USAMRAA W81XWH-15-2-0015

CLINICAL STUDY PROTOCOL

Study Title: 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

Sponsor:
RTI International
3040 Cornwallis Road
Research Triangle Park, NC
27709

Protocol ID:
SGB-201
Amendment 2.0 (Eisenhower Regional IRB)

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Protocol Version/Date:
Version #: Amendment 2.0
March 3, 2018

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10 REVISION HISTORY

Protocol version	Protocol Date	Section(s) revised	Description of revision(s)
Original Protocol	11 November, 2010	Not applicable	Not applicable
Amendment 1 October 2, 2015		Protocol Study Locations	Text revision.
		Protocol Additional Co-Investigators	Text revision.
		Protocol Table of Contents	Deleted 6.2.3.12; Deleted Joggle items; 6.2.3.13 changed to 6.2.3.12; Deleted Appendix 17; re-numbered subsequent appendices accordingly.
		Protocol Synopsis	Deleted Joggle text. Added CAPS-5 change. Clarified acceptability target population.
		Protocol Glossary of Abbreviations and Definitions	Deleted Joggle text.
		Protocol 1.1.1	Specified use of DSM-5.
		Protocol 1.2	Clarified frequency of SGB for PTSD.
		Protocol 2.1	Deleted Joggle text. Clarified timeline for assessments.
		Protocol 3.1	Added PCL-C to screener. Deleted Joggle text. Deleted Joggle assessments. Clarified that participants remain blinded. Clarified intent of MEDCOM 40-54. Added details regarding study incentives. Clarified participants will remain blinded to intervention. Changed “treatment” to “intervention.”
		Protocol 3.2	Corrected time for subjective assessment of change (4-week assessment). Revised participant-spouse eligibility criteria. Added text explaining scheduling of focus groups/individual interviews and clarified eligibility for incentive and the amount and delivery method.
		Protocol 4.1.2	Revised inclusion criterion. Clarified A-level modalities.

Protocol version	Protocol Date	Section(s) revised	Description of revision(s)
		Protocol 4.1.3	Revised final exclusion criterion and added exclusion criterion (PCL-C). Clarified assessment of psychiatric and TBI history.
		Protocol 4.2.2	Changed Appendix numbering. Changed spouse dyad language.
		Protocol 5.3	Changed “ultrasound-guided” to “ultrasound-visualized.”
		Protocol 6.1	Clarified possibility of randomization to a sham study group. Added language to clarify recruiting process.
		Protocol 6.2.2	Specified no AHLA encounter entered.
		Protocol 6.2.2.4	Clarified DRP.
		Protocol 6.2.3	Deleted Joggle text.
		Protocol 6.2.3.2	Clarified use of PCL-5 and PCL-C.
		Protocol 6.2.3.5	Deleted AUDIT scoring range.
		Protocol 6.2.3.6	Deleted K6 scoring range.
		Protocol 6.2.3.7	Deleted PHQ-9 scoring range.
		Protocol 6.2.3.8	Deleted GAD-7 scoring range.
		Protocol 6.2.3.10	Inserted references.
		Protocol 6.2.3.12	Deleted Joggle text.
		Protocol 6.2.3.13	Changed to 6.2.3.12. Changed Appendix numbering.
		Protocol 6.3	Deleted Joggle text. Changed Appendix numbering. Clarified MEDCOM 40-54.
		Protocol 6.4	Changed Appendix numbering.
		Protocol 6.4.13	Clarified command contact information to be listed and text of messages.
		Protocol 6.5.1.1	Changed Appendix numbering.
		Protocol 6.5.1.2	Changed Appendix numbering.
		Protocol 6.5.1.3	Changed Appendix numbering.
		Protocol 6.5.2	Changed Appendix numbering. Clarified burden for qualitative data collection. Clarified purpose of audio recordings.
		Protocol 7.2	Clarified Research Monitor notification.
		Protocol 8.2	Deleted Joggle text.

Protocol version	Protocol Date	Section(s) revised	Description of revision(s)
		Protocol 9.1.3.1	Changed Appendix numbering.
		Protocol 9.1.3.2	Changed Appendix numbering.
		Protocol 9.1.4	Clarified confidentiality of participants in group settings.
		Protocol 9.3.1	Deleted “routine.”
		Protocol Table 1	Deleted Joggle. Added PCL-C to screener.
		Protocol Table 3	Added NVivo 9 citation.
		Protocol References	Added References from protocol section 6.2.3.10.
		Appendix 1	Added PCL-C to screening.
		Appendix 3	Language clarifications. Revised questions 4 and 10. Added PCL-C.
		Appendix 10	Language clarifications.
		Appendix 17	Deleted; Joggle items.
		Appendix 18	Re-numbered to Appendix 17.
		Appendix 19	Re-numbered to Appendix 18.
		Appendix 20-1	Re-numbered to Appendix 19-1.
		Appendix 20-2	Re-numbered to Appendix 19-2. Updated dates.
		Appendix 20-3	Re-numbered to Appendix 19-3.
		Appendix 20-4	Clarifications. Re-numbered to Appendix 19-4.
		Appendix 20-5	Re-numbered to Appendix 19-5.
		Appendix 20-6	Re-numbered to Appendix 19-6.
		Appendix 20-7	Re-numbered to Appendix 19-7.
		Appendix 20-8	Re-numbered to Appendix 19-8.
		Appendix 20-9	Re-numbered to Appendix 19-9.
		Appendix 20-10	Re-numbered to Appendix 19-10.
		Appendix 20-11	Re-numbered to Appendix 19-11.
		Appendix 21-1	Language clarifications. Deleted Joggle text. Simplified language. Re-numbered to Appendix 20-1.
		Appendix 21-2	Provided contact number. Re-numbered to Appendix 20-2.
		Appendix 21-3	Provided contact number. Re-numbered to Appendix 20-3.

Protocol version	Protocol Date	Section(s) revised	Description of revision(s)
		Appendix 21-4	Provided contact number. Re-numbered to Appendix 20-4.
		Appendix 21-5	Re-numbered to Appendix 20-5.
		HIPAA Waiver	Clarified intent of waiver.
		Addendum Section 2 (Effectiveness Trial Recruitment)	Described recruitment strategy.
		Addendum Section 2 (Acceptability Study Recruitment)	Described recruitment strategy and group assignment. Revised Spouse Dyad eligibility.
		Addendum Section 3 (Consenting for Initial Screening)	Described consenting process for initial effectiveness study screening.
		Addendum Section 3 (Effectiveness Trial Consenting)	Described consenting process for effectiveness trial.
		Addendum Section 3 (Acceptability Study Consenting)	Described consenting process for acceptability study.
		Addendum Section 4	Clarified need for participant referral.
		Addendum Section 6	Clarified terms of records retention.
		Addendum Section 8	Clarified standard behavioral health care requirements.

11

Amendment 2 October 23, 2015	Protocol 4.1.3	Deleted pre-existing Horner's syndrome as study exclusion criterion.
	Protocol 6.2.1	Deleted pre-existing Horner's syndrome as study exclusion criterion. Clarified role of clinician in determining whether an individual

		with pre-existing Horner's syndrome should be excluded from the study.
	Protocol 6.4.13	Text addition regarding participant messaging when suicidal ideation is identified during online assessments.
	Protocol 7.2	Text addition to address potential risk to subjects in the event that they learn they were randomized to sham.
	Protocol 9.1.3	Text addition regarding suicidal/homicidal ideation and command notification.
	Protocol References	Deleted references associated with Joggle.
	Appendix 1	Deleted Joggle.
	Appendix 2	Text revisions regarding diagnosis of PTSD and additions regarding eligibility for gift cards. Clarification that those deemed ineligible for the study may still be able to get an SGB outside the study.
	Appendix 19-1	Text revisions.
	Appendix 19-3	Text revisions.
	Appendix 19-6	Text revisions.
	Appendix 20-1	Text revisions re: AHLTA and beneficiaries. Addition of text regarding the assigning of "quarters" following procedures.

12

Amendment 3 November 19, 2015	Protocol Additional Co-Investigators	Text revision.
	Protocol Synopsis	Text additions and revisions.
	Protocol 4.1.3	Text revision.
	Protocol 4.2.2	Text revision.
	Protocol 6.1	Text revision.
	Protocol 6.2.2	Text revision.
	Protocol 9.1.3	Highlighted text addition regarding suicidal/homicidal ideation and command notification.
	Appendix 2	Text revisions, primarily to clarify the remote consent and screening process.
	Appendix 19-1	Text revision.
	Appendix 19-3	Text addition.

	Appendix 19-4	Text addition.
	Appendix 19-5	Text addition.
	Appendix 19-6	Text addition.
	Appendix 20-1	Text additions to clarify that no diagnosis of PTSD will be placed in the participant's medical record.
	Appendix 20-3	Text revision.
	Appendix 20-4	Text additions.
	Appendix 20-5	Text revisions.
	Commander Letter	Text revision.
	WAMC Addendum	Personnel addition and text revision.
Amendment 4 December 1, 2015	Protocol 6.5.1.2	Text revisions.
	Appendix 10	Text deletions regarding scenario 5.
	WAMC Addendum	Text revision.
Amendment 5 January 8, 2016	Protocol 7.1, 7.2, 7.4, 7.6, 7.7	Revisions regarding HRPO reporting requirements; deletion of text regarding HSRRB.
	Protocol 7.10	Text additions summarizing HRPO reporting requirements.
	Protocol 9.1.2	Deletion of text regarding HSRRB.
	Appendix 18	Text revisions.
	Appendix 20-1	Text revisions.
Amendment 6 March 23, 2016	Protocol 3.1	Text revision.
	Protocol 6.2.1	Text revisions.
	Protocol 6.2.3	Text revision.
	Protocol 6.4.13	Text deletion.
	Protocol 6.5.1.1	Text revision.
	Protocol 7.1, 7.2, 7.4, 7.6.1, 7.6.3, 7.7	Text revisions and additions per HRPO specification.
	Protocol 7.5	Text deletion.
	Protocol 7.10	Text additions per HRPO specification.
	Protocol 9.1.2	Text deletion per HRPO specification.
	Appendix 2	Text addition.
	Appendix 18	Text addition regarding the importance of not

		discussing information about the study with other service members.
	Appendix 19-1	Text revisions.
	Appendix 20-1	Text addition elaborating on request that study participants not discuss study information with others.
Amendment 7 July 21, 2016	Protocol Study Locations Page	Text addition.
	Protocol Table of Contents	Added Appendix 19-12. Qualitative Study Telephone Script and Reminder Emails.
	Protocol 6.5.1.1	Text addition regarding Appendix 19-12.
	Appendix 9	Text additions.
	Appendix 19-12	Added.
	WAMC Site Specific Addendum	Text additions.
Amendment 8 (Disapproved) August 25, 2016	Protocol 6.1	Text addition.
Renumbering of Amendments Beginning Below		
Amendment 12 August 29, 2016	Protocol Synopsis	Replaced CAPS eligibility criterion with PCL-C criterion.
	Table 1	Clarification.
	Protocol 4.1.2	Replaced CAPS eligibility criterion with PCL-C criterion.
	Protocol 4.1.3	Removed concurrent psychological treatment from exclusion criteria; removed PCL-C.
	Protocol 6.2.1	Corrected CAPS text.
	Protocol 6.2.2	Removed CAPS eligibility, corrected text.
	Protocol 6.2.2.3	Corrected text.
	Protocol 6.2.3.3	Added PCL-C as eligibility criterion.
Amendment 13 (LRMC) August 12, 2016	WAMC Site Specific Addendum	Text revisions.
Amendment 14 October 11, 2016	Protocol Study Locations	Text revisions.
	WAMC Site Specific Addendum	Text additions regarding recruitment activities and revisions.

