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Award Number: W81XWH-06-1-0257

TITLE: Efficacy of Adjunctive Sleep Interventions for PTSD

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REPORT DATE: March 2009

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY) 01-03-2009		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 17 FEB 2008 - 16 FEB 2009	
4. TITLE AND SUBTITLE Efficacy of Adjunctive Sleep Interventions for PTSD				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-06-1-0257	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Anne Germain, Ph.D. ; Eric A. Nofzinger, M.D. E-Mail: germaina@upmc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Pittsburgh School of Medicine Pittsburgh PA, 15224				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Since the last report, we have successfully achieved all goals initially set in our statement of work and task timeline for the first 36 months of the award. Recruitment has been delayed and accrued at a slower pace than initially anticipated for clinician-initiated referrals. However, we have rapidly changed our recruitment strategy and continue to seek opportunities to collaborate effective with our colleagues at the VAPHS to facilitate and enhance recruitment of military veterans with sleep disturbances to our research program. This award has also significantly contributed to other reportable outcomes including several scientific, peer-review presentations and symposia, and provided preliminary data for a new successful application for federal funding by the PI.					
15. SUBJECT TERMS Sleep, PTSD, post-deployment adjustment disorders, prazosin, behavioral treatments of nightmares and insomnia.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	72	19b. TELEPHONE NUMBER (include area code)

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Efficacy of Adjunctive Sleep Interventions in PTSD (PR054093)

Updated Progress Report

Progress Period: May 1, 2008 to January 7, 2009

I. INTRODUCTION.

Sleep disturbances are common and often resistant to first-line treatments of typical mental health disorders and post-deployment adjustment difficulties experienced by veterans who served in combat zones, including posttraumatic stress disorder. Although adjunctive pharmacological or behavioral sleep interventions are often required to adequately reduce nightmares and insomnia in veterans with these psychiatric difficulties, the efficacy and durability of adjunct sleep interventions have not been formally evaluated and compared. The overarching objective of this study is to investigate and compare the efficacy and durability of adjunctive sleep-focused interventions on sleep, daytime symptoms of PTSD, mood, and anxiety in a sample of 90 male and female veterans who experience nightmares and insomnia following military deployment. The proposed study will contribute to the development of effective therapeutic strategies for post-deployment mental health difficulties, and provide novel information regarding predictors of sleep treatment response.

II. BODY.

Research accomplishments associated with each task outlined in the approved Statement of Work.

The tasks and timeline initially proposed and approved since September 2007 in the statement of work is provided here. Progress and outcomes on each of the task listed in Table 1 are detailed below.

Table 1. Proposed Task Timeline	Year 03			Status
	Months 1-4	Months 5-8	Mo 9-12	
Task				
<i>Subject recruitment & enrollment</i>				Ongoing
Randomization and treatment delivery				Ongoing
Telephone Follow-ups				Ongoing
Data safety and monitoring plan				Ongoing
Preliminary data analysis and report				Ongoing

Task 1: Subject recruitment and enrollment

Recruitment continues to use several venues for recruitment and advertisements. Since the initiation of recruitment in October 2006, we have been contacted by 1005 veterans (453 since 5/1/08). We spoke with 361 veterans (165 since 5/1/08) who saw the television advertisement for the study. Television advertisements are more expensive than our original recruitment plan which heavily relied on referral from the local VA clinics, but possible because costs associated with laboratory procedures have been significantly reduced institutionally since funds were awarded. At this time, we have paused the use of television advertisements as our primary source of recruitment due to 1) the elevated costs, and 2) the success of the VA mass mailing program.

By far, the most fruitful new approach for recruitment in the past funding year has been mass mailings through the VAPHS. Since the initiation of recruitment in October 2006, we have received 277 veteran (221 since 5/1/08) referrals from the VAPHS. We received approval to recruit from the PTSD, OEF/OIF, Behavioral Health, the Primary Care and the Women's clinic using mass mailings. The majority of the 221 mass mailing referrals came from the PTSD and OEF/OIF clinics, which we focused on during phase I and II of our mass mailing schedule. We were able to match the number of individuals contacted in the past 2 years during phase I and II of the mass mailing from May to Oct; we sent out 2,861 letters to inform veterans of our study and received back 142 postcards, 70 phone calls, and 9 VA referrals. Phase III will focus on 9,000 individuals from

the Behavior health clinic, we have currently mailed out 2.491 letters and received 66 post cards and 31 phone calls since 12/12/08. The new contacts are not included in the recruitment stats provided about due to the current suspension of this study at the VAPHS by the Research Compliance Committee below (see detail and memo below). Recruitment through mass mailing has exceeded the numbers we projected to get from the VA on a weekly basis and will help to ensure that we meet our recruitment goals within the next 6 to 8 months.

The study recruitment flow chart is provided in Appendix I. As shown in the study flow chart, a total of 1005 individuals have contacted us, and we were able to reach and initiate the telephone screen with 718, and to complete both the telephone script and screening telephone interview with 344 individuals out of which only 284 were eligible to be consented. All 284 were invited for a consent visit, and 106 provided written, informed consent. Reasons for withdrawal or exclusion at the different study phases are provided in the study flowchart. Demographic information for these 106 individuals is provided in Table 2, as of January 7, 2009. Ten percent of consented individuals to date have been women, and 21% have been African Americans. These demographics are consistent with our proposed recruitment plan. Efforts to enroll women have been increased, and we are confident that success in enrolling women in the study will be successful in this funding period, as we will strengthen our collaboration with the VAPHS Women's Health Clinic.

Of the 102 participants who provided written, informed consent, 46 have been randomized to Medications (Group 1 in study flow chart; Prazosin or Placebo, n = 32) or to the behavioral sleep intervention (Group 2; n = 14). Reasons for exclusion prior to randomization included obstructive sleep apnea, lack of interest and incompatible time requests, substance use disorder, and severe ongoing psychiatric conditions requiring immediate psychiatric care. (For more detail, please see Appendix I).

Table 2 presents the demographic of the 102 individuals who provided written, informed consent for this study as of January 7 2009. These demographics are consistent with our proposed recruitment plan. Efforts to enroll women have been increased, and we are confident that success in enrolling women in the study will be successful in this funding period, as we will strengthen our collaboration with the VAPHS Women's Health Clinic.

Table 2. Demographic information of participants who have provided written, informed consent as of January 7, 2009.			
Ethnic Category	Sex		
	Females	Males	Total
Hispanic or Latino	0	3	3
Not Hispanic or Latino	11	88	99
Ethnic Category Total of All Subjects*	11	91	102
<i>Racial Categories</i>			
American Indian/Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	20	22
White	9	70	79
Racial Categories: Total of All Subjects	11	91	102

We continue to use our website to recruit participants and provide information about the study and about sleep research conducted at the University of Pittsburgh (<http://www.veteranssleep.pitt.edu>). The website is provided in all local advertisement media. Data regarding the number of "hits" per month since May 2008 are provided in Appendix II. Since May 2008, the website had between 700 and 2400 "hits" per month, with increased number of "hits" coinciding with advertisements on public media. 76 (26 since 5/1/08) individuals saw a web

advertisement (military.com) and contacted us by email/phone or directly via the website. While this reflects a minority of individuals, we are confident that public knowledge about the study is increasing, and that this will translate into a growing number of contacts.

In the past funding period, we have also placed recruitment ads on 70 buses on the Pittsburgh Port Authority, from which 81 veterans (50 since 5/1/08) contacted us. We have also secured IRB approval from the VAPHS to conduct a mass mailing effort to send letters to inform all veterans registered at the PTSD and OIF/OEF clinics of our ongoing studies. Because of its success we have expanded the mass mailing to include other clinics at the VAPHS (e.g., behavior health, primary care clinics; women's health clinic; audiology; rehabilitation, etc.). The mass mailing has been a tremendous success for us in recruiting VAPHS individuals, we have reached over 5,352 veterans reached by mail. The effort is possible because of the support from Dr. Gretchen Haas, Ph.D. director of the VISN 4 MIRECC. The MIRECC will indeed be supporting the costs of the mass mailing.

Study Suspension by the VAPHS Compliance Research office: Our study was audited on December 18, 2008 by the Research Compliance Committee (RCC) of the VAPHS (documentation provided in Appendix V). The for-cause audit was set because of the deviation related to the initiation of medication treatment in a participant prior completion of the randomization process (see below, Event date: 10/24/2008). The auditors reviewed all 31 charts from participants recruited from VA-related recruitment efforts. The audit report is also provided here. The audit lead to the suspension of our study, because VA consent forms were not signed by a witness who is not affiliated with the research study. We had not implemented the signature of a witness other than the study staff members obtaining consents (coordinator and study physician) because of prior directive received by the VAPHS IRB board, indicating that only VA-credentialed staff members were allowed to have contact with VA-recruited participants, and that other staff members at the University should not have any contact with VA research participants. After the suspension of the study, and discussion with the VAPHS IRB and RCC, we have received directives that non-VA-credentialed individuals are now allowed to sign consent forms as witnesses, in addition to the study coordinator, study physician, and research participant (see attached correspondence). The response to the VAPHS RCC audit report was submitted on January 16, 2009, and will be reviewed by the VAPHS RCC committee on February 10, 2009.

Task 2: Randomization and treatment delivery

To date, 46 individuals have been randomized (14 to BSI, 32 to medications [prazosin or placebo]), since recruitment began. No deviation to the randomization or treatment delivery protocols has been reported. Unexpected, adverse side effects have not occurred. One participant randomized to medication withdrew his/her participation (randomized to placebo) and 8 participants randomized to medication were withdrawn by the study (5 randomized to prazosin, 3 unknown) and six participants randomized to BSI were withdrawn by the study, as well. Reasons for withdrawal included protocol noncompliance (n= 6), work-related relocation (n = 3), narcolepsy (n=1), medical related move (n=1), changed meds while in the study (n=2, sleep apnea (n=1; individual was randomized based on wrong AHI sent by the sleep lab) and side effects (n = 1; randomized to placebo).

One unanticipated event and one deviation to the randomization process occurred in the last funding period.

Unanticipated events

1.

On 10/24/2008, the study coordinator broke the blind with participant # 210640, who was completed the medication intervention sessions. Emergency notification card stated the participant was on the Placebo, but the randomization patient profile from the Pharmacy records indicated that the participant was actually randomized to and received prazosin, and was at 10mg at the end of the acute treatment phase. The participant did not experience any serious adverse event or unanticipated problem during her participation in the study. However, this unanticipated problem could have involved direct risk to the participant; and there was increased potential

risk. Specifically, if risk if there had been a need to break the blind for medical reasons, especially if the study drug is known to have moderate to severe drug interactions, erroneous information would have been provided based on the emergency card labels.

The coordinator took the emergency card and the patient profile to the WPIC pharmacy, where he explained the discrepancy to one of the research pharmacists. The research pharmacist verified the randomization of the participant was indeed to prazosin, and not to placebo. He informed the study coordinator that at the randomization they review the study stratification criteria and log the participants name to the appropriate group (placebo or prazosin) on paper, they then enter the data electronically for the emergency contact cards (labels with the participants 10 and randomization). The pharmacist then provided a corrected emergency card to the coordinator. The participant was informed that she was on the medication and the coordinator completed the post intervention interview. The PI was informed shortly after of this incident. Emergency envelopes provided to the medical monitor (Dr. Jeffrey Peter), and study physicians (Dr. Eric Nofzinger Dr. Mammen) were immediately verified. All had the incorrect randomization information, i.e., indicated that the participant was on placebo, rather than on prazosin as it was the case. A meeting was held with the pharmacy manager (Karen Fielding) on the following business day.

The problem arose in the process of the research pharmacist who makes the labels for the emergency cards, and looked at the wrong line on the randomization sheet. S/he did not verify that the subject's randomization and the information on the emergency cards matched.

To avoid future occurrences, Mrs. Fielding had the research pharmacist pull the emergency envelopes from the WPIC ER file & verify all their contents. All envelopes were correct. They were matched to the participant's profile & the actual randomization sheet. This appears to be an isolated incident. She will also review this incident with her research staff. Appropriate reports were submitted and reviewed by the University of Pittsburgh and VAPHS IRB (Appendix 4).

2.

