

10.2 Serious Adverse Event (SAE)

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;

- Life-threatening situation (subject is at **immediate** risk of death);

- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events);

- Persistent or significant disability/incapacity;

- Congenital anomaly/birth defect in the offspring of a subject who received study drug;

- Other: medically significant events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Clarification of Serious Adverse Events

- Death is an outcome of an adverse event, and not an adverse event in itself. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).

- All deaths, regardless of cause or relationship, must be reported for subjects on study and for deaths occurring within 30 days of last study drug dose or within 30 days of last study evaluation, whichever is longer.

- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

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ADDENDUM NUMBER 1 TO STATISTICAL ANALYSIS PLAN
FOR PROTOCOL SGB-201

A Randomized, Sham-procedure-controlled, Blinded Study to Evaluate the Effectiveness and
Acceptability of Right-sided Stellate Ganglion Block for Treatment of Posttraumatic Stress
Disorder Symptoms

SAP VERSION: 10.0

SAP DATE: July 12, 2018

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Timing of Addendum: ___ **Before unblinding** _X_ **After unblinding**

Reason for addendum:

After the approval of this clinical study plan and the analysis plan contained within it, clinical colleagues suggested that study results should include two additional efficacy outcome measures: the proportion of participants in each treatment arm who achieved a 10 point or greater improvement in the total symptom severity score (TSSS) on the CAPS-5 from baseline to week 8, and the proportion of participants in each treatment group who met CAPS-5 criteria for a PTSD diagnosis at baseline but no longer met criteria at 8-week follow-up. Additionally, clinical colleagues also suggested conducting a subgroup analysis on the primary outcome based on presence or absence of a clinical baseline PTSD diagnosis (based on the CAPS-5). The rationale for these investigative analyses was to provide additional information to increase interpretability and usability of results by clinicians. This addendum to the statistical analysis plan (SAP) details the investigative analyses that were performed, and hence this should be considered as post-hoc analyses that were determined post unblinding, and post approval of the original statistical analysis plan.

Addendum:

Section 2.3.11. Decrease in Total Symptom Severity Score (TSSS) exceeded by 10 or more points.

The proportion of participants in each treatment group who achieved a 10 point or greater improvement (reduction) in TSSS from baseline to week 8 was calculated. Contingency table analysis was used to compare both proportions descriptively.

Section 2.3.12. Change in PTSD diagnosis status based on CAPS-5.

The proportion of participants in each treatment group who met CAPS-5 criteria for a PTSD diagnosis at baseline but no longer met criteria at 8-week follow-up was calculated. Contingency table analysis was used to compare both proportions descriptively.

Section 8.5.1. Subgroup Analysis on the Primary Outcome based on Baseline PTSD Diagnosis.

The model specified in the SAP (section 8.5) will be re-run but will also include baseline PTSD diagnosis and its interaction with treatment group. Full subgroup analyses will be reported if there is evidence of a subgroup by treatment interaction (a p-value of ≤ 0.1). However, if there is no evidence of a subgroup by treatment interaction, then a sensitivity analysis will be

conducted by re-running the primary analysis only among participants that had a baseline PTSD diagnosis.

ADDENDUM NUMBER 2 TO STATISTICAL ANALYSIS PLAN
FOR PROTOCOL SGB-201

A Randomized, Sham-procedure-controlled, Blinded Study to Evaluate the Effectiveness and
Acceptability of Right-sided Stellate Ganglion Block for Treatment of Posttraumatic Stress
Disorder Symptoms

SAP VERSION: 10.0
SAP DATE: June 23, 2019

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Timing of Addendum: ___ **Before unblinding** _X_ **After unblinding**

Reason for addendum:

This addendum to the statistical analysis plan (SAP) is to document the methods to determine if the missingness observed in CAPS-5 week 8 data is random, and to describe the methods to impute the missing week 8 CAPS-5 values and the approach used to produce the final analysis.

The rationale for imputation of missing data for the primary outcome under the intention to treat (ITT) principle is that when the randomization process is disrupted by dropout or missing data outcomes, bias may be introduced that compromises the results.

The changes were made to provide additional clarification of the results in response to questions from journal reviewers.

Addendum:

Section 8.3 Missing Data Approaches.

The primary outcome analysis will be conducted using the intention-to-treat principle, and imputation will be used to adjust for the presence of missing data on the week 8 CAPS-5 assessment. We will compare baseline measurements between those with and without week 8 CAPS-5 scores to assess whether the data appear to be missing at random. Multiple imputation (via PROC MI, SAS) will be used to impute missing CAPS-5 values at week 8 based on information collected at the baseline visit. Five replicates of the imputed dataset will be generated, analyzed as specified in section 8.5 of the SAP, and PROC MIANALYZE will be used to generate final estimates and uncertainty measures (e.g. treatment effects and corresponding standard errors).

Analysis of secondary outcomes will generally include available data such that no data obtained within the study assessments windows will be discarded and no imputation for missing data will be done. Because these analyses were conducted with mixed model approaches, they are analyzed in a manner that is consistent with both the ITT principle and the missing at random assumption.