	Study Poster	Text revisions.
Amendment 15	Protocol Deviation	WAMC
Amendment 16 November 29, 2016	LRMC Site Specific Addendum	Text revisions regarding the expansion of Dr. Ryan Young's role and recruitment activities
	TAMC Site Specific Addendum	Text revisions regarding the expansion of Dr. Cuong Nguyen's role and recruitment activities
Amendment 17 January 23, 2017		Amendment retracted
Amendment 18 March 24, 2017	LRMC Site Specific Addendum	Text revisions regarding coordinator personnel change at LRMC
Amendment 19 April 12, 2017	Protocol Additional Investigators	Deletion of COL James Lynch as Co-Investigator
	Protocol 6.1	Text deletion regarding PTSD diagnosis; text additions regarding recruitment activities, role of the PI, use of POAs and mass e-mail for recruitment
	Appendix 2	Text addition of recruitment e-mails
	Appendix 19-1	Text addition of study closeout and thank you e-mail
	Appendix 19-2	Text revisions.
	LRMC Site Specific Addendum	Text deletion regarding PTSD diagnosis; text additions regarding recruitment activities, role of the PI, use of POAs and mass e-mail for recruitment
	TAMC Site Specific Addendum	Text deletion regarding PTSD diagnosis; text additions regarding recruitment activities, role of the PI, use of POAs and mass e-mail for recruitment
	WAMC Site Specific Addendum	Text deletion regarding PTSD diagnosis; text additions regarding recruitment activities, role of the PI, use of POAs and mass e-mail for recruitment
Amendment 20 June 9, 2017	Study video	Addition of study video
Amendment 21 August 4, 2017	Protocol Study Locations	Personnel title updates.
	Protocol Additional Co-	Personnel information updates.

Investigators	
Protocol Synopsis	Text revision to acceptability study design to broaden participant pool.
Protocol 2.2	Text revision to broaden participant pool.
Protocol 3.1	Text revision to allow electronic or physical gift cards.
Protocol 3.2	Text revision to acceptability study design to broaden participant pool.
Protocol 4.1.1	Text deletion to remove site enrollment limitation.
Protocol 4.2.1	Text deletion to remove site enrollment limitation.
Protocol 4.2.2	Text revision to broaden participant pool.
Protocol 4.2.3	Text clarification.
Protocol 6.1	Text deletion to remove site enrollment limitation.
Protocol 6.4	Text deletion regarding in-person follow-up visits.
Protocol 6.5.1.1	Text addition of new acceptability study recruitment methods; text clarification.
Protocol 6.5.1.2	Text clarification.
Protocol 6.5.1.3	Text revision to broaden participant pool.
Appendix 19-1	Addition of KRO and RVP.
Appendix 19-3	Text clarification and addition to broaden participant pool.
Appendix 19-4	Text clarification and revision to broaden participant pool.
Appendix 19-5	Text clarification and revision to broaden participant pool.
Appendix 19-6	Text revision to broaden participant pool.
Appendix 19-7	Text revision to broaden participant pool.
Appendix 19-8	Text revision to broaden participant pool.
Appendix 19-9	Text revision to broaden participant pool.
Appendix 19-10	Text revision to broaden participant pool.
Appendix 19-11	Text correction and revision to broaden participant pool.
Appendix 19-12	Text revision regarding gift card and addition to broaden participant pool.
Appendix 20-1	Increased checkbox size.
Appendix 20-2	Text clarification and addition.

	Appendix 20-3	Text clarification and addition.
	Appendix 20-4	Text clarification and addition.
	Appendix 20-5	Text clarification and addition.
	HIPAA Waivers	Text revision and addition for acceptability study recruitment.
	LRMC Site Specific Addendum	Removal of site enrollment limitation, inclusion of AFN for recruitment, and addition for acceptability study recruitment.
	TAMC Site Specific Addendum	Personnel information update, removal of site enrollment limitation and addition for acceptability study recruitment.
	WAMC Site Specific Addendum	Personnel information update, removal of site enrollment limitation, and addition for acceptability study recruitment.
	Data collection form	Addition of data collection form for acceptability study recruitment.
	Provider Fact sheet	Addition of a provider fact sheet as recruitment material to answer common questions.
	Patient Fact sheet	Addition of a patient fact sheet as recruitment material to answer common questions.
	Radio ad text	Addition of text for an AFN radio advertisement.
Amendment 22 August 2017	Continuing Review	
Amendment 23 September 22, 2017	Protocol 6.1	Addition of text regarding Facebook page and advertising for recruitment
	LRMC Site Specific Addendum	Addition of text regarding Facebook page and advertising for recruitment
	TAMC Site Specific Addendum	Addition of text regarding Facebook page and advertising for recruitment
	WAMC Site Specific Addendum	Addition of text regarding Facebook page and advertising for recruitment
	Facebook ad	Addition of Facebook advertisement
	AFN TV ad	Addition of AFN TV advertisement
Amendment 2.0 (numbering restarts in eIRB) March 3, 2018	Throughout protocol Protocol 8.3	Revise CAPS change from 15 to 10 Clarification of enrollment estimates Justification for CAPS change from 15 to 10

	Protocol 10	Addition of references

STUDY LOCATIONS

Womack Army Medical Center (WAMC)
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INVESTIGATOR'S AGREEMENT AND SIGNATURE PAGE

Efficacy and Patient Acceptability of Stellate Ganglion Block for Treatment of PTSD Symptoms

Protocol Issue Date:

I have read the protocol and agree:

- That the protocol contains all necessary details for carrying out the study and that I will complete the study within the time designated by RTI International.
- To assume responsibility for the proper conduct of the study according to the protocol and any other study-conduct procedures and requirements provided by RTI International.
- To read, understand, and provide the protocol to all physicians, nurses, and other study personnel accountable to me and participating in the conduct of this study.
- To ensure that all study personnel assisting me with the study are fully informed of their study-related duties and responsibilities as described in the protocol and other procedures/requirements provided by RTI International.
- That the participants will be under my personal supervision or under the supervision of an investigator responsible to me.
- Not to implement or initiate the study or make any changes to the protocol without agreement from RTI International and prior submission to and written approval from the institutional review board (IRB), except when necessary to eliminate the immediate hazard to the participants, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- To comply with all applicable regulatory requirements in the conduct and reporting of the study.
- To keep the conduct and results of this study confidential until it and all study analyses are complete.
- That RTI International and its designees shall have access to any source documents from which Case Report Form data have been collected.

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Principal Investigator's Signature Date

_____ _____

Principal Investigator's Printed Name Site

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

PROTOCOL SYNOPSIS

RTI International
3040 E. Cornwallis Road
Research Triangle Park NC 27709

Title of Study:	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
IND Number:	This is a non-IND study.
EudraCT Number:	This is a non-EU study
Study Centers Planned:	2 centers in USA 1 center in Germany
Effectiveness Objectives:	The primary objective of the clinical effectiveness trial is as follows: • to evaluate whether right-sided stellate ganglion block (SGB) performed at 0 and 2 weeks will result in a 10 point decrease in the mean Clinician Administered PTSD Scale for DSM-5 (CAPS-5) total symptom scores between baseline and 8 weeks The secondary objectives of the clinical effectiveness trial are as follows: • to evaluate whether right-sided SGB performed at 0 and 2 weeks will improve PTSD symptoms as reflected by corresponding PTSD Checklist for DSM-5 (PCL-5) items between baseline and 8 weeks • to explore the association between the main outcome and other potential confounding variables (e.g., concomitant medications, duration of Posttraumatic Stress Disorder [PTSD], post-block Horner's syndrome, etc.) • 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), depression (PHQ-9), alcohol use (AUDIT-C/AUDIT), or pain (short pain scale) between baseline and 8 weeks • to evaluate whether right-sided SGB at 0 and 2 weeks will improve physical and mental condition (SF-12) between baseline and 8 weeks

233

PROTOCOL SYNOPSIS (CONTINUED)

Effectiveness Study Design:	Blinded, multi-center, randomized, sham-procedure-controlled
Number of Participants Planned:	240
Target Population:	active-duty service members
Duration of Study:	10 weeks
Diagnosis and Main Eligibility Criteria:	Participants with PCL-C score of 32 or higher All participants must have anticipated assignment to installation for at least 2 months and have been offered an A-level modality PTSD treatment (see section 4.1.2 for definition)
Study Procedures/ Frequency:	CAPS-5 following screening (prior to week 0) and at week 8 Stellate ganglion block at weeks 0 and 2 PCL-5 and PCL-C at weeks 0, 2, 4, 6, and 8 M.I.N.I.-Plus Suicidality Items at screening and weeks 0, 2, 4, 6, and 8 K6 Scale at weeks 0, 2, 4, 6, and 8 SF-12, GAD-7, PHQ-9, AUDIT-C/AUDIT, pain scale at weeks 0, 4, and 8
Acceptability Objectives:	• to assess participants' perceptions of stellate ganglion block in relation to other PTSD treatment options • to inform communication with service members before, during, and after the procedure
Acceptability Study Design:	Qualitative study using focus groups, small group interviews, and individual interviews (both in person and over the phone).
Number of Participants Planned:	193
Target Population:	• participants in effectiveness clinical trial and their spouses • service members who have received SGB for PTSD symptoms at the participating study sites outside of the clinical trial and their spouse • providers who have referred or could potentially refer patients for SGB for PTSD symptoms at the study sites • clinicians who provide SGB for PTSD
Duration of Study:	no individual's participation will last more than 90 minutes
Main Eligibility Criteria:	• participants in effectiveness clinical trial who received at least one intervention and initial follow-up within the prior three months • service members who have received at least one SGB for PTSD symptoms at the study sites within the prior three months providers who have referred or could potentially refer service members for SGB for PTSD symptoms at the study sites • providers who perform SGB for PTSD symptoms at the study sites

234

PROTOCOL SYNOPSIS (CONTINUED)

Test Product, Dose, and Mode of Administration:	0.5% ropivacaine, 7-10 mL, under ultrasound visualization via needle ventral to right longus coli muscle (around and into the ventral fascia) and into the longus coli immediately dorsal to the presumed ventral fascia, at the level of the C6 anterior tubercle (landmarks for stellate ganglion)
Reference Therapy, Dose, and Mode of Administration:	Preservative-free normal saline, 1-2 mL, under ultrasound visualization via needle anterolateral to right anterior tubercle of C6
Study intervention:	Participants will be randomized 2:1 to either active (0.5% ropivacaine injection) or sham (normal saline injection).
Primary outcome:	CAPS-5 total symptom score
Criteria for Evaluation:	
Safety:	adverse events
Efficacy:	A 10 point decrease in mean CAPS-5 scores pre-treatment (prior to week 0) to 8 weeks post-treatment
Acceptability:	service members' and providers' decision-making processes and information needs related to stellate ganglion block
Statistical Methods:	Estimates of CAPS-5 total symptom score change between week 8 and pre-week 0 will be compared between the two treatment arms (active and sham) using a linear model that also accounts for study site, the initial (prior to week 0) CAPS-5 score, as well as potential confounding variables (e.g., concomitant medications, duration of PTSD, post-block Horner's syndrome, etc.) depending on availability. Output from the model will include adjusted point estimates of the average 8-week change in CAPS-5 symptom score for each treatment arm, the estimated average difference in the change between the two treatment arms, and corresponding 95% confidence intervals for each of these estimates, as well as a formal test of hypothesis of the difference in the scores between the two treatment arms. We will analyze the effect of SGB on clinical criteria of PTSD as measured by the PCL-5 over time. We will assess differential treatment effects at weeks 2, 4, 6, and 8. The outcome variable in each model will be the binary outcome of diagnosis and the models will account for arm classification, week and study site; two-way and three-way interactions of treatment will also be included in the model. Other secondary outcomes similarly will be assessed using linear mixed models or generalized models, as appropriate for the structure of the outcome measure.