In June 2008, During the first wave of the mass mailing effort with the VAPHS, a veteran's widow received a recruitment letter addressed to her deceased husband. The widow returned a letter expressing dissatisfaction with the care received at the VA by her husband, to the VA MIRECC liaison, Liubomir Andrei Pisarov. The study coordinator and liaison contacted the VA patients' advocate, who contact the widow and offered help to address her concerns. Following this unanticipated event, the database created by the VA honest broken was revised and corrected to verify that no veteran for who a date of death is available is sent a recruitment letter.

3.

On January 10th 2009, an unanticipated deviation to the randomization protocol occurred when a participant initiated treatment in the medical arm of the study before the participant was actually randomized to the medication arms by our statistician. This was the result by misplacement of the randomization request in two participants who completed the baseline assessment concurrently. One participant had already been randomized (on 12/30/2008), and his randomization was mistakenly assigned to the other participant, who had not yet been randomized. The coordinator realized this mistake, immediately informed the PI and the VAPHS IRB. The randomization was completed on 1/13/2009. Both participants were indeed randomized to medications. This deviation did not affect the risks to participants as both has completed the screening and baseline assessments, and were medically cleared. To ensure that this will incident will not occur again, we will now place larger labels on individual participants' binder to identify the randomization arm and date of randomization.

Deviations.

A list of deviations, reason, and outcomes is provided in Appendix IV. None were associated with change to the risk-benefit ratio associated with participation in this study.

Task 3: Telephone Follow-ups

As of January 7, telephone follow-up have been completed in all participants who completed the intervention phase. 19 participants have completed the entire post-treatment follow-up period, and 11 are currently in the follow-up period.

Task 4: Data safety and monitoring plan

The PI continues to hold and lead weekly team meeting to closely monitor the progress of the study. These meetings are also used to review, verify and achieve consensus on participants' eligibility and safety to participate in the study; verify if any member of team has become aware of the new information that alters the risk/benefit assessment of the present study, verify that confidentiality has been protected and no breach has occurred; and search the literature on new information that may affect the current assessment of the risk/benefit ratio. New literature relevant for the continuous assessment of the risks and benefits are the study is sought weekly, and reviewed when available.

A third Data and Safety Monitoring Board (DSMB) was held on July 2 2008. The DSMB includes Drs. Ellen Frank, Wesley Thompson, and Terry Keane. Summaries of recruitment results, study procedures, and any unexpected/adverse event were provided to the members for review. The DSMB expressed no concerns regarding the integrity of the data, participants' safety, and study procedures. The DSMB report is included with this report, in Appendix III. The next DSMB meeting is scheduled for January 21, 2009, and will include all members.

Task 5. Preliminary data analysis and report

Preliminary data analysis has been slightly delayed due to prior lags in recruitment. Nevertheless, the PI is now working with the study statistician, Mrs. Amy Begley, to update and undertake the preliminary data analysis plan. These analyses will focus on the demographic, clinical, military, and psychiatric correlates of subjective and objective sleep evaluations in the sample of veterans who completed baseline assessments (n = 45). We will also explore whether the nature of subjective and objective sleep disturbances and their relationship to the these correlates different between OEF/OIF veterans, and other cohorts of military veterans. Our preliminary observations suggest that OEF/OEF returnees show objective signs of sleep disruption compared to non-military samples, and that subjective complaints of sleep disturbances are strongly related to psychological difficulties and overall functioning.

Problems in accomplishing any of the tasks.

Recruitment: We originally proposed to consent 120 participants, of whom 90 (75% retention) would be randomized and 66 were expected to complete the acute intervention phase (73% retention of randomized individuals). These retention rates were based on data collected in other sleep-focused, randomized clinical trials conducted by our colleagues in Pittsburgh. However, it has become obvious based on data acquired in the current study that previously collected data in clinical trials that enroll civilians do not generalized to clinical trials enrolling military veterans. As shown in the Flow Chart (Appendix I), the retention rate of consented individuals into randomization is 45% (or 45 randomized / 102 consented). Since the last report, we have greatly intensified and diversified our recruitment efforts, by using television advertisements, bus advertisements, the the study website, and initiated mass mailing efforts through the VAPHS. The latter has been extremely successful since its initiating in September 2008, and we are confident that this will enable us to meet our recruitment goals within the last year of funding. Nevertheless, and to be able to meet our recruitment need and protect statistical power of the proposed analyses, we will plan request a no cost extension to complete this study.

KEY RESEARCH ACCOMPLISHMENTS.

None at this time.

REPORTABLE OUTCOMES.

Scientific Presentations at International Conferences:

The following abstracts have been submitted and accepted for oral presentation at the 2008 SLEEP Meeting to be held in Baltimore in June 2008, and at the 42nd Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT) held in Orlando, in November 2008.

- Germain A., Walsh C, Stoll M, Hall M, & Buysse DJ. Objective Sleep Disturbances in Returning Veterans with PTSD: Preliminary Findings. Oral Presentation. Sleep 2008, June 7-12, 2008, Baltimore, MD
- Walsh C, Germain A, & Buysse DJ. Sleep quality and disturbances in Returning Veterans: Preliminary Comparisons with Primary Insomnia and Good Sleepers. Oral Presentation. Sleep 2008, June 7-12, 2008, Baltimore, MD
- Germain A. & Buysse B. Brief Behavioral Treatment for Chronic Insomnia in Combat-Exposed Veterans: Preliminary Findings on Acceptability, Barriers to Adherence, and Outcomes. Oral presentation given at the 42nd Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT) held in Orlando. November 2008
- Germain A., Walsh CM, & Buysse DJ. Objective and Subjective Sleep Disturbances in Returning Veterans: Preliminary Findings. 42nd Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT) held in Orlando. November 2008
- Nature and Behavioral Treatments of Sleep Disturbances in Military Veterans with Posttraumatic Stress Disorder. In: G. Belleville (chair): Insomnia Comorbid with Medical and Mental Disorders: Nature, Impact, and Management. Symposium accepted for presentation at the Fourth Meeting of the Canadian Sleep Society, Toronto, ON, Canada. April 2009.
- Germain A, Raskind M., Ulmer C, and Edinger J, and Ross, R. Trauma and Sleep: Treatments and Health-Related Implications. Symposium to be presented at the 2009 Sleep Meeting, June 2009. Seattle, WA.
- Russo M, Germain A, Baumann C, and Tucker DM. Sleep, Wake, and Traumatic Brain Injury. Symposium to be presented at the 2009 Sleep Meeting, June 2009. Seattle, WA.

Invited Lectures & Post-Graduate Courses:

- Germain A. *Sleep in War Veterans*. Invited Lecture. American Academy of Sleep Medicine Series Course: Current Topics in Sleep Medicine. Los Angeles, CA February 2009.
- Germain A. *Imagery Rehearsal, CBT, and Other Non-Drug Interventions for Nightmares and Parasomnias*. Invited Lecture. American Academy of Sleep Medicine Series Course: Evaluation and Management of Insomnia. Oak Brook, IL, March 2009.
- Germain A: *Face it or Fake it: Cognitive-Behavioral Treatments of Nightmares*. In: J. Edinger (Chair): A comprehensive overview of behavioral sleep medicine techniques: A nuts and bolts course for enhancing your sleep medicine practice): SLEEP 2009 Meeting Pre-Conference Graduate Course, June

7, 2009.

- Germain A. *Treating Insomnia Comorbid with PTSD*. In: R Manber (Chair) CBT for Insomnia Comorbid w/Depressive & Anxiety. Course accepted at the 162nd American Psychiatric Association Annual Meeting, May 2009, San Francisco, CA.
- Germain A. *Brief Behavioral Treatment of Insomnia in Military Veterans*. Workshop to be presented at the Second Hidden Casualties of War Symposium sponsored by the UWF Center for Applied Psychology and the Naval Hospital Pensacola, May 2009.
- Germain A. *Treating Nightmares with Imagery Scripting and Rehearsal*. Workshop to be presented at the Second Hidden Casualties of War Symposium sponsored by the UWF Center for Applied Psychology and the Naval Hospital Pensacola, May 2009.

Funding requested and obtained based on work supported by this award:

- As anticipated, our NIMH proposal, entitled “Brief Behavioral Treatment of Comorbid Insomnia in Returning Veterans” was funded in May 2008. This grant was developed based on the observations that a considerable number of military veterans report insomnia related to post-deployment adjustment disorders, but do not meet diagnostic criteria for PTSD. The study aims at adapting and testing a brief behavioral treatment of insomnia previously developed by our team over the course of another study funded by National Institutes of Mental Health (NIMH) (AG20677). Recruitment data and clinical observations derived from the current clinical trial provided preliminary data for this application.
- The R21 proposal submitted to NIMH in January 2008 aimed at exploring the neurobiological underpinnings of PTSD during REM sleep relative to wakefulness was recently funded. Recruitment data derived from the current clinical trial provided preliminary data for this application.
- In May 2008, we received noticed that our proposal entitled, “Neurobiology of Sleep and Sleep Treatment Response”, submitted to the Post-Traumatic Stress Disorder and Traumatic Brain Injury (PTSD/TBI) Research Program was funded. This study will expand on our ongoing CDMRP clinical trial, by including wake and sleep PET imaging prior and after treatment with prazosin or placebo.
- Dr. Germain and a team of researchers from the University of Pittsburgh, Washington University, Howard University, Harvard, and University of California – Berkeley, submitted a translational research proposal entitled, “*Translational Studies of the Effects of Stress-Related Sleep Disruption on Learning and Memory*” was submitted in January 2009 to the Office of Naval Research Multidisciplinary University Research Initiative (MURI; BAA 08-019: Topic #1; PI: M. Hall, University of Pittsburgh). This multidisciplinary translational project focuses on investigating sleep-specific molecular, genetic, physiological, neurobiological, behavioral and environmental pathways contributing to and protective against the detrimental effects of stress-induced sleep disruption on learning and memory. The overarching goal is to discover, evaluate, and validate sleep-specific pathways impacted by acute, traumatic and chronic stress exposure that mediate learning and memory processes relevant to military training and operations. In this project, we proposed to conduct a series of integrated studies to advance knowledge from discovery (in drosophila models) to translation (in mouse and rat models) to application (in humans including urban minorities) with the goal of understanding the pathways of vulnerability and resistance to SRSD-induced learning and memory deficits.

Research training activities conducted under this award:

Undergraduate training: Ms. Jennifer Alman, a neuroscience and biology major at Washington and Jefferson College, completed a research internship in Dr. Germain's lab between May 2008 and August 2008. Her research project focused on assessing central (brain) arousal prior to sleep in participants enrolled in our study with Posttraumatic Stress Disorder (PTSD), in comparison to archival research subjects with Primary Insomnia (PI) and good sleepers (GS). Fast-frequency quantitative EEG (qEEG) activity (sigma: 12-16 Hz; beta: 16-32Hz) during waking EEG was used as a potential indicator of central arousal. It was hypothesized that both PTSD and PI participants groups would show increased fast-frequency activity during evening wakefulness compared to GS. The relationships between qEEG measures, PSG sleep measures, and symptoms of PTSD, depression, and anxiety in the PTSD group were also explored. Ten military veterans with PTSD (mean 37.6 ± 11.7 years old), 10 PI subjects (mean 35.3 ± 9.7 years old) and 8 GSC (mean 40.1 ± 22.8 years old) were included in this study. PI and GSC were free of medications, medical conditions, psychiatric disorders and other sleep disorders. Six of the 10 PTSD subjects were medication free. Automated and visual artifact rejection were conducted on 5-minute waking EEG samples recorded within 2 hours of participants' habitual bedtime using FFT. Non-parametric Kruskal-Wallis tests and Spearman's rho correlations were conducted. Results indicated that there was no significant group difference in absolute or relative power for sigma or beta activity bands. In PTSD subjects, absolute beta power during waking EEG was significantly and positively correlated with the severity of PTSD, depression, and anxiety symptoms were (all $p < 0.05$), but not with PSG sleep measures. These preliminary observations suggest that functional brain imaging methods may be necessary to identify neural correlates of the relationship between objective measures of arousal and clinical symptoms. In light of previously described changes in qEEG during sleep in PTSD and PI, the present data also suggest a state-dependent form of electrophysiological arousal. Ms. Alman's work was submitted as a research abstract for an oral presentation for the 2009 SLEEP meeting, to be held in Seattle in June 2009. Review is awaited.