All essential documents are being archived as required
by the study contractual agreements or protocol.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

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
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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (Continued)

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

1. INTRODUCTION

1.1. Background

1.1.1. PTSD

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). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), symptoms are generally categorized in terms of intrusive symptoms (diagnostic criterion B), avoidance (diagnostic criterion C), negative alterations in cognitions and mood (diagnostic criterion D), and alterations in arousal and reactivity (diagnostic criterion E) (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 also 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). There also is a host of related sequelae, and comorbidity with other mental health disorders is high. In particular, work impairment and decreased earnings, divorce, and difficulties with child rearing are common (Kessler, 2000), multiplying the impact of the disorder by an untold amount. Finally, PTSD often occurs together with other disorders, including depression and substance use disorders (Brady, Killeen, Brewerton, & Lucerini, 2000), further compounding the impact.

1.1.2. PTSD Treatment

Treatments for PTSD include both psychotherapeutic and pharmacologic modalities, with little existing systematic evidence for effectiveness. A 2008 Institute of Medicine (IOM) report on treatment effectiveness (2008) included a systematic review of available treatments and divided them into pharmacotherapies and psychotherapies, with an eye toward reviewing major clinical practice guidelines. At the time of publication, the research regarding the effectiveness of pharmacotherapies in the treatment of PTSD was deemed to be inadequate for making a determination of a preferred treatment. Similarly, the report found that, for all but one modality (exposure therapy), there was insufficient evidence to support the efficacy of psychotherapeutic treatments. An additional report released by the Agency for Healthcare Research and Quality (AHRQ) (Jonas et al., 2013), found similar results regarding the effectiveness of exposure therapy, but also characterized a handful of pharmacologic modalities as effective, though with significantly smaller effect sizes than exposure therapy.

Currently available treatment modalities for PTSD also have some significant disadvantages. Pharmacotherapies frequently come with side effects including, but not limited to, nausea, weight gain, headache, sexual dysfunction, and agitation. Furthermore, these medications may take up to 6 to 8 weeks of regular use before they begin to provide symptom relief (Alexander, 2012), during which time it is not uncommon for patients to develop side effects, which may result in discontinuation of the medication(s). Psychotherapeutic modalities tend to take an extended period of time to show an effect, frequently 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. Tarrier and colleagues (2006) conducted a study assessing the acceptability of different psychotherapeutic modalities for PTSD. They found that stigma associated with receiving treatment was a significant concern for study participants. Stigma has been shown to be a deterrent for service members to receive treatment for behavioral health concerns such as PTSD. In 2011, one of the key study researchers (Rae Olmsted et al., 2011) found that while all service members in their study reported stigma regarding treatment for behavioral health issues, those who had actually received behavioral health treatment perceived greater stigma associated with treatment. These researchers suggested that such stigma may result in higher likelihood of treatment failure or discontinuation (cf. Fung, Tsang, & Chan, 2010), and that those who had previously received treatment may share their perceptions with other service members, in turn dissuading those service members from seeking help should they need it. Kim and colleagues (2011) have reported similar findings.

1.1.3. Stellate Ganglion Block

Given these concerns, there is a clear need for therapies for PTSD that are safe, effective, fast-acting, with few side effects, and with good patient acceptability and adherence. Sympathetic blockade, and stellate ganglion block (SGB) in particular, is hypothesized to fill this need. 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. Sensory afferent projections from the heart and thoracic cavity to cervicothoracic dorsal root ganglia traverse the SG (Oldfield & McLachlan, 1978); second-order neurons in the ipsilateral spinal cord project to the thalamus, and via third-order neurons to the somatosensory cortex (Nozdrachev, Fateev, Jimenez, & Morales, 2003). The neurons in the paraventricular nucleus of the thalamus (PVN) appear to contact sympathetic preganglionic neurons (SPN) in the intermediolateral column of the spinal cord; those neurons project to the SG (Ranson, Motawei, Pyner, & Coote, 1998). Sympathetic postganglionic neurons then project from the SG to the heart and thoracic cavity. Other sympathetic efferents traverse the SG (Nozdrachev et al., 2003). 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 case reports and series have been published about the effectiveness of SGB in treating PTSD, but the findings are intriguing and warrant further scientific investigation. In 1990, Lebovits and colleagues (1990) described an adolescent female who had suffered multiple gunshot wounds and developed both reflex sympathetic dystrophy (RSD) and PTSD. The patient received 13 SGBs (for RSD) over 15 weeks and reported marked PTSD symptom improvement, characterized by significant reductions in intrusive memories and calmer mood. Nearly 20 years later, Lipov et al. (2008) 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 efficacy of SGB for treatment of PTSD symptoms.

1.1.4. Theoretical Models

There are few published theoretical models that seek to explain the effectiveness of SGB for PTSD. Lipov and colleagues (2009) proposed that the procedure causes its effect via an interaction between the SG and key brain areas known to modulate PTSD, including the insular cortex (Liberzon & Martis, 2006) and the amygdala (Rauch et al., 2000). This hypothesis has been challenged, however, as being based on faulty understanding of some of the explanatory

research cited by the authors (Alino, 2011). In another theoretical model, Uchida, Tateda, and Hino (2002) proposed that SGB effects are through the involvement of the pineal gland and the regulation of melatonin secretion. The authors note that their hypothesized mechanism of action is based on foundations of Oriental medicine, as opposed to Western medicine. Nonetheless, the case report and series literature provide support for the evaluation of SGB as a procedure to help ameliorate the symptoms of PTSD.

1.2. Rationale for the Current Study

Because SGB is routinely done in the military for indications such as complex regional pain syndrome, and occasionally for treatment of PTSD symptoms (i.e., approximately 25 per month at WAMC), there is an unequalled opportunity to collect data and assess the effectiveness and patient acceptability of the procedure for a relatively low cost. Though there is not compelling supporting evidence, currently SGBs are performed as treatment for PTSD at the request and referral from a behavioral health provider (BHP) or other provider. Efficacy of the treatment should be established now, before its use becomes more widespread and "accepted," and thus the conduct of a randomized, sham-procedure-controlled study becomes significantly less feasible.

In its original formulation, this study was envisioned to be fully double blinded, with the physicians performing the intervention administering 5-7 mL of study drug (either 0.5% ropivacaine or saline) at the stellate ganglion. However, in a recently presented randomized, controlled trial of SGB for treatment of PTSD (McLay et al., 2015), no differences in CAPS scores were observed between subjects who received a 7 mL 0.5% ropivacaine injection at the stellate ganglion and those who received 7 ml of normal saline superficial to the anterior tubercle of C6. The trial was smaller (42 subjects), only one of up to three SGB was placebo controlled and blinded (the first), and selection criteria were broad and included subjects with potential secondary gain. Nevertheless, it failed to meet a lower bar than afforded by a fully blinded study design. Given these data and also the fact that the injection of 5-7 mL of saline around and/or into the stellate ganglion could itself have significant (though likely brief) functional effects, addressing the question "does application of a long-acting anesthetic at the stellate ganglion have a different effect than that of an equal volume of saline on PTSD symptoms assessed by the CAPS?" seems to the Investigators a less practical and relevant question to address than "does interruption of function of the stellate ganglion with a standardized approach using a long-acting anesthetic have a different effect than a nearby sham injection (without any theoretically relevant mechanism of action) on PTSD symptoms as assessed by the CAPS?" Only the physicians administering the intervention and their immediate team will be unblinded; all other study personnel and the participants themselves will not be informed of treatment arm assignment.

In order for the benefits of SGB and other treatment to be realized, service members must be willing to initiate and engage in treatment. Individual understanding of treatment options, mechanisms, and effectiveness is a key determinant of treatment acceptability (Sayers et al., 2009; Shiner et al., 2013). However, individuals filter information about treatment options through values and beliefs that impact how information is processed and understood (Charles, Gafni, & Whelan, 1999; Charles et al., 2006). Extensive evidence supports the premise that service members' beliefs and values related to mental health treatment are powerfully influenced by military culture including their perceptions of stigma associated with mental health issues and treatment (Vogt, 2011). Therefore, we have integrated a concurrent qualitative study into the

clinical trial to examine the benefits and drawbacks of SGB in comparison to other treatment options for PTSD.

Should SGB be demonstrated to be effective, findings from the qualitative study will inform communication about the procedure between providers and service members. Our findings will also contribute to efforts to encourage utilization of other evidence based PTSD treatments.

2. OBJECTIVES

2.1. Clinical Effectiveness Trial

The primary objective of the effectiveness study is:

- to evaluate whether right-sided SGB performed at 0 and 2 weeks will improve the CAPS-5 total symptom scores between baseline and 8 weeks

The secondary objectives of this study are:

- to evaluate whether right-sided SGB performed at 0 and 2 weeks will improve PTSD symptoms as reflected by corresponding PCL-5 items between baseline and 8 weeks
- 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.)
- 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), depression (PHQ-9), alcohol use (AUDIT-C/AUDIT) or pain (short pain scale) between baseline and 8 weeks
- to evaluate whether right-sided SGB performed at 0 and 2 weeks will improve physical and mental (SF-12) condition between baseline and 8 weeks

2.2. Acceptability Study

- to assess perceptions of SGB in relation to other PTSD treatment options among service members who have received the procedure and inform communication with service members before, during, and after the procedure.

3. STUDY DESIGN

3.1. Clinical Effectiveness Trial Treatment Plan and Regimen

This will be a multisite, randomized, blinded, sham-procedure-controlled study to evaluate the efficacy 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. Randomization will be stratified by site so that each will have a 2:1 active:sham ratio.

On the day of the procedure, clinic nursing staff will perform standard nursing intake to include brief interim history, review of systems, vital signs, and placement of intravenous catheter. The attending physician will perform a targeted history and physical, paying attention to potential contraindications to SGB (e.g., infection at the site of injection, current anticoagulated state, presence of mass distorting the tissues, recent myocardial infarction, contralateral phrenic nerve palsy, glaucoma). The physician will also give a brief explanation of the procedure as well as a review of risks and potential benefits, though these will have been described to the participants beforehand.

Injections will be performed under ultrasound visualization. The study medication will be either 7-10 mL 0.5% ropivacaine injected ventral to the right longus coli muscle (around and into the ventral fascia) and into the longus coli immediately dorsal to the presumed ventral fascia at the level of the C6 anterior tubercle (landmarks for the stellate ganglion) (active study medication) or 1-2 mL preservative free normal saline injected anterolateral to the anterior tubercle of C6 (sham procedure). The participant will not be informed which treatment he or she has received; the interaction of the participant and treating physician will be scripted as much as possible. Customary vital signs will be recorded. MEDCOM 40-54 dated Feb 09 provides “a standard process and procedure for surgical and procedural site verification of patients undergoing operative or other invasive procedures”. In accordance with this regulation, the participant’s identity, the procedure to be performed, and the specific site of the procedure will be verified. A separate paper Case Report Form (CRF) will be created for the procedure; this information will not be shared with anyone outside the treatment suite (Research Coordinator (RC), participant, other members of the RTI project team, etc.). It is critical that only the physician administering the treatment (and his immediate team) be aware of the participant’s assignment to active or sham intervention. Following the intervention, the treating physician should have no further contact with the participant except as required for participant safety. At no point in time during the conduct of the trial should the physician or treatment team disclose by verbal or non-verbal communication the intervention received by the participant. Once an individual participant completes their participation in the trial, they may be offered an unblinded standard SGB as clinically indicated, but they will remain blinded to their treatment arm. After an individual participant completes their portion of the study (i.e., after completion of the Week 8 instruments and their second CAPS-5), if an independent clinician providing care to the participant needs to know the intervention assignment of that particular participant in order to make clinical treatment decisions, a request may be made to the study PI (Dr. Walters) for unblinding. Dr. Walters (blinded) will evaluate the request and, if granted, will notify an

unblinded RTI colleague to provide the intervention information to the clinician for use in clinical decision-making; the clinician, however, is not to disclose the participant's intervention information to anyone else.

Immediately following the procedure, the participant will be observed in the procedure suite prior to transport to the recovery area for assessment of potential complications that could require immediate intervention, according to local clinic policy. They then will be taken to the post-procedure recovery area, where monitoring of vital signs will continue under the supervision of the recovery nurse for 20 minutes or longer, as dictated by clinic policy and participant condition. The study RC will use metrics to assess for a Horner's syndrome (Section 6.3). A successful block will be recognized by the RC and perhaps by the participant (although we are unaware of data pertaining to possible signs and symptoms from saline injection near the SG). The RC will not share outcome information with the physician or the participant. While we cannot completely prevent the possibility of inadvertent un-blinding of study participants who may be familiar with the significance of developing signs and symptoms of SGB, no implicit or explicit confirmation will be given to the participants by the research team. This is a limitation of the proposed study and indeed any study with participant-accessible outcomes following an intervention.

Study intervention will be administered at week 0 and at week 2.

Participants will be evaluated for PTSD symptomatology prior to week 0 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), the PTSD Checklist – Civilian Version (PCL-C), and the M.I.N.I.-Plus Suicidality Items at 0, 2, 4, 6, and 8 weeks; they also will complete the M.I.N.I.-Plus items 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.

Table 1. Assessment Schedule

	Screener	Baseline	2 Weeks	4 Weeks	6 Weeks	8 Weeks
CAPS-5 and LEC-5	X*					X
PCL-5		X	X	X	X	X
PCL-C	X	X	X	X	X	X
M.I.N.I.-Plus SI Items	X	X	X	X	X	X
AUDIT-C/AUDIT	X	X		X		X
K6		X	X	X	X	X
PHQ-9		X		X		X
GAD-7		X		X		X
SF-12		X		X		X
Short pain scale		X		X		X
Current medications		X		X		X

*Not an inclusion/exclusion criterion despite being administered before baseline.

Individuals who participate in study assessments during off-duty hours will be eligible for payments as follows:

1st CAPS interview: $15
Week 0 assessment: $10
Week 2 assessment: $10
Week 4 assessment: $15
Week 6 assessment: $15
Week 8 assessment: $15
2nd CAPS interview: $15
Qualitative Interview: $20

Payment will be in the form of Amazon or Visa gift cards.

3.2. Acceptability Study Design

The qualitative study will use focus groups, small group interviews, and individual interviews to compile a range of perspectives on service members' decision-making processes and information needs related to SGB. Participants will include service members, spouses, and providers. Data collection will occur at each study site because attitudes conveyed by leadership and chain of command may vary across installation. Scheduling will be based on the accumulation of ample service members indicating an interest in participating.

Participating service members will have received at least one SGB and/or study procedure within the prior 3 months, although this interval may be expanded if necessary for recruitment into focus groups. Because all study staff (with the exception of the physicians administering the study intervention) are blind with respect to treatment status, participants will include participants from both active and sham procedure arms. To increase homogeneity within focus groups and avoid potential distress among participants who do not experience symptom relief, groups will be stratified based on positive versus neutral or negative subjective assessment of change at the 4-week assessment (see Section 6.4.12) or at the time of screening for the qualitative study. Because beliefs and attitudes related to behavioral health treatment are likely to vary according to pay grade, separate groups will be held for lower enlisted service members and NCOs. Officers, if available as participants, will be interviewed individually. Data collection will address perceived benefits and drawbacks of SGB and other treatment options for PTSD; information needs before, and during the procedure; and participants' description of the effects of the procedure.

Spouses may have questions and concerns regarding SGB and other treatment options that differ from those of their service members. Spouses can also provide input that may vary from that which is perceived or reported by service members. All married service members and their spouses will be eligible to participate in a participant-spouse interview. Data collection with spouses will be conducted in joint interviews, in which both members of the couple are interviewed at the same time by one interviewer. Interview topics will parallel those used in the service member focus groups. Joint interviews will avoid the risk of inadvertent breach of confidentiality among spouses. They will also allow comparison of the perspectives of the spouse and the service member.

Providers will include physicians who administer SGBs, and both Behavioral Health providers and other (e.g., Family Medicine) physicians who have or could potentially refer service members for the procedure. Data collection with providers will consist of small focus

groups, addressing provider views of how SGB complements or adds to available modalities, and how the procedure should be communicated to service members. If scheduling small focus groups with providers is unfeasible, we will conduct individual interviews with providers according to their availability.

Focus groups, small group interviews, and individual interviews will be scheduled to best accommodate the participants. This will include evenings and weekends if these are deemed to be the most appropriate time. Active duty participants will be reminded that in order for them to be given an incentive for taking part in this component of the study, their participation must be on their own time. Those who participate in the acceptability study on their own time will receive a $20 Amazon or Visa gift card following the completion of their participation.

4. PARTICIPANT POPULATION

4.1. Clinical Effectiveness Trial

4.1.1. Number of Participants

A total of up to 240 participants will be enrolled at the three sites.

4.1.2. Inclusion Criteria

Participants must meet *all* of the following inclusion criteria to be eligible for participation in this study.

- 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). A-level psychotherapies are defined as individually provided "trauma-focused psychotherapy that includes components of exposure and/or cognitive restructuring; or stress inoculation training" (Narration/imaginal exposure; cognitive restructuring; in-vivo exposure; relaxation or stress modulation skills; psychoeducation). Relevant manualized treatments include Prolonged Exposure Therapy, Cognitive Processing Therapy, and Eye Movement Desensitization and Reprocessing. A-level pharmacotherapies include Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors, as well as adjunctive prazosin.
- PCL-C score of 32 or greater at screening
- Acceptable clinically indicated preoperative laboratory studies, per standard site-specific protocols

4.1.3. Exclusion Criteria

Potential participants who meet *any* of the following exclusion criteria are not to be enrolled in this study.

- Prior SGB
- Allergy to amide local anesthetics (e.g., ropivacaine, bupivacaine)
- Pregnancy (evaluated by urine test pre-procedure)
- 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 Items
- 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, significant illness in participant or family)

4.2. Acceptability Study

4.2.1. Number of Participants

A total of up to 193 participants across the 3 sites will be enrolled in the qualitative study. Participants will include up to 131 service members, up to 14 spouses of service members, and up to 48 providers. The expected allocation of participants by pay grade and subjective assessment of change is shown in **Table 2**. These numbers will be adjusted to proportionally reflect study participants.

Table 2. Number of Participants in Qualitative Study

		Total					
		Reporting Improvement		No Improvement		Total	
		Groups	Individuals	Groups	Individuals	Groups	Individuals
Service members							
	Lower enlisted	8	48	4	24	12	72
	NCOs	3	18	3	18	6	36
	Officers		6		3		9
Service member/ spouse interviews							
	Lower enlisted	6	12	6	12	12	24
	NCOs	1	2	1	2	2	4
Providers							
	Family Medicine					4	16
	Behavioral Health					4	16
	SGB Physicians					4	16

		Total					
		Reporting Improvement		No Improvement		Total	
		Groups	Individuals	Groups	Individuals	Groups	Individuals
Total		18	86	14	59	44	193
	Service members						131
	Spouses						14
	Providers						48

4.2.2. Inclusion Criteria

The following inclusion criteria apply to the qualitative study:

- Service members must have received at least one SGB and/or study procedure during the past three months at a participating study site (as a participant in the clinical effectiveness trial or outside of the study)
- For clinical trial participants, they must have indicated willingness to participate in the qualitative study when asked by the RC at baseline data collection
- For non-clinical trial participants, they must be active-duty status
- A service member/spouse dyad will consist of a service member meeting the above criterion and his/her spouse, when the spouse has responded to the fact sheet describing the study (**Appendix 19-5**, given to the service member at screening)
- Providers will be Behavioral Health or other (e.g., Family Medicine) clinicians who have referred orcould potentially refer service members to the study, and physicians who administer SGBs.

4.2.3. Exclusion Criteria

Service members will be excluded from the qualitative study if participation would cause them undue distress, in the opinion of the RC or treating clinician.

5. STUDY DRUGS

5.1. Randomization and Blinding

Participants eligible for the study will be randomized to either the sham or active treatment. Randomization will be conducted using a permuted block design and stratified by site to ensure that the 2:1 active:sham ratio is achieved at each center.

The control will be a sham injection of saline near the SG. The physicians administering the intervention will perforce be unblinded. However, all others involved in the trial (RC, participants, RTI study personnel, etc.) will be blind to the administered treatment, and the sole interaction of the participants with the treating physicians will be in the treatment suite (except as required for participant safety). Also, the RC will not discuss the post-procedure presence or absence of a Horner's syndrome with the Investigator or participant.

5.2. Description and Handling of Study Drug

Ropivacaine hydrochloride 0.5% for injection is FDA approved for use in SGB. Sterile normal saline for injection also is commercially available. There will be site-specific protocols for drawing up the study drug; these will produce sufficient documentation to identify which participants received active or sham intervention.

5.2.1. Formulation

The sterile saline for injection and ropivacaine will be used as commercially formulated and approved.

5.2.2. Packaging and Labeling

Packaging and labeling of ropivacaine and saline will be per site procedure and protocols. The syringes used to administer the active and sham interventions will be indistinguishable by the participants.

5.2.3. Storage and Handling

The storage and handling of the agents will be per site procedures and protocols.

5.3. Dosage and Administration of Study Drug

The study drug (7-10 mL 0.5% ropivacaine or 1-2 mL saline) will be administered by the site Investigator per the ultrasound-visualized protocol used at the site.

6. STUDY PROCEDURES (APPENDIX 1)

6.1. Participant Enrollment and Treatment Assignment

Participants will be active duty service members who meet inclusion criteria (as described above). Based on our power calculations, we anticipate enrolling approximately 240 participants (80 per site) into the trial, with 160 being randomized into the active arm and 80 into the control arm. Assignment to active or sham will be stratified per site.

At each of the three study sites, a qualified Research Coordinator (RC) will be staffed by the project to oversee all recruiting, screening, enrollment, and assessment activities. While these activities will generally be considered the RC's responsibility and will primarily be completed by the RC, the site PI and approved RTI staff may also complete all recruiting, screening, enrollment, and assessment activities. For conventional forces, the primary mechanism for recruitment will be through Behavioral Health providers (BHP) or Family Medicine or other physicians within the installation referral area. They will identify individuals whom they think are good candidates for participation in the clinical trial and then briefly explain the study. If the service member is interested in participating, then the provider will give the individual an interest card on which contact information can be written (Name, email address, phone number). These interest cards will be kept by the providers and the RC will collect them periodically. The interest card also will have the email address of the RC. If the individual prefers he/she can simply email the RC to indicate interest rather than filling out the interest card.

We will also post the study's approved poster at appropriate locations and send both approved poster and e-mail (**Appendix 2**) through the study sites' social media outlets, as well as in bulletins, newsletters, listservs, mass e-mail, an Armed Forces Network (AFN) advertisement, and other electronic means. We will go through proper approval channels for official military outlets. RCs may disseminate approved study materials at various locations where approval to do so has been obtained. Examples may include but are not limited to on-post events where service members, spouses, or others may be present; presentations to Family Readiness Groups and similar organizations; and distribution of study materials at locations within the facilities where large numbers of people are known to pass. We will post approved material on a study Facebook page and ads including only approved materials via Facebook advertising. Additionally, we will engage Public Affairs Officers (PAO) at each study site to promote the study via approved news/press and other electronic means.

We also anticipate that some individuals may "self-refer" to the study as a result of having seen one of the posters or interest cards that may be displayed at the clinics or simply by word of mouth. If these "self-referrers" contact either the local RC or other study staff, they will be thanked for their interest and then informed that in order to take part in the study, they need to be referred by a mental health or medical provider. For USASOC, there are two potential referral routes. First, currently there are WAMC Behavioral Health assets embedded within USASOC; that is, when Dr. Bartoszek briefs the WAMC Behavioral Health providers, the USASOC-embedded assets will be included. Second, unit assets within USASOC will be made familiar with the study's protocols and will refer appropriate individuals to the study RC.

The RC will contact by telephone (**Appendix 2**) those who have expressed interest in the study, to explain the study, including the possibility of being randomized to a sham group, 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 basic eligibility (i.e., lack of prior SGB procedure, currently on active duty, with access to the Internet, no plans to transfer to a different installation in the coming 2 months, not undergoing medical board/retirement, and not undergoing UCMJ or pending legal administrative actions; also **Appendix 2**). Those who pre-screen by phone as ineligible will be thanked for their time and will not be contacted again for the study. Participants who pre-screen as eligible and are located geographically close to the study site will be asked to come to the RC's office to complete the consenting process in person, and to complete computer-based screening which will assess our other study inclusion and exclusion criteria. We expect this to be the majority of our participants.