Since May 2008, all research personnel completed the following continuing training and education activities:

- *Traumatic Brain Injury and Posttraumatic Stress Disorder.* Ryan Stocker, B.S. EASI-P Monthly training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. May 30, 2008
- *Bereavement.* Catharine Hebdon, MSW Graduate Student. EASI-P Monthly training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. July 11, 2008
- *EKG Presentation.* Jennifer Alman, Psychology Undergraduate Intern. EASI-P Monthly training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. August 1, 2008.
- *The Wounded Healer: A Brief Overview of Psychotherapy for and by Mental Health Clinicians and Researchers.* Robin Richardson, LCSW. EASI-P Monthly Training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. August 22, 2008
- *Complementary and Alternative Medicine for PTSD.* Abdul Hakim, LSW. EASI-P Monthly training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. September 26, 2008
- *Conducting the History and Physical Exam.* Lisa Hilal, CRNP. EASI-P Monthly training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. October 31, 2008.
- *Readjustment Issues Experienced by OEF/OIF Veterans.* James Martorella, LSW, Brian Avant, LSW, & Cpt. Michael Clark. Clinical Grand Rounds, Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. November 7, 2008
- *Prolonged Exposure Therapy for PTSD.* Rita Feske, PhD. Invited presenter for EASI-P Monthly training. Western Psychiatric Institute & Clinic, Room 1449. Pittsburgh, PA. November 21, 2008.

- *Grief: Immediate, Practical, and Effective Interventions.* Duane Bowers, LPC. PESI Telephone Seminar, WPIC E-1107. November 13, 2008.
- *Imagery Rehearsal for Post Traumatic Nightmares.* Richard J. Ross, MD. VA Teleconference, WPIC E-1116. December 15, 2008

All staff members continue to regularly attend Grand Rounds presentations held at Western Psychiatric Institute and Clinic on relevant topics, such as assessment and treatment of PTSD in returning veterans, assessment of mild traumatic brain injury, assessment and treatment of anxiety, mood, grief, and sleep disorders, and updates on pharmacological and non pharmacological treatments of anxiety, mood, grief, and sleep disorders.

CONCLUSIONS

Recruitment and research activities are ongoing. At this point, we have most achieved all goals initially set in our statement of work and task timeline for the first 35 months of the award. Recruitment has been delayed and accrued at a slower pace than initially anticipated for clinician-initiated referrals to the study, but as recently accrued significantly through mass mailing efforts. The recent suspension of enrollment by the APHS has slowed down recruitment, but other sources of recruitment are enhanced to make sure we continue to enroll study participants. We are thus confident that we can achieve our recruitment goal within the coming months. Preliminary data analysis has been initiated, and preliminary reports are being prepared for peer-review publications.

REFERENCES.

None.

APPENDICES

Appendix I	Study Flow Chart From May 1 2008 January 7, 2008
Appendix II	Website “hits” from September 2007 to April 2008.
Appendix III	Report from the Data Safety and Monitoring Board Meeting, July 2, 2008
Appendix IV	Documentation of unanticipated event and deviation
Appendix V	Documentation of VAPHS audit by the Research Compliance Committee
Appendix VI	University of Pittsburgh AND VAPHS IRB letters of approvals, and approved consent forms.

SUPPORTING DATA.

None provided at this time.

Appendix I
Study Flow Chart (as of 01/07/2009)

EASIP DOD REPORT

January 7, 2009

Total Contacts
1005

Not Interested: 41

Interested
962

Scripted
718

Not Eligible: 285

Screened 344

Excluded at Screening 195

OTHER EXCLUSION	53
NO LONGER OR NOT INTERESTED	17
USE OF ALPHA-1 ANTAGONIST OR BETA-BLOCKER	17
TOO BUSY / TIME COMMITMENT	16
OTHER WITHDRAWAL	15
BIPOLAR DISORDER	11
OBSTRUCTIVE SLEEP APNEA	11
SUBSTANCE ABUSE DISORDER	7
INSUFFICIENT FINANCIAL COMPENSATION	7
CAPS SCORE > 80, DIAGNOSTIC INELIGIBILITY (DOES NOT MEET CRITERIA FOR PTSD)	5
PSYCHOTIC DISORDER	5
PSYCHOTROPIC OR NEUROLOGICAL MEDICATIONS AND/OR DOSAGE CHANGED IN PAST 2 MONTHS	4
SEVERE MAJOR DEPRESSIVE DISORDER	3
HOSP FOR OR REQUIRED TREATMENT FOR SUICIDE IN PAST 6 MONTHS	3
AGE (< 18 OR > 60)	3
AHI>15	3
CALLED TO ACTIVE DUTY	2
DOESN'T WANT TO DO A RESEARCH STUDY	2
FAMILY BURDEN	2
NO SLEEP COMPLAINT	2
OTHER MEDICAL ISSUES FROM PHYSICAL/LAB TESTS	1
PREGNANT OR BREAST-FEEDING	1

Consented
102

Excluded prior to randomization 33

CAPS SCORE > 80, DIAGNOSTIC INELIGIBILITY (DOES NOT MEET CRITERIA FOR PTSD)	5
OTHER EXCLUSION	4
OBSTRUCTIVE SLEEP APNEA	3
POOR COMPLIANCE WITH STUDY PROCEDURES	2
OTHER WITHDRAWN	2
OTHER WITHDRAWAL	2
NO LONGER OR NOT INTERESTED	2
HOSP FOR OR REQUIRED TREATMENT FOR SUICIDE IN PAST 6 MONTHS	2
AHI>15	2
TOO BUSY / TIME COMMITMENT	1
SUBSTANCE ABUSE DISORDER	1
OTHER MEDICAL ISSUES FROM PHYSICAL/LAB TESTS	1
NO SLEEP COMPLAINT	1

Passed Apnea Screen	48
Randomized	46
Completed Baseline	45
W/D Drop Out	2

GROUP 1: Blind to Medication 4

GROUP 2: n = 14

INTERVENTION: Completed	9
INTERVENTION: W/D Drop Out	4
FOLLOW UP: Completed	8
FOLLOW UP: W/D Drop Out	0
POST FOLLOW UP: Active	2
POST FOLLOW UP: W/D Drop Out	0
COMPLETED PROTOCOL	2

GROUP 3: n = 13

INTERVENTION: Completed	11
INTERVENTION: W/D Drop Out	2
FOLLOW UP: Completed	10
FOLLOW UP: W/D Drop Out	0
POST FOLLOW UP: Active	3
POST FOLLOW UP: W/D Drop Out	0
COMPLETED PROTOCOL	4

GROUP 4: n = 15

INTERVENTION: Completed	12
INTERVENTION: W/D Drop Out	2
FOLLOW UP: Completed	10
FOLLOW UP: W/D Drop Out	0
POST FOLLOW UP: Active	4
POST FOLLOW UP: W/D Drop Out	0
COMPLETED PROTOCOL	3

Appendix II

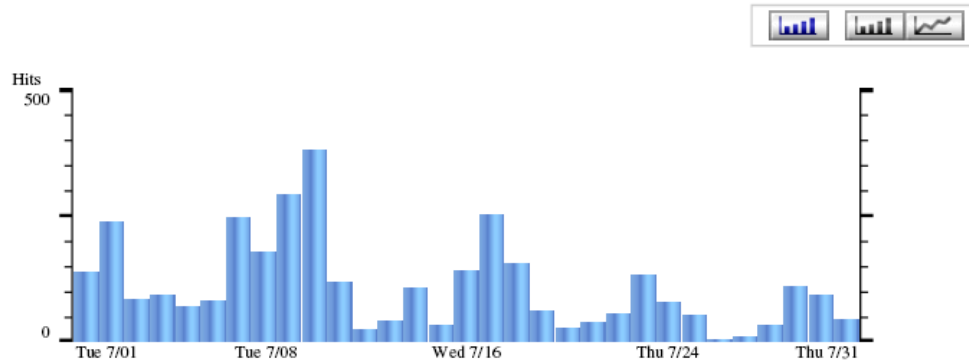
Website “hits”: 05/01/2008 to 01/09/2009

<http://www.veteranssleep.pitt.edu>

July 2008

Report: Hits Graph - www.veteranssleep.pitt.edu
Date Range: 07/01/2008 - 07/31/2008

Range Total: 3,439 **Daily Average:** 110.94



? Help Information:

Hits Graph

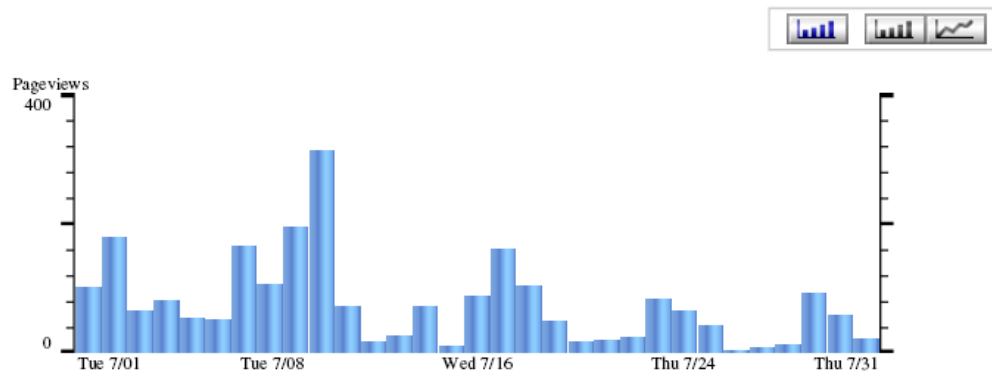
This report shows the trend of recent activity on your website in terms of successful Hits over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodolgy

A 'Hit' is simply a successful request to your web server from a visitor's browser for any type of file, whether an image, HTML page, an MP3 file, or any other type. A single web page can cause many Hits -- one for each image included on the page, etc.

Report: Pageviews Graph - www.veteranssleep.pitt.edu
Date Range: 07/01/2008 - 07/31/2008

Range Total: 2,375 **Daily Average:** 76.61



? Help Information:

Pageviews Graph

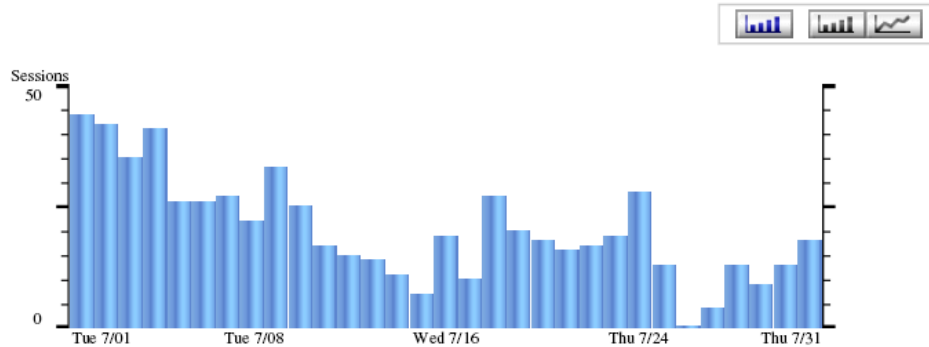
This report shows the trend of recent activity on your website in terms of Pageviews over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Pageview' is defined as a request from a visitor's browser for a displayable web page, generally an HTML file. Urchin's configuration controls which file extensions are treated as Pageviews. In general, images and other embedded content, such as style sheets and javascript, are not considered to be Pageviews.

Report: Sessions Graph - www.veteranssleep.pitt.edu
Date Range: 07/01/2008 - 07/31/2008

Range Total: 629 **Daily Average:** 20.29



? Help Information:

Sessions Graph

This report shows the trend of recent activity on your website in terms of Visitor Sessions over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Session' is defined as a series of clicks on your site by an individual visitor during a specific period of time. A Session is initiated when the visitor arrives at your site, and it ends when the browser is closed or there is a period of inactivity. Sessions quantities will vary to some degree based on what type of visitor tracking method is employed. For the most accurate numbers, the Urchin Traffic Monitor (UTM) should be used.

Report: Summary - www.veteranssleep.pitt.edu
Date Range: 07/01/2008 - 07/31/2008

Total Sessions	629.00
Total Pageviews	2,375.00
Total Hits	3,439.00
Total Bytes Transferred	60.68 MB
Average Sessions Per Day	20.29
Average Pageviews Per Day	76.61
Average Hits Per Day	110.94
Average Bytes Transferred Per Day	1.96 MB
Average Pageviews Per Session	3.78
Average Hits Per Session	5.47
Average Bytes Per Session	98.78 KB
Average Length of Session	00:01:57

? Help Information:

Summary

The Summary shows totals and averages for Sessions, Pageviews, Hits, and Bytes for the currently selected Date Range. Visitors information is not shown here because it is only available when UTM visitor tracking is employed.

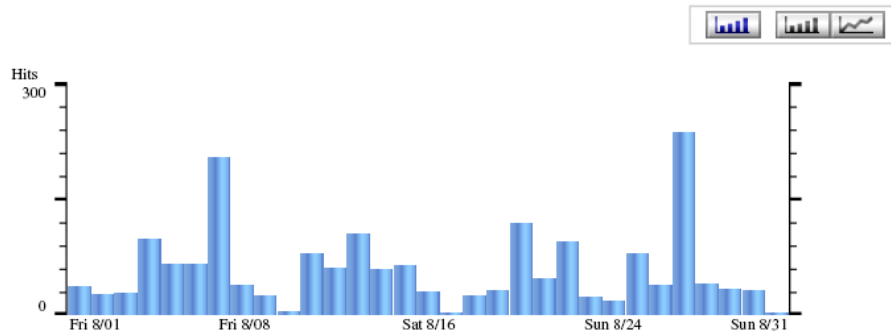
Calculation Methodology

- Session: A series of Hits to your site over a specific period of time by one visitor.
- Pageview: A request to the web server by a visitor's browser for any web page; this excludes images, javascript, and other generally embedded file types.
- Hit: Any successful request to a webserver from a visitor's browser.
- Bytes: The quantity of network bandwidth used by the files requested during the selected Date Range.

August 2008

Report: Hits Graph - www.veteranssleep.pitt.edu
Date Range: 08/01/2008 - 08/31/2008

Range Total: 1,811 Daily Average: 58.42



? Help Information:

Hits Graph

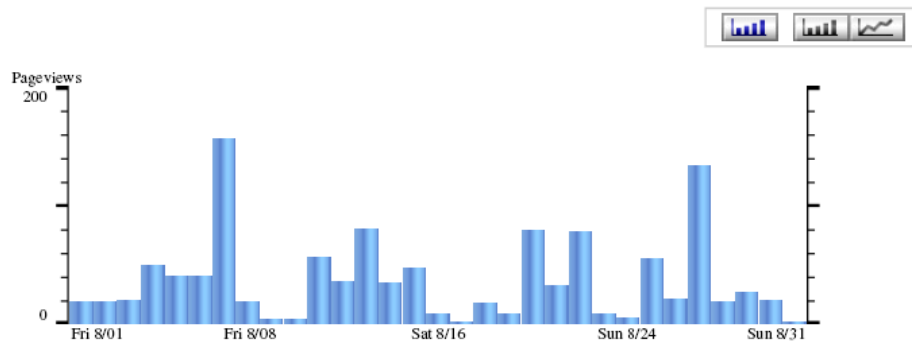
This report shows the trend of recent activity on your website in terms of successful Hits over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Hit' is simply a successful request to your web server from a visitor's browser for any type of file, whether an image, HTML page, an MP3 file, or any other type. A single web page can cause many Hits -- one for each image included on the page, etc.

Report: Pageviews Graph - www.veteranssleep.pitt.edu
Date Range: 08/01/2008 - 08/31/2008

Range Total: 1,148 Daily Average: 37.03



? Help Information:

Pageviews Graph

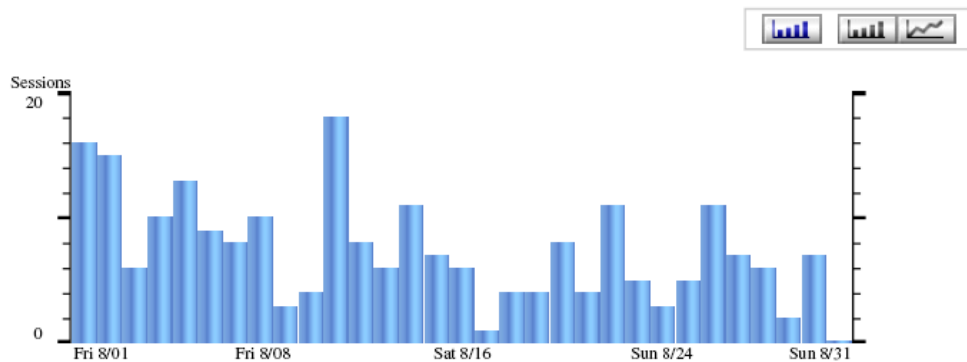
This report shows the trend of recent activity on your website in terms of Pageviews over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Pageview' is defined as a request from a visitor's browser for a displayable web page, generally an HTML file. Urchin's configuration controls which file extensions are treated as Pageviews. In general, images and other embedded content, such as style sheets and javascript, are not considered to be Pageviews.

Report: Sessions Graph - www.veteranssleep.pitt.edu
Date Range: 08/01/2008 - 08/31/2008

Range Total: 228 **Daily Average:** 7.35



? Help Information:

Sessions Graph

This report shows the trend of recent activity on your website in terms of Visitor Sessions over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Session' is defined as a series of clicks on your site by an individual visitor during a specific period of time. A Session is initiated when the visitor arrives at your site, and it ends when the browser is closed or there is a period of inactivity. Sessions quantities will vary to some degree based on what type of visitor tracking method is employed. For the most accurate numbers, the Urchin Traffic Monitor (UTM) should be used.

Report: Summary - www.veteranssleep.pitt.edu
Date Range: 08/01/2008 - 08/31/2008

Total Sessions	228.00
Total Pageviews	1,148.00
Total Hits	1,811.00
Total Bytes Transferred	34.21 MB
Average Sessions Per Day	7.35
Average Pageviews Per Day	37.03
Average Hits Per Day	58.42
Average Bytes Transferred Per Day	1.10 MB
Average Pageviews Per Session	5.04
Average Hits Per Session	7.94
Average Bytes Per Session	153.67 KB
Average Length of Session	00:01:41

? Help Information:

Summary

The Summary shows totals and averages for Sessions, Pageviews, Hits, and Bytes for the currently selected Date Range. Visitors information is not shown here because it is only available when UTM visitor tracking is employed.

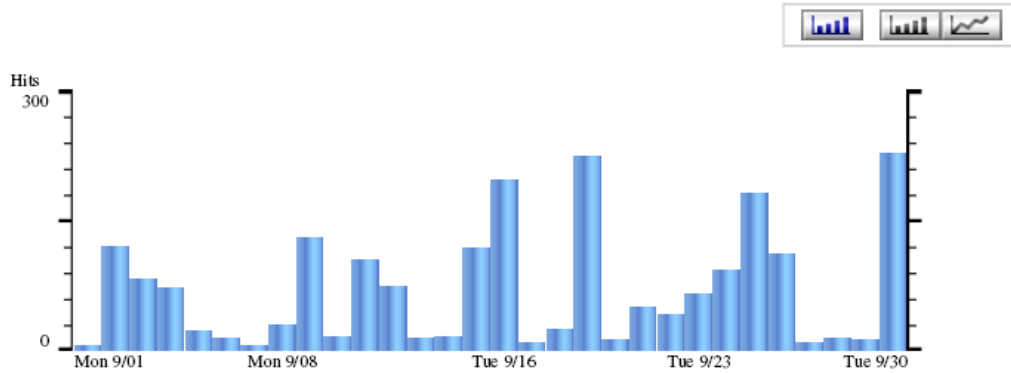
Calculation Methodology

- Session: A series of Hits to your site over a specific period of time by one visitor.
- Pageview: A request to the web server by a visitor's browser for any web page; this excludes images, javascript, and other generally embedded file types.
- Hit: Any successful request to a webserver from a visitor's browser.
- Bytes: The quantity of network bandwidth used by the files requested during the selected Date Range.

September 2008

Report: Hits Graph - www.veteranssleep.pitt.edu
Date Range: 09/01/2008 - 09/30/2008

Range Total: 2,116 **Daily Average:** 70.53



? Help Information:

Hits Graph

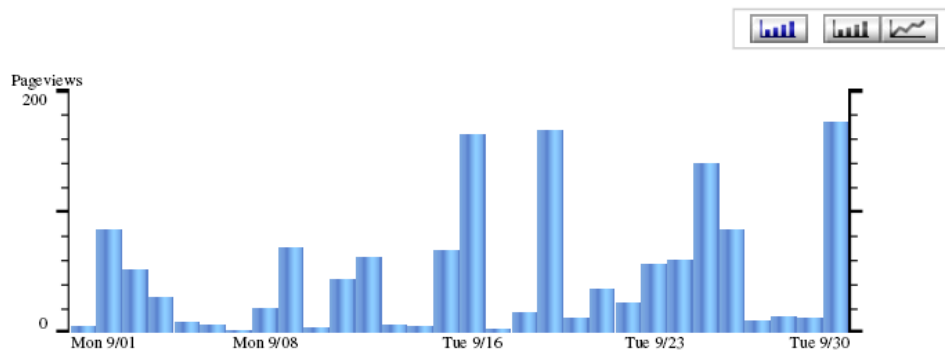
This report shows the trend of recent activity on your website in terms of successful Hits over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Hit' is simply a successful request to your web server from a visitor's browser for any type of file, whether an image, HTML page, an MP3 file, or any other type. A single web page can cause many Hits -- one for each image included on the page, etc.

Report: Pageviews Graph - www.veteranssleep.pitt.edu
Date Range: 09/01/2008 - 09/30/2008

Range Total: 1,447 **Daily Average:** 48.23



? Help Information:

Pageviews Graph

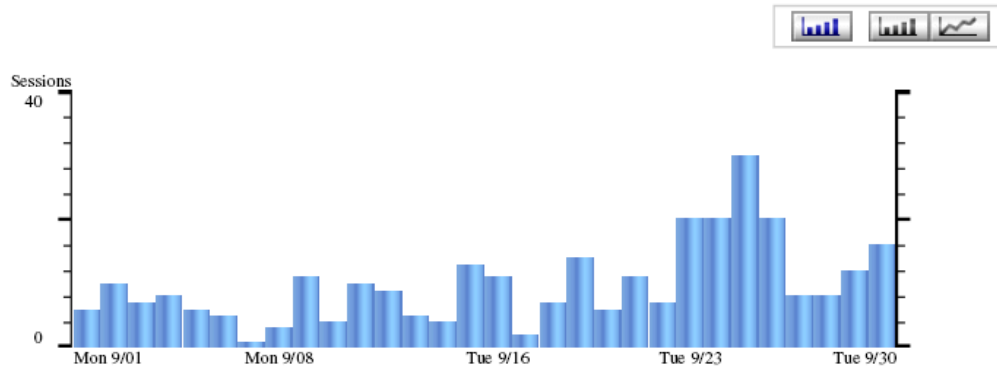
This report shows the trend of recent activity on your website in terms of Pageviews over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Pageview' is defined as a request from a visitor's browser for a displayable web page, generally an HTML file. Urchin's configuration controls which file extensions are treated as Pageviews. In general, images and other embedded content, such as style sheets and javascript, are not considered to be Pageviews.

Report: Sessions Graph - www.veteranssleep.pitt.edu
Date Range: 09/01/2008 - 09/30/2008

Range Total: 294 **Daily Average:** 9.80



? Help Information:

Sessions Graph

This report shows the trend of recent activity on your website in terms of Visitor Sessions over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Session' is defined as a series of clicks on your site by an individual visitor during a specific period of time. A Session is initiated when the visitor arrives at your site, and it ends when the browser is closed or there is a period of inactivity. Sessions quantities will vary to some degree based on what type of visitor tracking method is employed. For the most accurate numbers, the Urchin Traffic Monitor (UTM) should be used.

Report: Summary - www.veteranssleep.pitt.edu

Date Range: 09/01/2008 - 09/30/2008

Total Sessions	294.00
Total Pageviews	1,447.00
Total Hits	2,116.00
Total Bytes Transferred	36.47 MB
Average Sessions Per Day	9.80
Average Pageviews Per Day	48.23
Average Hits Per Day	70.53
Average Bytes Transferred Per Day	1.22 MB
Average Pageviews Per Session	4.92
Average Hits Per Session	7.20
Average Bytes Per Session	127.03 KB
Average Length of Session	00:05:02

? Help Information:

Summary

The Summary shows totals and averages for Sessions, Pageviews, Hits, and Bytes for the currently selected Date Range. Visitors information is not shown here because it is only available when UTM visitor tracking is employed.