However, because our study sites provide coverage for large geographic areas, we also likely will encounter some potential participants who are located a considerable distance from the study site, to the degree that it is impractical for them to physically come to the RC's office for the screening assessment, only to return home to wait for their CAPS phone interview. Consent will be obtained and documented as described below, and then these participants will be asked to complete the screening questions on-line or via telephone.

- An electronic copy of the ICF will be made available to the potential participant via the study website or email.
- The potential participant will be asked to print out a copy of the ICF.
- The RC will contact the potential participant and go through the consent form in detail to insure that the potential participant has read it. The RC will answer any questions.
- The RC will ask for a verbal consent from the potential participant and have that verbal consent confirmed by a witness who is with the participant.
- The RC will ask the participant and the witness to sign the ICF and return the signed signature page of the ICF to RTI in one of the following ways: 1) scan the page and upload it via RTI's secure web system, 2) fax the ICF to the RC, 3) take a photograph of the page with a mobile phone or digital camera and upload it via RTI's secure web system, or 4) return the page via mail.
- If the participant is deemed eligible and comes into the RC's office for the baseline interview, he/she will be asked to initial and sign a new (and newly witnessed) copy of the consent form before beginning the assessment.

6.2. Pre-Treatment Assessments

6.2.1. Screening Visit

Participants will be screened within 4 weeks prior to randomization to determine eligibility for participation in the study. The following will be performed and documented at screening in the RC's office, or over the phone if the participant is unable to make a dedicated screening trip to the RC's office (**Appendix 3**):

- Obtain written informed consent (see below for subjects unable to come to RC's office)

- Assessment of eligibility (see inclusion criteria [4.1.3] and exclusion criteria [4.1.4])
- Demographics and screening medical history performed by participant on RC laptop (**Appendix 3**)
- Life Events Checklist-5 (LEC-5; **Appendix 4**), PCL-C (**Appendix 6**), M.I.N.I.-Plus Suicidality Items (**Appendix 7**), AUDIT-C/Audit (**Appendix 8**) – performed by participant on RC laptop

Participants meeting all of the inclusion criteria and none of the exclusion criteria will be scheduled for a baseline CAPS-5. Following administration of the CAPS-5, the RC will contact RTI to randomize the participant and will schedule the participant's return to the clinic within 4 weeks at week 0, their treatments in the clinic at weeks 0 and 2, their Web follow-ups at weeks 4, 6, and 8, and their post-treatment CAPS-5 at week 8.

Participants who are not eligible for the study will be so informed, and if they choose this information will be provided back to their referring healthcare provider.

Because some study participants are physically located at a distance from the study site, it is possible that some may need to complete their screening remotely. In these instances, the prospective participant will receive the same screening content as those who are located locally and can complete the assessment in the RC's office; however, they will provide their consent over the phone and then the screening will be performed by the RC. In addition, pre-existing Horner's syndrome will be assessed at the first study visit (i.e., week 0) when they present for their initial study condition. At that time, intervening physicians will use their clinical judgment to determine whether an individual with a pre-existing Horner's syndrome would be at increased risk from participating in the study. (Note that we expect presentation with a pre-existing Horner's syndrome to be very rare - Dr. Bartoszek has indicated that he has never seen this in a patient.) If it is determined by the intervening physician that the reason for the Horner's syndrome represents a risk to a study participant, the physician will inform that individual that they are ineligible and will answer any questions the individual might have.

6.2.2. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Appendix 9)

The primary outcome measure will be the Clinician-Administered PTSD Scale, or CAPS-5 (Weathers et al., 2013) (**Appendix 9**), which is the gold standard in clinical PTSD assessment. The CAPS-5 clinical interview 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.

As part of the trauma assessment, the CAPS-5 includes the Life Events Checklist, or LEC-5 (Weathers et al., 2013). The LEC-5 is a 17-item self-administered checklist of potential traumatic events. The CAPS-5 is our central outcome measure in support of primary objective 1. No notes will be added to a participant's medical records record regarding the CAPS-5 assessment, as the clinicians administering the CAPS-5 will be subcontractors to RTI and will not have access to medical records.

6.2.2.1. CAPS-5 Administration

The LEC-5 will be administered at the time of initial screening by the RC. These data will be uploaded to a secure website accessible by the clinical interviewer (CI) in preparation for the CAPS-5 interview. The CAPS-5 was designed to be administered by clinicians and clinical researchers who have a working knowledge of PTSD, and will be conducted over the telephone by trained CIs, who will record all notes and clinical information on hardcopy CAPS-5 forms.

6.2.2.2. Field Preparations: Clinical Interviewer Recruiting and Training

Necessary CI credentials will include having completed doctoral coursework in clinical psychology, a willingness to participate in study training, and a willingness to meet specific scheduling requirements for the position. Study CIs will be recruited from a pool of approximately 100 seasoned veteran CIs located throughout the United States who meet these criteria. These CIs have completed hundreds of diagnostic interviews over the telephone for both the NSDUH Mental Health Surveillance Study (2008-2012) and the Group Project for Holocaust Survivors and Their Children (2013). Based on experience hiring CIs of this caliber for the NSDUH Mental Health Study, the NSDUH Clinical Validation Study, and the National Vietnam Veterans Longitudinal Study, we anticipate between 20% and 30% CI attrition; therefore, we will train two more CIs than our goal of four for data collection.

6.2.2.3. Clinical Quality Control

CAPS-5 training and clinical quality control will be led by a credentialed, licensed, and experienced clinical supervisor (CS) with expertise in PTSD and the CAPS-5. The CS will review 100% of hard-copy study clinical interview notes, item-by-item, comparing the notes provided by the CI and the scoring, and listening to the accompanying audio files as needed to ensure data accuracy. The CS will also review the full audio recordings for a randomly selected 10% of the clinical interviews.

6.2.2.4. Managing Distressed Respondents During CAPS-5 Administration

A number of measures will be taken to enhance the safety of potentially distressed participants during telephone CAPS-5 administration. First, we will provide explicit protocols for CIs to follow if they encounter either passive or active suicidal or homicidal thoughts. Training and supervision will be provided for managing respondents who express sadness, agitation, frustration, or any other strong emotion during the course of the clinical interview. A detailed Distressed Respondent Protocol (DRP) (**Appendix 10**), which has been successfully used for the NSDUH Mental Health Surveillance Study, will be employed for this study. The DRP provides definitions and examples of five types of distressed respondents, along the continuum of no risk of harm (i.e., respondent is agitated or upset) to imminent danger (e.g., respondent reports active suicidal thoughts, a plan, and a means to carry out that plan). The DRP then gives step-by-step instructions for handling each of the five types of distressed respondents. CIs will be thoroughly trained in the use of the DRP.

The DRP will be very similar to the system described in Section 6.4.13 regarding management of distressed participants during automated assessments. Clinical interviewers will inform individuals at the beginning of the CAPS-5 that they need to obtain the individual's physical location (address) for the purposes of safety, that such information will not be stored, and that it will only be used in the case of an emergency. In the event that a respondent indicates

active suicidal or homicidal ideation during their CAPS-5, the clinician administering the CAPS-5 will call or (in the event that keeping the respondent on the phone is advisable) send a text message to study co-investigator Kristine Rae Olmsted and study logistics director Russ Vandermaas-Peeler indicating the nature of the ideation, physical location of the respondent (if known), and contact information for the respondent. Ms. Rae Olmsted or Mr. Vandermaas-Peeler will immediately call the respondent's CQ/duty phone number, CO, or 1SG to report the incident. Given the emergent nature of *active* suicidal or homicidal ideation, we believe that using text messaging and/or telephone communications is justified.

A second measure taken to enhance participant safety relates to the credentials of our CIs and the CS. Our study CIs will be seasoned clinicians with experience assessing risk and providing direct care for distressed individuals. Similarly, the CS will be a licensed clinical psychologist and certified health care provider. This supervisor will be integrally involved in supervising the CIs so that if a distressed respondent is encountered, his/her level of risk can be verified, and consultation and debriefing can be provided. After each encounter with a distressed respondent, the CI will immediately contact the supervisor to review the details of the incident, the assessment of risk, and the application of the DRP. If unusual circumstances arise, the supervisor will contact the study director and IRB.

Together, these methods have been effective and allowed us to properly handle 201 incidents of distressed respondents in the NSDUH Mental Health Surveillance Study, which included cases involving suicidal ideation (n=155), homicidal ideation (n=4), and respondents who were agitated or upset (n=42).

6.2.3. Baseline Assessments (Week 0, immediately before SGB)

All instrument assessments in the following section will be administered via secure computer. Paper-and-pencil (PAPI) versions of the assessments will be available in the event that Internet services should be interrupted at a study site. If use of PAPI assessments becomes necessary, the RC will hand-key the participant's data upon restoration of Internet services; the original forms will be sent to RTI via a secure FTP site so that a second person can review the RC's data entry for accuracy.

6.2.3.1. Urine Pregnancy Test for Females of Child-bearing Potential

A urine pregnancy test will be performed on all females of child-bearing potential. A positive test will end participation in this study.

*6.2.3.2. PTSD Checklist for DSM-5 (PCL-5; **Appendix 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). Data on a clinically meaningful change are not yet available, nor are full psychometrics. We will administer the PCL-5 at baseline in order to be consistent with our use of the CAPS-5, and in order to establish a baseline score in support of secondary objective 1. (Note that we are including the instrument in this study at all assessment time points, despite its current lack of psychometric testing and clinically meaningful change data, because it represents the most up-to-date standard of self-administered PTSD assessment.) We anticipate that full psychometrics will be available for our final data analysis in 2017.

*6.2.3.3. PTSD Checklist - Civilian Version (PCL-C; **Appendix 6**)*

There are three versions of the PCL for DSM-IV, including the PCL-C for civilians. This standardized assessment comprises 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 (Convbeare, Behar, Solomon, Newman, Borkovec, 2012; Weathers et al., 1993). Because data regarding clinically meaningful change are unavailable for the PCL-5, and because full psychometrics for the PCL-5 are not yet available, we will be administering the PCL-C at baseline in order to establish study eligibility as well as a baseline score in support of secondary objective 1.

*6.2.3.4. Mini-International Neuropsychiatric Interview (M.I.N.I.)-Plus Suicidality Items (**Appendix 7**)*

The M.I.N.I.-Plus is a structured interview for diagnosing DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998). This study will use a subset of items from the full instrument geared toward identifying individuals experiencing suicidal ideation in the past 2 months. 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. Individuals answering affirmatively to any of the first 7 items regarding suicidal ideation in the previous 2 months 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.

The suicidal ideation assessment will be administered at initial screening so as to identify (and exclude) individuals deemed to be at elevated risk for suicide attempt. Those who screen positive on the M.I.N.I.-Plus items, who are then asked the follow-up items regarding current ideation, will be excluded from the study; they will be evaluated and managed per the appropriate site-specific Standard Operating Procedure (SOP). The assessment will also be administered on weeks 0, 2, 4, 6, and 8. Because screening will already have taken place, these enrolled participants will still be included in the study. This instrument will enhance participant safety and support secondary objective 3.

*6.2.3.5. AUDIT-C/AUDIT (**Appendix 8**)*

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).

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. In order to decrease participant burden, we will administer the AUDIT-C first; only those screening positive on these items will receive the remaining 7 items of the full AUDIT. It is administered in support of secondary objective 3.

*6.2.3.6. K6 (**Appendix 11**)*

The K6 was developed for use in the U.S. National Health Interview Survey (NHIS) as a means of assessing nonspecific psychological distress. While this study's active duty military population with PTSD may not be representative of the U.S. general population (Kessler et al., 2003; Kessler et al. 2002), we are including the K6 so as to assess any changes in serious psychological distress over time among study participants (secondary objective 3).