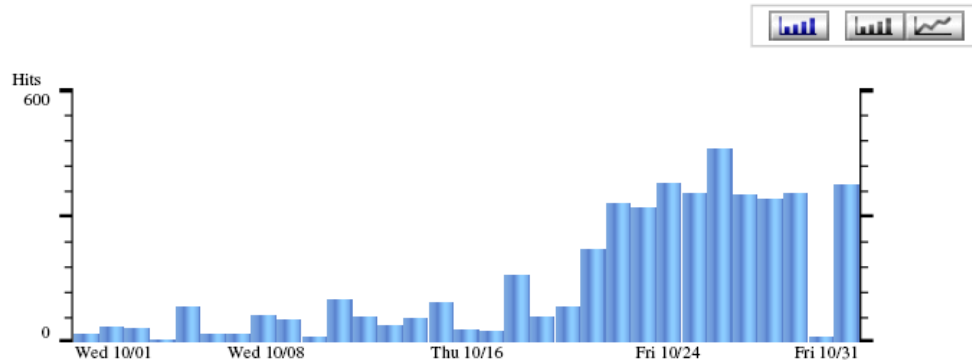
Calculation Methodology

- Session: A series of Hits to your site over a specific period of time by one visitor.
- Pageview: A request to the web server by a visitor's browser for any web page; this excludes images, javascript, and other generally embedded file types.
- Hit: Any successful request to a webserver from a visitor's browser.
- Bytes: The quantity of network bandwidth used by the files requested during the selected Date Range.

October 2008

Report: Hits Graph - www.veteranssleep.pitt.edu
Date Range: 10/01/2008 - 10/31/2008

Range Total: 4,574 **Daily Average:** 147.55



? Help Information:

Hits Graph

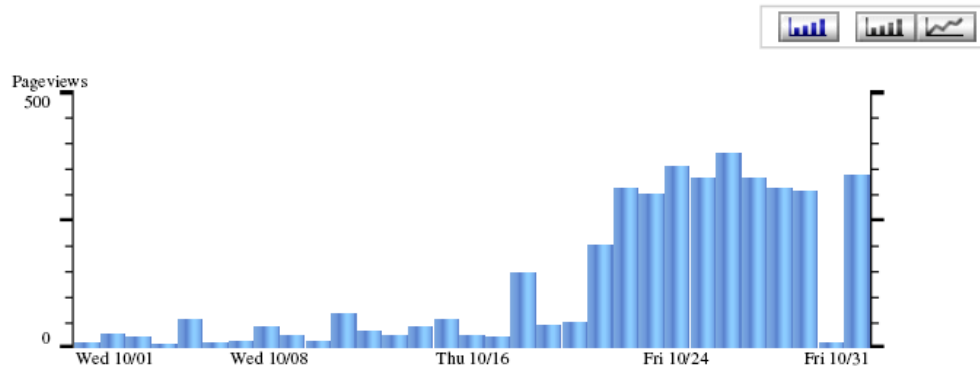
This report shows the trend of recent activity on your website in terms of successful Hits over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodolgy

A 'Hit' is simply a successful request to your web server from a visitor's browser for any type of file, whether an image, HTML page, an MP3 file, or any other type. A single web page can cause many Hits -- one for each image included on the page, etc.

Report: Pageviews Graph - www.veteranssleep.pitt.edu
Date Range: 10/01/2008 - 10/31/2008

Range Total: 3,933 **Daily Average:** 126.87



? Help Information:

Pageviews Graph

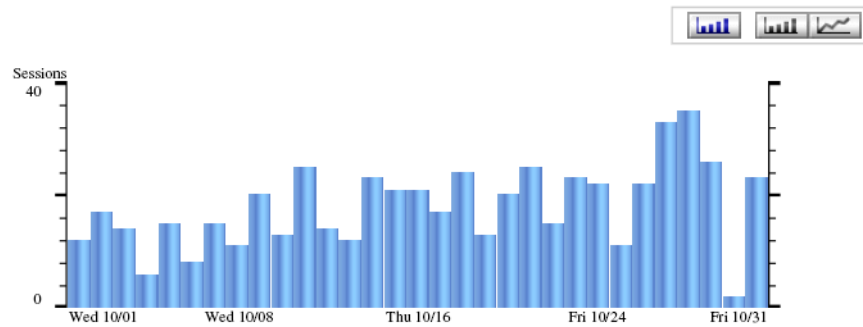
This report shows the trend of recent activity on your website in terms of Pageviews over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Pageview' is defined as a request from a visitor's browser for a displayable web page, generally an HTML file. Urchin's configuration controls which file extensions are treated as Pageviews. In general, images and other embedded content, such as style sheets and javascript, are not considered to be Pageviews.

Report: Sessions Graph - www.veteranssleep.pitt.edu
Date Range: 10/01/2008 - 10/31/2008

Range Total: 558 **Daily Average:** 18.00



? Help Information:

Sessions Graph

This report shows the trend of recent activity on your website in terms of Visitor Sessions over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Session' is defined as a series of clicks on your site by an individual visitor during a specific period of time. A Session is initiated when the visitor arrives at your site, and it ends when the browser is closed or there is a period of inactivity. Sessions quantities will vary to some degree based on what type of visitor tracking method is employed. For the most accurate numbers, the Urchin Traffic Monitor (UTM) should be used.

Report: Summary - www.veteranssleep.pitt.edu
Date Range: 10/01/2008 - 10/31/2008

Total Sessions	558.00
Total Pageviews	3,933.00
Total Hits	4,574.00
Total Bytes Transferred	46.91 MB
Average Sessions Per Day	18.00
Average Pageviews Per Day	126.87
Average Hits Per Day	147.55
Average Bytes Transferred Per Day	1.51 MB
Average Pageviews Per Session	7.05
Average Hits Per Session	8.20
Average Bytes Per Session	86.08 KB
Average Length of Session	00:31:19

? Help Information:

Summary

The Summary shows totals and averages for Sessions, Pageviews, Hits, and Bytes for the currently selected Date Range. Visitors information is not shown here because it is only available when UTM visitor tracking is employed.

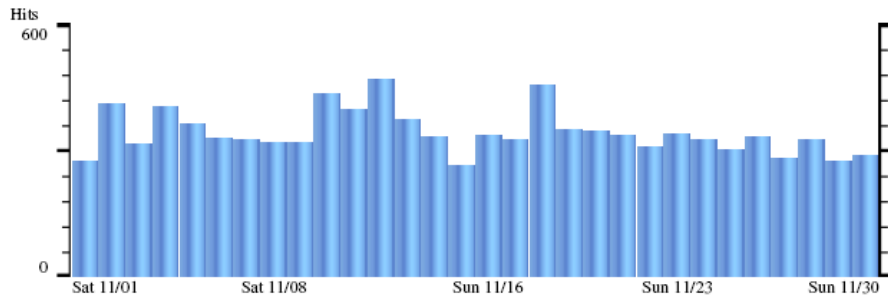
Calculation Methodology

- Session: A series of Hits to your site over a specific period of time by one visitor.
- Pageview: A request to the web server by a visitor's browser for any web page; this excludes images, javascript, and other generally embedded file types.
- Hit: Any successful request to a webserver from a visitor's browser.
- Bytes: The quantity of network bandwidth used by the files requested during the selected Date Range.

November 2008

Report: Hits Graph - www.veteranssleep.pitt.edu
Date Range: 11/01/2008 - 11/30/2008

Range Total: 10,303 **Daily Average:** 343.43



Help Information:

Hits Graph

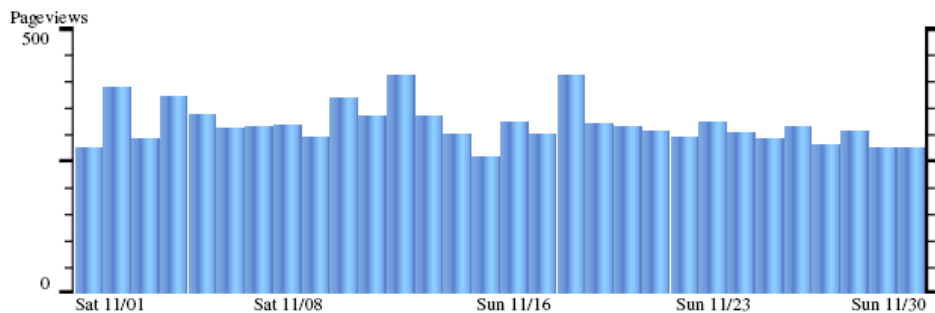
This report shows the trend of recent activity on your website in terms of successful Hits over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodolgy

A 'Hit' is simply a successful request to your web server from a visitor's browser for any type of file, whether an image, HTML page, an MP3 file, or any other type. A single web page can cause many Hits -- one for each image included on the page, etc.

Report: Pageviews Graph - www.veteranssleep.pitt.edu
Date Range: 11/01/2008 - 11/30/2008

Range Total: 9,572 **Daily Average:** 319.07



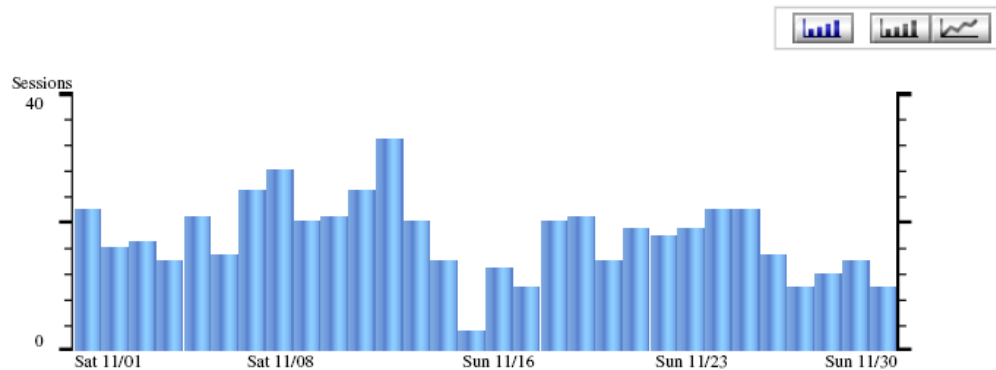
Help Information:

Pageviews Graph

This report shows the trend of recent activity on your website in terms of Pageviews over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Report: Sessions Graph - www.veteranssleep.pitt.edu
Date Range: 11/01/2008 - 11/30/2008

Range Total: 533 **Daily Average:** 17.77



? Help Information:

Sessions Graph

This report shows the trend of recent activity on your website in terms of Visitor Sessions over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Report: Summary - www.veteranssleep.pitt.edu
Date Range: 11/01/2008 - 11/30/2008

Total Sessions	533.00
Total Pageviews	9,572.00
Total Hits	10,303.00
Total Bytes Transferred	88.92 MB
Average Sessions Per Day	17.77
Average Pageviews Per Day	319.07
Average Hits Per Day	343.43
Average Bytes Transferred Per Day	2.96 MB
Average Pageviews Per Session	17.96
Average Hits Per Session	19.33
Average Bytes Per Session	170.84 KB
Average Length of Session	01:28:16

? Help Information:

Summary

The Summary shows totals and averages for Sessions, Pageviews, Hits, and Bytes for the currently selected Date Range. Visitors information is not shown here because it is only available when UTM visitor tracking is employed.

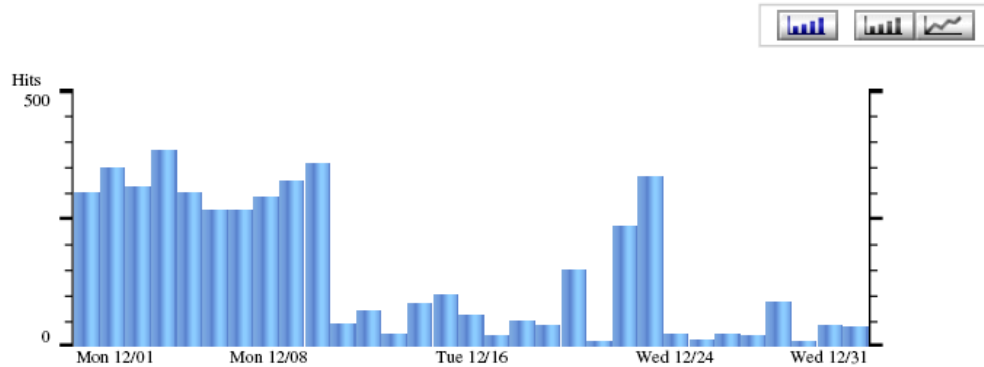
Calculation Methodology

- Session: A series of Hits to your site over a specific period of time by one visitor.
- Pageview: A request to the web server by a visitor's browser for any web page; this excludes images, javascript, and other generally embedded file types.
- Hit: Any successful request to a webserver from a visitor's browser.
- Bytes: The quantity of network bandwidth used by the files requested during the selected Date Range.

December 2008

Report: Hits Graph - www.veteranssleep.pitt.edu
Date Range: 12/01/2008 - 12/31/2008

Range Total: 4,658 **Daily Average:** 150.26



? Help Information:

Hits Graph

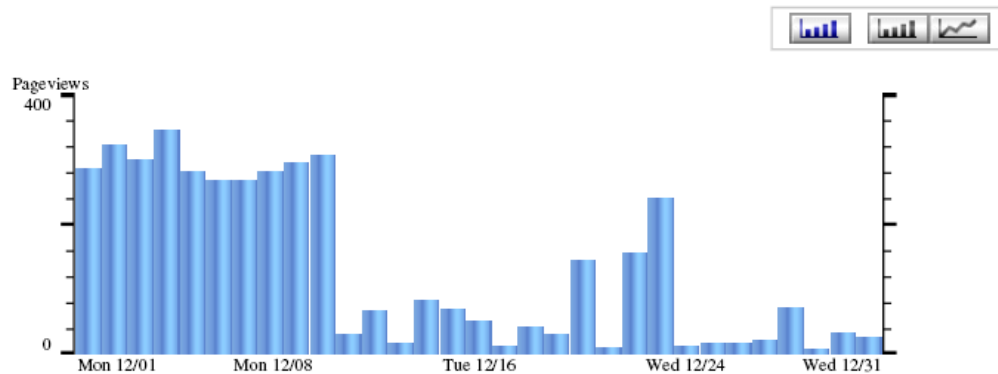
This report shows the trend of recent activity on your website in terms of successful Hits over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Calculation Methodology

A 'Hit' is simply a successful request to your web server from a visitor's browser for any type of file, whether an image, HTML page, an MP3 file, or any other type. A single web page can cause many Hits -- one for each image included on the page, etc.

Report: Pageviews Graph - www.veteranssleep.pitt.edu
Date Range: 12/01/2008 - 12/31/2008

Range Total: 4,137 **Daily Average:** 133.45



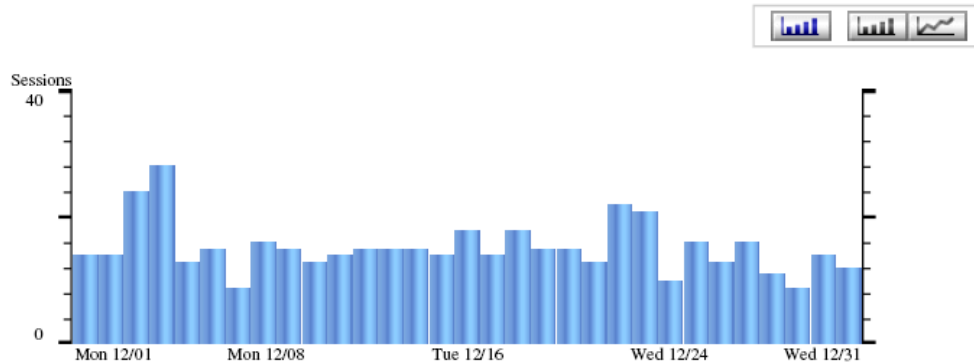
? Help Information:

Pageviews Graph

This report shows the trend of recent activity on your website in terms of Pageviews over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Report: Sessions Graph - www.veteranssleep.pitt.edu
Date Range: 12/01/2008 - 12/31/2008

Range Total: 471 **Daily Average:** 15.19



? Help Information:

Sessions Graph

This report shows the trend of recent activity on your website in terms of Visitor Sessions over time. The default timeframe is one week, but this can easily be changed in the Date Range control area.

Report: Summary - www.veteranssleep.pitt.edu
Date Range: 12/01/2008 - 12/31/2008

Total Sessions	471.00
Total Pageviews	4,137.00
Total Hits	4,658.00
Total Bytes Transferred	51.65 MB
Average Sessions Per Day	15.19
Average Pageviews Per Day	133.45
Average Hits Per Day	150.26
Average Bytes Transferred Per Day	1.67 MB
Average Pageviews Per Session	8.78
Average Hits Per Session	9.89
Average Bytes Per Session	112.29 KB
Average Length of Session	00:36:21

? Help Information:

Summary

The Summary shows totals and averages for Sessions, Pageviews, Hits, and Bytes for the currently selected Date Range. Visitors information is not shown here because it is only available when UTM visitor tracking is employed.

Calculation Methodology

- Session: A series of Hits to your site over a specific period of time by one visitor.
- Pageview: A request to the web server by a visitor's browser for any web page; this excludes images, javascript, and other generally embedded file types.
- Hit: Any successful request to a webserver from a visitor's browser.
- Bytes: The quantity of network bandwidth used by the files requested during the selected Date Range.

Appendix III

Data Safety and Monitoring Board Reports

July 2, 2008

January 21, 2009

Pittsburgh, July 11 2008

3811 O'Hara Street
Pittsburgh, PA 15213-2593
412-246-6413
Fax: 412-246-5300

**Meeting Minutes, Data Safety and Monitoring Board (DSMB)
Efficacy of Adjunctive Sleep Interventions for PTSD (PR054093)
July 2, 2008**

DSMB members: Drs. Wesley Thompson, Ph.D. (Chair), Ellen Frank, Ph.D., Terrence Keane, MD, (not able to attend)

In attendance: Anne Germain, Ph.D. (PI), Eric A. Nofzinger MD, (Co-I), Abdul Hakim (Program Coordinator), and Catharine Hebdon (Research Specialist)

A. Brief review of progress since last DSMB meeting**1. Recruitment/Enrollment Data**

We have consented 65 individuals and randomized 27 individuals as of 5/31/2008. While the number of individual consented matches our initial target enrollment plan, the number of individual randomized is clearly behind schedule. Of all individuals with whom we initiate the telephone screen, only 4% make it to randomization.

The main reasons for exclusion between the telephone script and consent visit include:

- Age > 60 years old
- No longer interested /unable to reach
- Use of medications incompatible with the study
- Bipolar / psychotic disorders

Recommendation 1: Dr. Frank recommended that the upper age limit be lifted so that older veterans, who also endorse clinically meaningful sleep disturbances and who would be able to participate in and potentially benefit from the study. This should be done if Dr. Keane is in agreement with this recommendation.

The main reasons for losing participants after the initial visit are no-shows.

Recommendation 2: After discussing the possible reasons for no-shows, it was recommended that all trauma-related assessments be completed at the last screening visit, rather than at consent visit as currently conducted. The SCID & H&P will be conducted first. The CAPS and THQ will be completed at the subsequent visits, when we have had additional time to create a safe rapport with participants.

Drop out rates. It is noted that there seems to be a higher drop out rate in the BSI arm of the study when compared to the medication arm. Reasons for drop-outs in the BSI arm included re-deployment and employment-related relocations.

Recommendation 3: For the next meeting, the DSMB members would like us to distinguish individuals who dropped out against medical advice and those who drop-out for other life events.

Summary of new recruitment efforts in the last 6 months:

- A new mass mailing effort is underway with the VAPHS MIRECC. To date, 1,000 letters have been sent, and we have received 18 inquiries. 1500 more letters will be sent from lists drawn from patients enrolled at the the OIF/OEF and PTSD clinics. We plan to repeat this mass mailing with lists of patients registered in other clinics (Audiology, Women's Clinic, and Primary Care Clinics) with the mass mailing should bring additional inquiries.
- Armories and military Family Support groups have also been re-contacted which has resulted in many calls from wives.
- The website has about 300 hits per week but it is not too effective as a stand alone recruitment tool as.
- As recommended at the last DSMB meeting, we used bus ads in the last 6 months. A few participants were recruited via this medium. However, the bus ad pooled many individuals who were not veterans.

Treatment-related aspects:

Participants who have completed the interventions tend to show at least some improvements in sleep and daytime function.

Recommendation 4: For the next DSM meeting, the members would like to be able to review changes in sleep across the 8-week of the intervention phase for each participant who initiate treatment. Pre- and post-treatment scores on PTSD, depression, and anxiety scales will also be provided.

2. Safety Issues

- None to report at this time. There were no serious adverse events.
- One unanticipated events occurred during the mass mailing: A letter was sent to a deceased individual, and his widow wrote a response letter. The VA patient advocate addressed her concerns, which were not related to the research study, but to financial difficulties in obtaining a veteran's plaque for her husband's grave.

3. Deviations

- The most frequent reason for deviations is a delay between scheduled visits to accommodate participants' schedule.

4. Summary and recommendations

The PI and her team must continue to ensure and promote accrued recruitment efforts to meet the targeted enrollment goals. Other aspects of the study appear to be on target the standards of procedures and quality control.

Four recommendations were made by the DSMB members, and include:

Recommendation 1: Dr. Frank recommended that the upper age limit be lifted so that older veterans, who also endorse clinically meaningful sleep disturbances and who would be able to participate in and potentially benefit from the study. This should be done if Dr. Keane is in agreement with this recommendation.

- Action Item: We will submit this modification to the IRB promptly before the end of this month. Once IRB approves this modification, we will re-contact individuals over the age of 60 years old who were initially excluded to offer participation in the study.

Recommendation 2: After discussing the possible reasons for no-shows, it was recommended that all trauma-related assessments be completed at the last screening visit, rather than at consent visit as currently conducted. The SCID & H&P will be conducted first. The CAPS and THQ will be completed at the subsequent visits, when we have had additional time to create a safe rapport with participants.

- Action Item: We will implement this change promptly as there is already flexibility built into the screening process as approved by the IRBs.

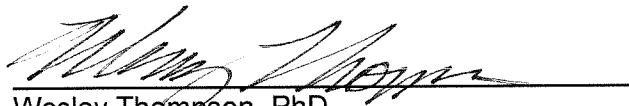
Recommendation 3: For the next meeting, the DSMB members would like us to distinguish individuals who dropped out against medical advice and those who drop-out for other life events.

- Action Item: This information will be provided for the next meeting.

Recommendation 4: For the next DSM meeting, the members would like to be able to review changes in sleep across the 8-week of the intervention phase for each participant who initiate treatment. Pre- and post-treatment scores on PTSD, depression, and anxiety scales will also be provided.

- Action Item: This information will be provided for the next meeting.

The next meeting is scheduled for Wednesday, January 7 2009 at 12 pm.



Wesley Thompson, PhD
DSMB Chair
Assistant Professor of Statistics and Psychiatry
University of Pittsburgh

Pittsburgh, January 21 2008

**Meeting Minutes, Data Safety and Monitoring Board (DSMB)
Efficacy of Adjunctive Sleep Interventions for PTSD (PR054093)
January 21, 2009**

DSMB members: Drs. Wesley Thompson, Ph.D. (Chair), Ellen Frank, Ph.D., Terrence Keane, MD (not able to attend)

In attendance: Anne Germain, Ph.D. (PI), Danielle Stein, BA (Research Projects Assistant), Miriam Stoll, BS (Student Research Assistant)

A. Brief review of progress since last DSMB meeting

1. Recruitment/Enrollment Data

We have consented 106 individuals and randomized 45 individuals as of 12/1/2008. While the number of individuals consented matches our initial target enrollment plan, the number of individual randomized is behind schedule. Of all individuals with whom we initiate the telephone screen, only 4.6% make it to randomization.

Our goal is a total of 66 participants; 22 in each treatment group.