*6.2.3.7. PHQ-9 (**Appendix 12**)*

Depression symptoms will be assessed using the validated PHQ-9 (Kroenke, Spitzer, & Williams, 2002) in support of secondary objective 3. 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 (Kroenke, Spitzer, & Williams, 2001; Kroenke & Spitzer, 2002; Löwe, Unutzer, Callahan, Perkins, & Kroenke, 2004).

*6.2.3.8. GAD-7 (**Appendix 13**)*

Generalized anxiety symptoms will be assessed via the GAD-7 (Spitzer, Kroenke, Williams, & Löwe, 2006) in support of secondary objective 3. The instrument was designed to be administered in general health settings as part of the Primary Care Evaluation of Mental Disorders (PRIME-MD) assessment (Spitzer et al., 1994), and has been validated by a number of studies (Spitzer et al., 2006; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007).

*6.2.3.9. SF-12 (Version 2.0) (**Appendix 14**)*

The SF-12 is a shortened version of the SF-36, which was designed as a general health utility index. Consisting of 12 items, the SF-12v2 improves on the original SF-12 and includes simplified wording, better usability, and multi-level response options. 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; SF-36.org, n.d.). This assessment will be used as a measure of general functioning in support of secondary objective 4.

*6.2.3.10. Short pain scale (**Appendix 15**)*

Because pain frequently presents with PTSD and may play a confounding role in treatment effectiveness (Beck & Clapp, 2011; Kulich, Mencher, Bertrand, & Maciewicz, 2000; Moeller-Bertram, Keltner, & Strigo, 2012), we will administer a 0-10 Likert-type numeric pain scale where 0 represents "No pain," 5 represents "Moderate pain," and 10 represents "Worst possible pain." While Visual Analog Scales, Verbal Rating Scales, and Numeric Rating Scales have all been deemed valid and reliable (Williamson & Hoggart, 2005), we opted for a numeric scale due to prospective study participants' likelihood of being familiar with the scale, which is commonly used in clinical practice at the three participating study sites. The pain scale will be administered in support of secondary objective 3.

*6.2.3.11. Current Medications (**Appendix 16**)*

In order to assess the potential impact of medication use concurrent with study participation, we will ask study participants about their use of prescription psychotropics (including stimulants, anxiolytics, and depressants), anticonvulsants, anticholinergic drugs, and sympathomimetics/sympatholytics. Given that the mechanism of action of SGB is unknown but likely involves some combination of central, peripheral, and autonomic pathways, use of these medications could be confounding. These data will be collected to support secondary objective 2.

*6.2.3.12. Other Questions (**Appendix 17**)*

Additional questions will be asked at week 0 that are not part of an established, standardized assessment. In order to determine whether duration of PTSD symptoms moderate any treatment effects that may be seen in our study, we will ask study participants whether they have been diagnosed with posttraumatic stress (PTS) or posttraumatic stress disorder (PTSD), and if so, the month and year when they received this diagnosis. For those who indicate that they have not been diagnosed, we will ask for the approximate month and year when their symptoms started.

Similarly, because nicotine has a direct impact on the sympathetic nervous system, we will ask study participants four items that will allow for calculation of estimated pack years for cigarette smoking. These items will establish age at initiation of regular smoking, smoking longevity (whether they have smoked at least 100 cigarettes in their lifetime), recency of regular smoking, and number of cigarettes typically smoked. The resulting pack-year estimate will be assessed for any moderation of treatment effects among study participants. A similar estimate will be computed for chewing tobacco, snuff, or other smokeless tobacco exposure.

6.3. Treatment and Treatment Assessments (Weeks 0 and 2)

The PCL-5, PCL-C, K6, and the M.I.N.I.-Plus Suicidality Items will be administered prior to the procedure at week 2.

Standard right-sided SGBs will be performed in accordance with this protocol (Section 3.1). On the day of the procedure, clinic nursing staff will perform standard nursing intake to include brief interim history, review of systems, vital signs, and placement of intravenous catheter. Females of child-bearing potential will have a urine pregnancy test. The treating physician will perform a targeted history and physical, paying attention to potential contraindications to SGB. At week 0, the physician will also give a brief explanation of the procedure as well as a review of risks and potential benefits, though these will have been described to them beforehand.

Injections will be performed under ultrasound visualization. The study medication will be either 7-10 mL 0.5% ropivacaine injected ventral to the right longus coli muscle (around and into the ventral fascia) and into the longus coli immediately dorsal to the presumed ventral fascia, at the level of the C6 anterior tubercle (landmarks for the stellate ganglion; active study medication) or 1-2 mL preservative free normal saline injected anterolateral to the anterior tubercle of C6 (sham procedure). The treating physician will access participant assignment (performed at RTI per protocol) via email from RTI's central office. The participant will not be informed which treatment he or she is receiving; for blinding purposes, the same type of syringes will be used for both injections. Similarly, the same number and types of syringes and other supplies should be placed on the sterile procedure table regardless to which intervention (SGB or sham) the participant has been randomized. The interaction of the treating physician with the

participant will be scripted as much as possible (**Appendix 18**). Customary vital signs will be recorded. MEDCOM 40-54 dated Feb 09 provides "a standard process and procedure for surgical and procedural site verification of patients undergoing operative or other invasive procedures". In accordance with this regulation, the participant's identity, the procedure to be performed, and the specific site of the procedure will be verified. A separate paper CRF will be created for the procedure; this information will not be shared with anyone outside the treatment suite (RC, participant, other members of the RTI Project Team, etc.). It is critical that only the physician administering the treatment (and his immediate team) be aware of the participant's assignment to active or sham intervention. Following the intervention, the treating physician should have no further contact with the participant except as required for participant safety.

Immediately following each SGB procedure, the subject will be observed in the procedure suite prior to transport to the recovery area for assessment of potential complications that could require immediate intervention, according to local clinic policy. The participant then will be taken to the post-procedure recovery area, where monitoring of vital signs will continue under the supervision of the recovery nurse for 20 minutes or longer, again per local clinic policy and participant condition.

The RC will assess the participant at 30 minutes post-procedure for his/her Horner's syndrome, recording the time post-SGB and using the following metrics (0 for absent, 1 for slight, 2 for obvious) when the participant is sitting up straight and not facing a bright light:

ptosis
scleral injection
miosis

Assuming the absence of complications requiring further evaluation or treatment, the participant will be given discharge instructions, and will be required to verbally indicate understanding of signs and symptoms that would require emergency care (e.g., shortness of breath or difficulty breathing, increasing neck pain). In addition, the clinic nurse will remind the participant that soreness at the injection site, a full sensation of the throat, and Horner's symptomology may occur for 6-18 hours (the duration of effect of the local anesthetic); if the recurrent laryngeal nerve has been blocked, there may also be hoarseness and difficulty swallowing. The participant then will be allowed to leave the clinic per local site policy.

6.4. Post-Treatment Assessments (Weeks 4, 6, and 8)

With the exception of the final CAPS-5, it is expected that these instruments will be completed by the participants on their own devices using a secure Web-based platform. For analytical purposes, each follow-up period will begin 2 days before the exact date of the follow-up and will end 11 days after the exact date of the follow-up. For example, the 2-week follow-up period will begin on day 12 and will end on day 25, the 4-week follow-up period will begin on day 26 and will end on day 38, etc. See **Appendix 19-1** and **19-2** for email communications, phone reminder script and contacting schedule.

6.4.1. CAPS-5

The CAPS-5 will be repeated, again via phone interview, at approximately 8 weeks following the first SGB, in support of the primary objective.

6.4.2. PCL-5

The PCL-5 will be repeated at weeks 4, 6, and 8 in support of secondary objective 1.

6.4.3. PCL-C

The PCL-C will be repeated at weeks 4, 6, and 8 in support of secondary objective 1.

6.4.4. M.I.N.I.-Plus Suicidality Items

The M.I.N.I.-Plus Suicidality Items will be repeated at weeks 4, 6, and 8, and is intended to enhance participant safety and support secondary objective 3. In most cases these assessments will take place via a secure web portal on the participant's device of choice (i.e., there will be no interaction between the participant and the RC at these times). If an individual affirmatively on any of the first seven M.I.N.I.-Plus items regarding suicidal ideation in the previous 2 months, they will be asked an additional 4 questions regarding *current* suicidal ideation or plans. If a participant answers affirmatively to currently wanting to harm themselves, thinking about committing suicide, having a plan, or planning to act on a plan, an automated participant safety system will be triggered (see Section 6.4.13).

6.4.5. AUDIT-C/AUDIT

The AUDIT-C and, if the participant screens positive, the full AUDIT, will be repeated at weeks 4 and 8 in support of secondary objective 3.

6.4.6. K6

The K6 will be repeated at weeks 4, 6, and 8 in support of secondary objective 3.

6.4.7. PHQ-9

The PHQ-9 will be repeated at weeks 4 and 8 in support of secondary objective 3.

6.4.8. GAD-7

The GAD-7 will be repeated at weeks 4 and 8 in support of secondary objective 3.

6.4.9. SF-12

The SF-12 will be repeated at weeks 4 and 8 in support of secondary objective 4.

6.4.10. Short Pain Scale

The short pain scale will be repeated at weeks 4 and 8 in support of secondary objective 3.

6.4.11. Current Medications

Current medications will be reassessed at weeks 4 and 8 in support of secondary objective 2.

6.4.12. Additional Questions

Additional questions will be asked of study participants at follow-up time points as follows.

Subjective Assessment of Change. For purposes of stratifying participants for qualitative analysis (see Section 3.2), we will ask participants overall how they are feeling at 2, 4, 6, and 8 weeks post initial treatment compared to how they were feeling before having the procedure. Response options will be categorical.

Subjective Assessment of Treatment Group. At week 4, in order to analyze participants' beliefs regarding whether they were randomized to the study's active or sham treatment arm (in support of secondary objective 2), we will ask participants whether they believe they received an "active" procedure or an "imitation" procedure.

6.4.13. Managing Distressed Participants during Automated Assessments

Ensuring the well-being of study participants is of paramount importance, particularly when utilizing web-based self-assessments to monitor PTSD symptoms and suicidal ideation. Our web-based system will have the capability to send messages to the participant and to key study staff in the event that a participant indicates a clinically significant risk of suicide. If an individual answers "yes" to any of the initial seven questions concerning suicidal ideation in the past two months, they then will be asked an additional 4 questions regarding *current* suicidal ideation or plans. If a participant answers affirmatively to currently wanting to harm themselves, thinking about committing suicide, have a plan, or are planning to act on a plan, an automated system will be triggered with the following results:

- A message will be displayed on the participant's screen that says the following: "Given your responses to some of these questions, we are concerned about your safety. As you were told when you signed your consent form to participate in this study, we are contacting your Command in an effort to make sure that you are safe. We would like for you to please go to your nearest Emergency Room for assistance. In addition, please click below to indicate that you agree not to harm yourself before you get to the Emergency Room."
- A text message providing the service member's name and his/her command contact information (name, telephone number, and email) will be generated and sent to the following RTI staff:
  - The RC at the site
  - Kristine Rae Olmsted (KRO)
  - Russ Vandermass-Peeler (RVP)
- RTI staff will contact the participant's command by first calling the CQ/duty phone number. If that is unsuccessful, they will contact the participant's First Sergeant or Commanding Officer.
  - The RC will be the first level responder, since he/she is local
  - If the RC doesn't respond in 2 hours, KRO and RVP will respond.
- Per site policy, Behavioral Health will be notified by the following business day.

6.5. Acceptability Study Procedures

6.5.1. Participant Recruitment and Group Assignment

6.5.1.1. Service Members

Clinical Effectiveness Trial Participants

All service members enrolled in the trial will be eligible for the qualitative study if they have received at least one SGB study procedure during the three months prior to qualitative data

collection and if participation would not cause undue distress, as described below. During Baseline Assessment, the RC will describe the qualitative study, following the recruitment script included in **Appendix 19-3** and providing the Fact Sheet included as **Appendix 19-4**. The RC will keep a list of all service members who indicate willingness to participate in the qualitative study. Recruitment for actual qualitative data collection will be determined by the pace of accrual into the clinical trial. When qualitative data collection is scheduled, the RC will draw on this list to invite service members to participate in the qualitative study, either in the course of a follow-up visit or by email, following the scripts included as **Appendix 19-12**. Service members will not be contacted for qualitative study participation if the RC or treating provider considers that participation would cause undue distress based on their most recent contact with the individual.

Other Service Members

Service members who did not participate in the clinical trial are eligible for the qualitative study if they have received at least one SGB for PTSD symptoms at a study site in the 3 months prior to qualitative data collection and if participation would not cause undue distress as described above. These participants will be recruited in the clinic as well as through a medical record search conducted by the Site PI or other clinical staff.

The RCs or clinic staff will identify individuals coming into the clinic for an SGB who may be good candidates for participation in the qualitative study. Once at the clinic, the RC or clinical staff will briefly explain the study to patients using the scripts included in **Appendix 19-3**. If the service member is interested in participating, then the RC will screen the individual at that time or contact them later and provide the Fact Sheet included as **Appendix 19-4**. If the individual prefers, he/she can also email the RC later to indicate interest.

Additionally, site PI or clinic staff at the three study sites will review clinic records to identify those patients who have come in for an SGB in the three months prior to qualitative data collection. This list will be securely stored in a locked cabinet and securely shredded when recruitment for the qualitative has been completed. The PI, clinic staff, or RCs will contact potentially eligible individuals by phone or e-mail to see if they are interested in the qualitative study following the recruitment script included in **Appendix 19-3**. Potentially eligible individuals will receive up to 2 e-mails and 2 phone calls regarding the study. E-mail contact will refer only to SGB and will not mention PTSD symptoms. This will ensure confidentiality of the potential participant in the event that the contact is seen by someone other than the intended recipient. Phone contacts will confirm potential participant identity prior to providing any information regarding the study.

If the service member is interested in participating, then the RC will speak with the individual at that time or contact them later and provide the Fact Sheet included as **Appendix 19-4**. If the individual prefers, he/she can also contact the RC later to indicate interest.

Group Assignment

Assignment to specific focus groups will be based on pay grade and subjective assessment of change as reported at the 4 Week assessment or at the time of screening for the qualitative study. In order to maximize homogeneity, lower enlisted service members and NCOs will be assigned to different groups. These groups will be further divided so that those reporting positive change since the procedure will be assigned to a different group than those reporting no change or feeling worse than at the time of the procedure. Depending on the number of eligible participants by pay grade, officers may be interviewed individually.

6.5.1.2. Service Member/Spouse Dyads

Eligible participants will be service members who meet the above criteria and whose spouse has expressed interest in participating in the qualitative study. Joint interview participants will not be allowed to also participate in focus groups. For service members who have indicated an interest in participating in focus groups, the RC will identify marital status from participants' demographic data or by asking the participant and inquire whether the service member's spouse is currently living with him/her. If so, the RC will offer these service members a recruitment Fact Sheet (**Appendix 19-5**) for the joint interviews. Interested spouses will contact the RC, who will use the recruitment script (**Appendix 19-6**) to describe the study and confirm interest. The RC will invite service members and spouses by email (again including the Fact Sheet) or phone to participate in a dyadic interview.

Participants in joint interviews will include lower enlisted and NCOs, and service members will be stratified by whether they report positive versus neutral or negative change since the procedure.

6.5.1.3. Providers

Eligible participants for the provider focus groups will be Behavioral Health or other (e.g., Family Medicine) clinicians who have referred or could potentially refer service members for SGB for PTSD symptoms, as well as physicians who provide SGBs. The RC will identify eligible clinicians in consultation with the site PIs and study records. These individuals will be invited to participate in a small focus group through an email sent by the site PI or RC. Sample text for this email is included in **Appendix 19-7**. A Fact Sheet describing the study will be attached to this email, included as **Appendix 19-8**.

6.5.2. Data Collection

Focus group interviews are planned; these are structured discussions on a particular topic involving a small number of people under the direction of a moderator (Krueger & Casey, 2000). The method relies on both the interactive social context of the discussion and on the individual experiences of each of the group members to produce a rich discussion in which shared experiences stimulate individual contributions. A methodological review by Polak and Green (2015) notes that joint interviews in which couples who are interviewed together offer similar advantages, with the opportunity for individuals to support and prompt each other, and offer contrasting perspectives on shared events. The authors further note that interviews have been found particularly useful in describing health-related decision-making.

The qualitative study will explore participants' perceptions of SGB in relation to other options for treatment of PTSD, from the perspectives of service members, service member/spouse couples, and providers. Broad topics covered in service member focus groups, service members/spouse interviews, and provider focus group are compared in in **Table 3**. The topic guide for service member focus groups is included as **Appendix 19-9**, for service member and spouse interviews as **Appendix 19-10**, and for provider focus groups as **Appendix 19-11**. If it is necessary to interview officers individually, questions will follow those in the service members topic guide. We anticipate that focus groups and small group interviews will take approximately 90 minutes, service member-significant other interviews will take approximately 60 minutes, and individual interviews will take approximately 45 minutes.

Table 3. Topics Addressed in Focus Groups and Interviews

Topic	Service Members	Service Member/ Spouse Couple	Provider
Context for mental health and treatment	•	•	
Advantages and drawbacks of treatment options	•	•	•
Information and decision-making	•	•	•
Experience and expectations	•	•	

All focus groups and interviews will be led by a study team member with prior experience in qualitative data collection with clinicians and service members engaged in mental health treatment. Real-time notes will be collected by a second team member. We will also audio-record each focus group or interview, if all participants give permission to do so. The purpose of the audio recordings is to augment any notes taken by the second team member (for instance, if the note-taker misses something said by a group participant, they may need to consult the audio recordings to clarify). We will use a digital recorder for this purpose, with each session's file transferred to an encrypted laptop immediately after the session, then deleted from the digital recorder. Participants will not be personally identified in these notes, but will instead be indicated generically, such as "Respondent 1" or "Respondent 2."

Data from focus groups and interviews will be summarized in topline notes as soon as feasible after data collection. In-depth analysis will employ standard qualitative methods. All notes will be entered into qualitative data base software such as NVivo 9 (QSR International Pty Ltd. Version 9, 2010) to facilitate coding and retrieval. Analysis will be both deductive, following a hierarchical coding structure based on topic guide questions, and inductive, creating queries to assess patterns observed in the data and hypotheses emerging from preliminary analyses. We will also construct analytic matrixes to compare responses across respondent types. Comparisons of interest include:

- Enlisted, NCO, officer
- Service member, spouse
- Service member, provider
- Self-assessed improvement, no self-assessed improvement
- Behavioral Health clinicians, Family Medicine physicians
- Study sites

6.5.3. Managing Distressed Participants During Data Collection

Discussion of PTSD treatment experiences may be distressing to participants. We will remind all participants of counseling resources available to them if they wish to discuss further any issue addressed or suggested by the focus group. Contact information for the installation's chaplain services, Behavioral Health services, and substance abuse services, as well as Military OneSource, will be attached to each participant's copy of the informed consent forms. In addition, research team members will have contact information for the clinical staff available

during and immediately after each of the focus groups. These providers will be contacted immediately if any participants' behavior raises concerns that they will harm themselves or another person. Study staff will also have contact information for installation Military Police to be used in the event of any urgent threat to safety.

6.6. Assessments for Premature Discontinuation from Study

The study is designed as intention-to-treat, 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 (AE, Section 7), every attempt should be made to continue to perform the required study-related follow-up and procedures (see Section 6.7, Criteria for Suspension of Study Treatment). If this is not possible or acceptable to the participant or Investigator, the participant may be withdrawn from the study.

6.7. Criteria for Suspension of Study Treatment

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. ADVERSE EVENTS AND DEVIATION MANAGEMENT

7.1. Research Monitor

This trial is not a safety study; SGB is a well-studied procedure with a low probability of serious adverse events (Wulf & Maier, 1992), and a smaller volume of saline injected superficially to the region of the SG would be expected to result in even fewer serious adverse events. Nevertheless, 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. At a minimum the Research Monitor should comment on the outcomes of the event or problem and in the case of a SAE or death comment on the relationship to participation in the study. The Research Monitor should also indicate whether he/she concurs with the details of the report provided by the Study Investigator. All unanticipated problems involving risk to subjects or others will be promptly reported to the USAMRMC Office of Research Protection (ORP) Human Research Protection Office (HRPO) by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

At a minimum, the Research Monitor may discuss the research protocol with the Investigators, interview the participants, observe study interventions, and consult with others outside of the study about the research. The Research Monitor has the authority to stop this trial, remove individual participants from the protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the Monitor's report. It is the Research Monitor's responsibility to promptly report their observations and finding to the IRB. There should be no conflict of interest for the Monitor, and the Monitor cannot be under the supervision of the PI or other Investigators or research staff. If the duties of the Research Monitor could require disclosure of participants' Protected Health Information outside a covered entity (i.e., the Monitor is not an agent of the covered entity), the institution responsible for the protection of human subjects may require the identity and location of the Research Monitor to be described in the study Health Information Portability and Accountability Act authorization.

7.2. Adverse Events

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.

Any reported medical condition or clinically significant laboratory abnormality with an onset date before the screening visit and not related to study procedures is considered to be pre-existing, and should be documented in the case report form.

Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after the screening visit up to the last day on study (including the follow-up, off study medication period of the study), should be recorded as an AE on the appropriate CRF page(s).

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.

The risks attributable to the trial itself originate from the sham procedure arm and include those associated with the sham saline injection itself. These would be expected to be significantly lower than those associated with the "active" SGB, for which "severe complications" (e.g., seizures, epidural and subarachnoid blocks, pneumothorax, allergic reactions) have been reported to be 0.17% (Wulf & Maier, 1992). It is also possible that participants may learn inadvertently the intervention group to which they were randomized, and that those who learn they were randomized to a sham procedure may react negatively to this information. These individuals may present to their regular health care provider(s), the Department of Behavioral Health, their local emergency department, or other relevant resources should they wish.

Unanticipated problems involving risk to volunteers or others, SAE related to participation in the study and all volunteer deaths related to participation in the study should be promptly reported to the HRPO by telephone (301-619-2165), by e-mail (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), by facsimile (301-619-7803), or by mail to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000. The Research Monitor also should be promptly informed.

7.3. 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.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4. Adverse Event Reporting Requirements

AE reports (including SAE reports, Section 7.5) will be included in the continuing review reports and in the regularly scheduled re-approval applications to the IRB of record.

7.5. Serious Adverse Events

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.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization

- Development of drug dependency or drug abuse

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.

A distinction should be drawn between serious and severe AEs. An AE that is assessed as grade 4 (potentially life-threatening) should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as grade 4. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described above.

7.6. Serious Adverse Event Reporting Requirements

7.6.1. All Serious Adverse Events

RTI International, the Research Monitor, and HRPO must be notified immediately regarding the occurrence of any unanticipated and/or serious adverse event that occurs after the screening visit, including serious adverse events resulting from study procedures performed from screening onwards. The procedures for reporting all serious adverse events, regardless of causal relationship, are as follows:

- Record the unanticipated and/or SAE on the AE CRF and complete the "Serious Adverse Event Report" form.

- Fax and email the serious adverse event report to the attention of RTI International and HRPO within 24 hours of the investigator's knowledge of the event. Contact information is below.
- For fatal or life-threatening events, also fax and email copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

RTI International Principal Investigator:	Name: Bradford B. Walters MD, PhD Title Chief Medical Officer Phone: 919-316-3509 Mobile Phone: 919-614-6273 Email: bwalters@rti.org
RTI International Co-Investigator:	Name: Kristine Rae Olmsted Phone: 919-541-8035 Mobile Phone: 919-632-4079 Fax: 919-485-5555 Email: krolmsted@rti.org
HRPO:	Phone: 301-619-2165 Fax : 301-619-7803 Email: usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil
Research Monitor:	Name: MAJ Samuel Blacker MD Phone : 910-907-7318 Fax : 910-907-8570 Pager : 301-957-0958 Email : samuel.n.blacker.mil@mail.mil

RTI International may request additional information from the Investigator to ensure the timely completion of accurate safety reports.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's CRF.