The main reasons for exclusion between the telephone script and consent visit include:

- Subject does not pass apnea screen that takes place on first night in sleep lab
- No longer interested /unable to reach
- Use of medications incompatible with the study

Recommendation 1: Dr. Frank recommended that anyone who speaks with participants should have motivational interviewing training, which has been successful in helping people enroll participants for studies on substance dependence and other types of groups who are ambivalent about treatment. The technique focuses on the ambivalence people feel towards treatment and helps them address it. Allan Zuckoff is local and a world-wide expert on this topic – possibly we could pay him a consulting fee to give a few presentations for our team. Dr. Germain will follow up on this recommendation.

Participant Demographics

We plan to recruit more female veterans – our target is 30% of study participants female. Attempts to recruit more through VA Women's Clinic were not successful; no interest was being shown through that avenue.

More women are responding to the mailing.

Race/ethnicity distribution is right on target and reflects the percentage of ethnicities of veterans in the Pittsburgh area.

Exclusion/Dropout

We have modified the procedures so that trauma-related assessments are completed at the last screening visit, rather than at the consent visit as was previously the procedure. The SCID & H&P are conducted first. The CAPS and THQ are completed at the subsequent visits. This has lessened the dropout rate as it gives us additional time to create a safe rapport with participants.

We had two participants in treatment withdraw from the study because of issues with medication. One no longer had insurance coverage to pay for medication, another was prescribed by their physician a new medication that was incompatible with participation in the study.

Recommendation 2: Dr. Frank recommended looking into possible alternatives to participant withdrawing in situations where medication issues arise during the study – if an insurance issue, see if there are samples of the medication available; pay for medications out of pocket; include cost of medications in study budget. If patient is starting a new medication, ask the participant's physician if it's possible to wait a few weeks until study completion to start participant on new medication.

Summary of recruitment efforts in the last 6 months:

- We have a mailing effort through the VA that is getting excellent returns – around 10%. We have 90 returned postcards to call back once we are no longer on hold. We have about 7000 more to send out.
- We continue to advertise through television, radio, and local newspapers.
- We spent almost \$85,000 in last year on recruitment, but the return rate for radio, TV, etc. is low, the budget is limited, and the mailings are having a much better return rate.

Recruitment through the VA is currently on hold

The VA performed an audit in December, and VA IRB approval is currently on hold.

Two events led to the audit:

1. The VA checked up on an outdated form, calling the physician's number listed on it, and reached Dr. Moul, who directed them to Dr. Mammen.
2. Adverse Event – a participant's signature on a consent form wasn't witnessed. The rules were ambiguous previously on whether signatures had to be witnessed and who could be a witness for that purpose. This policy has now been clarified that all consents must be witnessed, and anyone can witness who is not on the study.

We are able to continue treatment on participants who were already enrolled while recruitment is on hold.

Recommendation 3: In the future, DSMB members should be contacted immediately if the study is placed on hold or if any other similar situations arise.

Treatment

Participants in the medication arm of the study have reported very few and minimal side effects, consisting mostly of mild dizziness and headaches.

Number of completed participants so far:

- 9 intervention
- 11 Prazosine
- 11 placebo

Recommendation 4: Dr. Thompson recommended recruiting and running as many participants as possible for a better statistical analysis. To get .5, we would need 60 people per group. At least 40 people per group would be a good goal.

Recommendation 5: Dr. Frank and Dr. Thompson recommended that, when submitting modifications to the IRBs to add additional participants, we reflect that additional relevant information has been published in the interim during the time over which the study has been conducted so far.

Recommendation 6: For the next DSMB meeting, members would like to be provided a file list that gives the file name, brief overview of the content, and file location, and we can bring patient binders rather than copying and compiling the patient information into new binders.

2. Safety Issues

- The unexpected event regarding randomization cards was reviewed, discussed, and properly addressed. The matter has been resolved.
- No safety issues to report at this time. There were no adverse events that were a threat to safety.

3. Deviations

- The most frequent reason for deviations is a delay between scheduled visits to accommodate participants' schedule.

4. Summary and recommendations

The PI and her team must continue to ensure and promote accrued recruitment efforts to meet the targeted enrollment goals. Other aspects of the study appear to be on target the standards of procedures and quality control.

Six recommendations were made by the DSMB members, and include:

Recommendation 1: Dr. Frank recommended that anyone who speaks with participants should have motivational interviewing training, which has been successful in helping people enroll participants for studies on substance dependence and other types of groups who are ambivalent about treatment. The technique focuses on the ambivalence people feel towards treatment and helps them address it. Allan Zuckoff is local and an expert – possibly we could pay him a consulting fee to give a few presentations for our team.

- Action Item: We will get in touch with Dr. Zuckoff and make arrangements for training with him.

Recommendation 2: Dr. Frank recommended looking into possible alternatives to participant withdrawing in situations where medication issues arise during the study – if an insurance issue, see if there are samples of the medication available; pay for medications out of pocket; include cost of medications in study budget. If patient is starting a new medication, ask the participant's physician if it's possible to wait a few weeks until study completion to start participant on new medication.

- Action Item: We will try to implement these alternatives to participant withdrawal in applicable situations.

Recommendation 3: In the future, DSMB members should be contacted immediately if the study is placed on hold or if any other similar situations arise.

- Action Item: We will follow this procedure going forward.

Recommendation 4: Dr. Thompson recommended recruiting and running as many participants as possible for a better statistical analysis. To get .5, we would need 60 people per group. At least 40 people per group would be a good goal.

- Action Item: We will continue with recruiting efforts when the VA IRB has re-approved, and we will modify the protocol to specify a higher number of participants.

Recommendation 5: Dr. Frank and Dr. Thompson recommended that, when submitting modifications to the IRBs to add additional participants, we reflect that additional relevant information has been published in the interim during the time over which the study has been conducted so far.

- Action Item: We will report on recently published literature to reflect recent findings in sleep medicine to justify modifications to our study.

Recommendation 6: For the next DSMB meeting, members would like to be provided a file list that gives the file name, brief overview of the content, and file location, and we can bring patient binders rather than copying and compiling the patient information into new binders.

- Action Item: We will provide the meeting materials accordingly.

The next meeting will take place in July, 2009. A specific date for this meeting will be scheduled in the near future.

Appendix IV

Documentation of unanticipated event and deviation

LIST OF DEVIATIONS BETWEEN MAY 31, 2008 TO JANUARY 7, 2009

ID #: 209999

Type: Protocol Deviation not affecting risk

Deviation: Participant was randomized after getting an AHI estimate of 6.8 on 3/22/08. His actual AHI was 33.22.

Action: Spoke with the lab manager who said that the tech made a mistake and sent the wrong information.

Outcome: Participant was excluded for sleep Apnea and sent back to VA for treatment.

ID #: 210640

Type: Protocol Deviation not affecting risk

Deviation: *Participant did not complete blood draws.*

Action: Participant is unable to complete the blood draws required for the medication arm of the study due to a work conflict. The participant begins work @ 0600hrs at the Pittsburgh Planetarium and will not be able to have her blood drawn in the CTNRC or Primary care at WPIC.

Outcome: Dr. Germain has determined we will not have bi weekly blood draws for this participant. This does not change the risk-benefit ratio of participating in the study. This decision reduces the risks (associated with blood draws) of participating in the study. Participant has been compliant with medication and study regimen. No adverse or unexpected events were reported or observed with the participant.

ID #: 210675

Type: Protocol Deviation not affecting risk

Deviation: *Participant did not complete blood draws.*

Action: Participant is unable to complete the blood draws required for the medication arm of the study due to a school conflict. The participant attends Indiana University of Pennsylvania and has classes daily until 1400hrs. He will not be able to have his blood drawn in the CTNRC or Primary care at WPIC.

Outcome: Dr. Germain has determined we will not have bi weekly blood draws for this participant. This does not change the risk-benefit ratio of participating in the study. This decision reduces the risks (associated with blood draws) of participating in the study. Participant has been compliant with medication and study regimen. No adverse or unexpected events were reported or observed with the participant.

ID#: 209692

Type: Protocol Deviation not affecting risk

Deviation: Participant returned to study and repeated baseline procedures.

Action: Participant was withdrawn from study on 11 April 08 due to Alcohol abuse. He requested to return to the study and met with the PI on 08/26 08. The PI informed the participant he could come back to the study but he would have to remain clean the entire time and repeat his baseline procedures (completed initial baseline procedures on 12/11/07)

Outcome: Participant completed baseline procedures on 09/4/08. Protocol Deviation not affecting risk

ID #: 210364

Type: Protocol Deviation not affecting risk

Deviation: Participants H&P and sleep dates were outside of the study range

Action: Participant consented on 4/23/08 but due to her AT was unable to scheduled for an H&P before 5/30 08. However the participant was a no show for that appointment and was rescheduled for 6/17/08 which she attended.

Outcome: Participant was rescheduled for and completed her APSCREEN and sleep studies on 6/20/08 and 29-30 June.

ID #: 210925

Type: Protocol Deviation not affecting risk

Deviation: Participant procedures are outside of study range

Action: Participant consented on 9/30/08 but was unable to schedule an H&P until 10/27/08 due to her active reserve status. The participant was able to complete her APSCREEN on 11/15/08 but had to cancel her scheduled baseline visit on 11/23-24/08 due to work related issues.

Outcome: Participant completed her baseline sleep procedures on 12/14/08.

ID #: 210060

Type: Protocol Deviation not affecting risk

Deviation: N4-N5 Sleep nights are outside of study range

Action: Participant completed his visit #8 on 4 June 08, but is unable to conduct his N4-N5 Sleep studies within 7-10 days.

Outcome: Participant completed his N4-N5 sleep nights on 6/18/08.

ID #: 210631

Type: Protocol Deviation not affecting risk

Deviation: Participant was unable to conduct her initial BSI visit 7 to 10 days after her baseline sleep due reconstructive knee surgery.

Action: Participant completed he baseline studies on 08/4/08 and completed reconstructive knee surgery on 08/13/08. She was unable to operate a motor vehicle while in her cast.

Outcome: Participant completed her week 1 BSI visit on 24 Sept 08.

ID #: 210858

Type: Protocol Deviation not affecting risk

Deviation: *Participant did not wear actigraphy nor have all BSI visits audio taped.*

Action: Participant is unable to wear actigraphy or to have all of his BSI visits audio taped because he travels over two hours to come to the visits. The participant lives and works outside of Harrisburg PA and doesn't finish working until 1600hrs. Because of the distance and for safety reasons, Dr. Germain gave him permission to conduct most of the BSI visits by phone. He will not be able to have his sessions audiotaped or wear actigraphy.

Outcome: Dr. Germain has determined we will not have weekly audio taped sessions or give actigraphy to this participant. This does not change the risk-benefit ratio of participating in the study. This decision reduces the risks (associated with driving two hours to attend a session) of participating in the study. Participant has been compliant with BSI and study regimen. No adverse or unexpected events were reported or observed with the participant.

ID #: All

Type: Protocol Deviation not affecting risk

Deviation: Participants visits were outside the study range during the Christmas holidays

Action: Participants canceled most of their holiday appointments during December for the holidays.

Outcome: Participants returned to normal schedules after New Years.

ID #: 211070

Type: Protocol Deviation not affecting risk

Deviation: Participants information was sent to the pharmacy for randomization before the individual was randomized to meds.

Action: Participants information requesting the pharmacy tp to further randomize him to med/placebo was sent on 30 December 2008. The coordinator was preparing to request a randomization for 211061 on 12 January 08 and realized that he was already randomized to meds, which led him to look up the randomization for 211070. He discovered that this participant wasn't randomized and immediately requested a randomization and informed me of his error.

Outcome: Participants was randomized to medication on 13 January 08. Protocol Deviation not affecting risk

Appendix V

Documentation of VAPHS audit by the Research Compliance Committee

**DEPARTMENT OF
VETERANS AFFAIRS**

MEMORANDUM

Date: December 19, 2008

From: Tammy Capozzoli, CCRC
Research Compliance Officer



Subj: MIRB #02386; *Efficacy of Adjunct Sleep Interventions for Post Deployment Stress Disorders (PDSD)*

To: Anne Germain, PhD

I would like to take this opportunity to thank you for your cooperation with the Research Compliance Program. Enclosed please find the report of the audit conducted on the above-named study.

The main objective of such a review is to enhance the quality of clinical research and to ensure proper documentation, record keeping, data analysis and adherence to all the components that constitute good academic research practice. The audit assesses the study conduct procedure, identifies errors and omissions, and is a means to provide the investigator with recommendations for corrections and improvement.