Follow-up of adverse events will continue through the last day on study (including the follow-up, off study medication period of the study), until the Investigator and/or RTI International determine that the participant's condition is stable, or up to 30 days after the last dose of study drug, whichever is longer. RTI International may request that certain adverse events be followed until resolution.

7.6.2. Investigator Reporting Requirements for SAEs

The Investigator should notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as soon as is practical of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

7.6.3. Post Study Reporting Requirements

All deaths, regardless of cause or relationship, must be reported to RTI for participants on study and for all deaths occurring within 30 days of last study drug dose. Protocol Deviation Reporting Requirements

Any deviation from this protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study must be promptly reported to RTI and the IRB. Any corrective actions taken to avoid future such deviations should be included in the report. Documentation of any actions taken by the IRB related to the deviation report should be provided when available.

7.7. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as adverse events or serious adverse events unless they are associated with clinical signs and/or symptoms. However, laboratory abnormalities (e.g. clinical chemistry, hematology, urinalysis, etc.) independent from the underlying medical condition, that require medical or surgical intervention, or lead to study drug interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g. electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an adverse event (or serious adverse event) as described in Sections 7.1 and 7.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis.

Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For adverse events associated with laboratory abnormalities, the event should be graded based on the clinical severity in the context of the underlying conditions, which may or may not be in agreement with the grading of the laboratory abnormality.

7.8. Risks for Women of Childbearing Potential or during Pregnancy

The FDA classes ropivacaine as Pregnancy Category B, and pregnant women are not to be enrolled in this trial. The participant must be instructed to discontinue all study drugs and inform the investigator **immediately** if she becomes pregnant during the study.

The investigator should report all pregnancies to RTI International within 24 hours of becoming aware of the pregnancy. The investigator should counsel the participant regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE.

A spontaneous abortion is always considered to be a SAE and will be reported as described in the adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to RTI International.

7.9. HRPO Reporting Requirements

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, change to the IRB of Record, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged

8. STATISTICAL CONSIDERATIONS

8.1. Primary Analysis

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. The primary outcome will be analyzed using a linear model for continuous variable that accounts for treatment assignment, site and other factors. Adjusted estimates of the difference in the change between the two arms and corresponding 95% confidence intervals will be produced.

8.2. Secondary Analysis

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. The outcome variable will be a binary variable denoting positive diagnosis. Because the psychometric properties of this instrument are still under development, details of the cut point definitions will be described more fully in the Statistical Analysis Plan (SAP), based on either published results of those psychometric studies currently ongoing, or preliminary psychometric analyses of data from this study, as deemed most appropriate when the SAP is developed. Adjusted and unadjusted probabilities of benefit of treatment at each time point will be produced using contingency table analysis (log-likelihood chi-square) and generalized-mixed models, correspondingly.

Effects of treatment on individual items from the PCL-5 through time will be evaluated descriptively using shift tables and shift frames. Details of these descriptive analyses will be included in the SAP.

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) and pain (short pain scale) will be analyzed using similar modeling techniques with either linear mixed models or generalized models used appropriately for the structure of the outcome measure (continuous, binary, ordinal, nominal). Each model will incorporate treatment, baseline measure, site, and time as categorical variables and two-way interactions between treatment and time and appropriate confounding variables. Models exploring change through time will account for the repeated measures (longitudinal) and clustering effects (participants). Models evaluating the different scores at different time points will account for the site effect, baseline measure and concomitant variables and comorbidities relevant to the different outcomes.

Similarly, improvement in physical and mental composite measures (SF-12) due to treatment effect will be analyzed using linear mixed models at each time point, or comparing the scores at different time points. As before, the effects will be adjusted by corresponding baseline measure, site, and concomitant variables and comorbidities relevant to these measures.

Another secondary analysis of interest is to determine the efficacy 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." 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 as described in the SAP to select the appropriate sub-population among the control arm participants.

8.3. Power and Sample Size

Because the proposal for the current study was written before the publication of the DSM-5, we initially based sample size estimates on known characteristics of the CAPS related to the DSM-IV. Weathers et al. (2001) indicate that a minimum clinically significant change in the prior version of CAPS total symptom score was 15, and data available from multiple PTSD trials in both civilian and military populations indicate that a reasonable conservative estimate of post-treatment standard deviation in CAPS-IV total symptom score was 25. Based on these assumptions, a study of 240 participants randomized at a 2:1 ratio of active treatment to sham will provide a power of 0.99 to detect a minimal clinically important difference of 15 in the CAPS-IV total symptom score between active and sham intervention participants with a Type I error rate of 0.05. Because this effect size doesn't account for a placebo effect, we also examined the power of a study of this size to detect a 10-point difference in the two arms, and the proposed study will have a power of 0.83 to detect that effect, indicating that the study is statistically feasible across the three study sites.

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 (rather than 15-point) change in CAPS score from baseline to follow-up eight weeks after stellate ganglion block as our primary outcome measure to indicate clinically significant and meaningful decrease in PTSD symptoms.

8.4. Attrition

Loss to follow-up is always a concern where statistical power is necessary for rigorous research. In the event that we see as high as 25% attrition between our baseline and 8-week

follow-up assessment, we will still have power of more than 0.88 to detect a treatment difference of 15 in CAPS-5 total symptom score between active and sham procedure participants with a Type I error rate of 0.05. We believe this rate of attrition is unlikely, however, given our success in implementing similar recruitment and retention methods for a multisite RCT regarding treatment of PTSD and depression in Army primary care, where we have seen a greater than 80% follow-up rate at 3 months, whereas the current study entails only 2 months of participation.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. Each study Investigator, as well as staff charged with the handling of confidential study data, will be required to maintain current human subjects training affiliated with their respective institution through the Collaborative Institutional Training Initiative (CITI).

9.1.2. Institutional Review Board (IRB) Approval

This protocol and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the Investigator, to an IRB. Approval from the committee must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB approval must also be submitted to the committee for approval prior to implementation.

9.1.3. After local IRB approval, the Protocol then must be submitted to HRPO for approval, which also must be documented before enrolling of participants may begin. ' Informed Consent

9.1.3.1. Effectiveness Clinical Trial

For the effectiveness clinical trial, it is the responsibility of the Investigator or his designee (e.g., the Research Coordinator) to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The discussion must take place in a private setting. The Investigator must utilize an IRB-approved consent form for documenting written informed consent. A model consent form is provided in **Appendix 20-1**. Each informed consent will be appropriately signed and dated by the participant and the person obtaining consent; all other pages of the consent are to be initialed by the participant, also. The informed consent form does not explicitly describe the Horner's syndrome evaluations to be performed by the RC; they add no risk, and we do not wish to draw attention to this participant-observable phenomenon which may unblind the participant.

During the consent process it will be made clear to potential participants that if they indicate an intention to harm themselves or somebody else during the trial, their command will be notified. This includes verbal indications as well as those during online assessments, should relevant items be answered in such a way as to indicate emergent suicidal ideation. Those indicating emergent suicidal ideation during an online assessment (Section 6.4.13) will see a message on their screen recommending that they go to their nearest Emergency Department (ED)

for assistance. These individuals will also be asked to confirm (via checking a box on the screen) that they will not act on any suicidal thoughts before presenting to the ED.

There may be potential participants referred to the study who are unable to travel to one of the three trial sites prior to a scheduled intervention (given TAMC's catchment area is the Pacific Basin and LRMC provides care for active duty service members throughout Europe, Africa, and the Middle East). In those instances, an initial informed consent will be obtained via telephone and secure digital communication (see Section 6.1) prior to the screening evaluation. In such cases, a second physical informed consent document will be signed when the participant comes for his or her baseline evaluation.

9.1.3.2. Acceptability Study

The Fact Sheet provided to service members at baseline data collection will describe the voluntary and confidential nature of the qualitative acceptability study. A second copy of this document will be provided to participants when they are scheduled to take part in a focus group or interview.

At each focus group or interview, the study team will review the Informed Consent Form with participants. The consent form for service member focus groups is included as **Appendix 20-2**; for service members who are interviewed individually as **Appendix 20-3**; for service member and spouse interviews is included as **Appendix 20-4**; and for provider focus groups as **Appendix 20-5**. Consent forms explain who we are, how participants were selected, the voluntary nature of participation in the qualitative study, including the right not to participate, the right to not answer specific questions, and the right to withdraw from the focus group at any time with no consequences. The consent form also explains the time required to complete the focus group, the nature of the topics to be discussed, the purpose of the focus group, and the protection of confidentiality of participants. Additionally, the consent form provides contact information for the RTI project director and RTI's Office of Research Protection in case a respondent has any questions about the study or his or her rights as a participant.

To protect confidentiality of participants who have been diagnosed with a serious mental health condition, we are requesting a waiver of signed consent for service members. All participants will be given a copy of the consent form to take with them if they choose. A list of counseling resources (on-installation and Military OneSource) will be attached to participant's copy of the consent form.

9.1.4. Confidentiality

The Investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties regarding the randomized controlled trial portion of the study. Only participant initials and an identification code (i.e., not names) should be recorded on any form submitted to the sponsor and IRB. The Investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial. Regarding the qualitative acceptability study, participants in group settings will be provided the same assurances of anonymity and data protection from the study staff's perspective, and we will request that those participating in group settings not reveal the identities of any other participants. Study staff, however, cannot guarantee that participants will keep their own participation (or that of others) confidential.

Study Files and Retention of Records.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories (although not limited to) the following: (1) Investigator's study file, and (2) participant clinical source documents.

The Investigator's study file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Participant clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not be limited to) the following: participant hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram (ECG), electroencephalogram (EEG), X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

All clinical study documents must be retained by the Investigator and/or RTI until seven years from the date when the financial status report is submitted. Investigators may be required to retain documents longer if required by applicable regulatory requirements or an agreement with RTI International. The Investigator must notify RTI International prior to destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, RTI International must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and RTI International to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of an audit. Where source documents are required for the continued care of the participant, appropriate copies should be made for storage outside of the site.

9.1.5. Case Report Forms

For each participant enrolled in the clinical trial, a CRF must be completed and signed by the site Principal Investigator or sub-Investigator within a reasonable time period after data collection. This also applies to records for those participants who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a participant withdraws from the study, the reason must be noted on the CRF. If a participant is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

9.1.6. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of administered study drug (ropivacaine or saline). This includes participant dispensing records. The intervention CRF will document quantities administered to participants, including lot number, date dispensed, participant identifier number, participant initials, and the initials of the person administering the medication.

All drug-associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

9.1.7. Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from RTI International or its representatives, to IRBs, or to regulatory authority or health authority inspectors.

9.1.8. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by RTI International. All protocol modifications must be submitted to the IRB in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

The final study report, including any acknowledgement documentation and supporting documents, must be submitted to HRPO when available.

With prior RTI approval, Investigators may communicate, orally present, or publish in scientific or other scholarly media at any time. After conclusion of the study and **without prior written approval from RTI International**, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- the results of the study in their entirety have been publicly disclosed by or with the consent of RTI International in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include confidential information (see Section 9.1.4).

The Investigator will submit for RTI approval any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation. The Investigator will comply with RTI International's request to delete references to its confidential information (other than the study results) in any paper or presentation. All publications will follow appropriate industry guidelines for determining authorship.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of RTI International may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority the investigator agrees to notify RTI International immediately. The Investigator agrees to provide to representatives of a regulatory agency or RTI International access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.3. Study Discontinuation

Both RTI International and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs. In terminating the study, RTI International and the Investigator will assure that adequate consideration is given to the protection of the participants' interests.

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