Please review the report of the audit and provide a written response no later than **January 21, 2009**. Your response should address all requests for clarification(s) and, if applicable, descriptions of corrective action that will be implemented to resolve problems identified during the course of the audit. The signed and dated response to the audit should be sent to:

- Dr. George Dougherty, Acting IRB Chair
VAPHS Highland Drive, Building 2, 2-West (151U-H)
Pittsburgh, PA 15206

To complete your file in the compliance office, please send a copy of the response to:

- Tammy Capozzoli
VAPHS Highland Drive, Building 2, 2-West (151U-H)
Pittsburgh, PA 1520

Thank you once again for your cooperation in facilitating this audit. If you have any comments or questions regarding the audit findings, please do not hesitate to call me at 412-954-5388.

Enclosure (1)

Cc: Dr. George Dougherty, Acting IRB Chair
VAPHS Highland Drive

Cc: Dr. Jeffrey Peters
VAPHS Highland Drive

REPORT ON INTERNAL STUDY AUDIT CONDUCTED BY THE VAPHS RESEARCH EDUCATION AND COMPLIANCE OFFICE

Principal Investigator: Anne Germain, PhD

Study Title: Efficacy of Adjunct Sleep Interventions for Post Deployment Stress Disorders (MIRB #02386)

Study Coordinator: Abdul Hakim

Audit Dates: December 18, 2008

VA Audit Staff: Tammy Capozzoli, CCRC
Krisssa Caroff

Source of Funding: Department of Defense

Level of Risk: Greater Than Minimal Risk; Low Scrutiny

Date of Report: January 5, 2009

Report Prepared by: Tammy Capozzoli, CCRC

Due to the results of a Quality Assurance Audit of the VAPHS Research Telephone Answering Service conducted by the Research Education and Compliance Office and an Unanticipated Problem Report involving the emergency cards associated with the randomization of the investigational study medication, the Research Compliance Committee has requested a for-cause audit be performed of this research study.

The overarching objective of this study is to investigate the efficacy and durability of prazosin (PRZ) and a brief, evidence based behavioral sleep intervention (BSI) for reducing deployment related sleep disturbances. The investigator proposes to conduct a randomized, controlled trial in a sample of 90 men and women veterans between the ages of 18 and 60 years old, who experience significant nightmares and insomnia. The two sleep treatments will be administered over an eight week period, and will be compared to placebo (PLA). Secondary outcomes include PTSD symptom severity, depression, anxiety, health related quality of life, and disability. The specific aims and hypotheses are:

- Aim A: To investigate the efficacy of PRZ and BSI on primary outcome measures of sleep as determined by sleep diary parameters, laboratory based sleep measures, and validated sleep questionnaires compared to PLA. Hypothesis A: PTSD subjects randomized to either PRZ or BSI will have higher categorical response rate for sleep symptoms than subjects randomized to PLA.
- Aim B: To evaluate the effects of active sleep interventions on secondary outcome measures of daytime PTSD symptoms, depression, anxiety, health related quality of life and disability. Hypothesis B: PTSD subjects randomized to either PRZ or BSI will show greater improvements in mental and physical health outcomes than subjects randomized to PLA.
- Aim C: To determine whether PRZ is associated with more rapid response rates than BSI. Hypothesis C: PTSD subjects randomized to PRZ will show more rapid improvement in sleep symptoms than subjects randomized to BSI.
- Aim D: To compare the durability of therapeutic gains four month post treatment. Hypothesis D: PTSD subjects randomized to BSI will show greater improvements in sleep and mental/physical

health outcomes than subjects randomized to PRZ at the end of a four month naturalistic follow up period.

Investigating the efficacy and durability of interventions for PTSD related sleep disturbances will improve the short term and long care management of veterans who suffer from PTSD. Data derived from this study will inform the development of prevention and intervention strategies aimed at reducing acute stress related sleep disturbances, and that may be amenable to high demand military settings such as battle fields. Finally, the study findings will be directly generalizable to individuals suffering from PTSD to the general public.

This study has been approved to enroll 120 subjects. At the time of the audit, the investigator had telephone screened a total of 253 subjects with a total of 36 VAPHS subjects enrolled.

Pre-audit Interview

A pre-audit interview was held on December 18, 2008, with Dr. Germain, Abdul Hakim, Tammy Capozzoli and Krissa Caroff. The following table represents topics covered in the pre-audit interview.

Procedure	Responsibility / Comment
IRB Submissions	Abdul Hakim is responsible for the preparation and submission of all IRB correspondence. Dr. Germain stated that she reviews all correspondence prior to submission.
Regulatory File	Abdul Hakim is responsible for maintaining and filing regulatory documents/correspondence.
Research Staff Communication	Dr. Germain states that she holds weekly meetings (Tuesdays) with research personnel as well as correspond on a daily basis.
Recruitment Measures and Advertising	To avoid cold calling, individuals who express interest to members of their treatment team (PTSD Treatment, OIF/OEF, Treatment for Addictive Disorders, Mental Health, Women's Health and PCP clinics) of the VA hospital will sign consent to provide their contact information, which allows the PI or designated asst. to contact this individual by telephone and to ascertain eligibility. Advertisements are also posted at the VAPHS. A partial HIPAA waiver/authorization has been granted in order to conduct a mass mailing from specified clinics. Mr. Chris Fleissner and John Walker accesses the Data warehouse to review VAPHS patients for basic eligibility criteria. Mr. Fleissner and Mr. Walker then compile a list of potential participants and forwards to Mr. Pisarov. Mr. Pisarov completes the process of mailing letters to the potential participants identified by Mr. Fleissner and Mr. Walker. Mr. Pisarov forwards the reply postcards of interested veterans to Mr. Hakim and Dr. Germain.

Procedure	Responsibility / Comment
Screening	Part I: A waiver of HIPAA authorization for screening was granted so that the coordinator or investigator may use a telephone script to describe the study goals and procedures prior to obtaining oral informed consent to collect eligibility information. After the completion of the telephone screening, if it is determined that a participant meets inclusion/exclusion criteria they are asked to come in for a face to face interview and undergo the formal informed consent process. Part II: Once participants have completed the face to face interview and formal informed consent process, they will have additional screening procedures. This part of screening may take up to 2-3 days.
Informed Consent	Mr. Hakim stated that he meets with potential subjects in his private office or designated interview room and thoroughly reviews the informed consent document. Following Mr. Hakim's review of ICF either Dr. Nofzinger, Dr. Moul or Dr. Mammen are responsible for administering and obtaining informed consent. Per Dr. Germain and Mr. Hakim, consenting subjects takes approximately 2 hours. All questions and concerns are addressed and subjects are asked if they would like to take ICF home and discuss with family or friends prior to study participation.
Randomization	Following Baseline evaluation, participants will initially be randomized in a 2:1 manner to medication (PRZ or PLA) or BSI. The initial randomization is currently done by one of the data personnel off a sheet created by statistician Amy Begley. Participants randomized to medication will then be randomized by pharmacy in a 1:1 manner to either PRZ or PLA.
Adverse Events	Dr. Germain stated that AE reports will be prepared by Mr. Hakim. Dr. Germain will review AE's prior to submission to VAPHS IRB.
Questionnaires	There are several questionnaires utilized throughout the study for participants randomized to medication or BSI. Per the protocol, to minimize assessment bias to the non-blind BSI, a CNRC RN will perform the clinician administered post-treatment assessments (e.g CAPS-2)
Test Article Accountability	Dr. Germain noted that PRZ and PLA are located and dispensed by the WPIC pharmacy. Mr. Hakim sends the RX script request to one of the investigators for signature and once obtained forwards it to the pharmacy. Mr. Hakim then picks up the RX at the pharmacy. Mr. Hakim does not keep an accountability log for the medication to monitor and document what participants receive and return. The RCO's were unable to visit the WPIC pharmacy to review accountability logs, however copies of the WPIC pharmacy patient profile which includes information such as when drug was dispensed and dosage was included in some subject records.

Procedure	Responsibility / Comment
Physical Examination	PE's including Medical history questionnaire (listing of all current medications and substance use), height & weight, routine lab tests (including blood count & chem., thyroid func, electrolytes, CBC, diabetes & liver func.), EKG, urine drug screens for amphetamines, marijuana, heroin, barbiturate, PCP alcohol and other narcotics, pregnancy test for women, BP resting and standing are completed on all subjects and are done by NCTRC nurses or physicians in the Primary Physicians office located on the 1 st floor of WPIC
Specimen Collection and Storage	Blood is collected from the PRZ/PLA subjects on weeks 2, 4, 6 and 8. Blood is drawn by NCTRC nurses and stored in the psychopharmacology laboratory. Dr. Germain stated the blood is collected and stored for pharmacokinetic testing only.
Record Keeping and Record Storage	All subject records and regulatory files are located in Abdul Hakim's office in a locked filing cabinet located within WPIC, 11th floor, office E-1109. Audio tapes are located in Robin Richardson's private office.
Data Analysis	Dr. Germain stated data is not currently being analyzed. Data analysis will begin at study completion. Data will be analyzed by MIRECC statisticians and Dr. Germain.
Data Monitoring	Per the protocol, the data safety and monitoring plan (DSMP) will address the following areas: progress of the research study (including assessment of data & timeliness and participants recruit, accrual & retention) review of outcome and adverse event data to determine if changes should be made to protocol or ICF 3) assessment of external factors or relevant information 4) review study procedures for protection of research participants privacy. Each of the above will be addressed in weekly to monthly meetings with research staff. All study data in these areas will be summarized on a yearly basis. Reports of the DSMP will be submitted to the IRB at the time of annual renewal. Dr. Germain noted there is an independent DSMB to review the validity and integrity of the data. The Board meets by teleconference bi-annually. Per the protocol, minutes will be kept for each meeting and submitted at continuing review or more often as requested by the IRB.
Data Security	See VA Data Security and Privacy Section
Staff Training	Per the protocol, the research coordinator will participate in an initial training program and ongoing maintenance of training for interrater reliability with assessors involved in other research studies. For BSI therapist must be a masters' degree level interventionist. Mr. Hakim mentioned that he worked with Dr. Germain to ensure that he was competent to conduct clinician-administered assessments which included interrater reliability assessments.

1.0 IRB CORRESPONDENCE AND PROTOCOL RELATED ISSUES

This study was initially approved by the VA Pittsburgh Healthcare System IRB on January 3, 2006 as greater than minimal risk and low level of scrutiny (AE1). There have been no lapses in approval.

The study was initially approved by the VA Pittsburgh Healthcare System R&D Committee on February 22, 2006. There have been no lapses in approval.

2.0 CONSENT FORM REVIEW

For the purpose of this audit, records all subjects enrolled from 12-2007 to 12-2008 were reviewed for the presence of informed consent documents. These files contained the signed consent documents for those who agreed to study participation.

	Evaluation Criteria	Comments
2.1	Were consent forms present in each research record?	Yes.
2.2	Were the consent form documents signed and dated prior to the implementation of any research related procedures?	Yes.
2.3	Was each consent form signed and dated by the research subject?	Yes.
2.4	Was each consent form signed and dated by a witness?	No. See comment 2.4
2.5	Was each consent form signed and dated by an investigator?	No. See comment 2.5
2.6	Was a progress note present in each subjects medical record?	No. See comment 2.6
2.7	Was the IRB approval date listed on each consent form?	Yes.
2.8	Was the appropriate version of the IRB approved consent form utilized for each subject?	No. See comment 2.8
2.9	Was the consent form free of extemporaneous modification?	Yes.
2.10	Was each subject consented with VA form 10-3203 prior to audio recording?	Yes.

2.0 Comments and Recommendations

2.4 All 31 subjects reviewed lacked the signature of a witness whose role is to witness the subject's signature. Often times, Dr. Mammen signed in both the investigator and witness lines of the informed consent documents.

Please explain why all of the 31 subjects reviewed lacked the signature of a witness to the subject's signature.

Note: VAPHS Standard Operating Procedures do not permit an individual listed on the research staff form to serve as a witness to the participant or the legally authorized representative's signature.

2.5 Multiple subjects were found to have informed consent administered and obtained by Dr. Ooman Mammen prior to his being authorized by the IRB to administer informed consent. Specifically, a modification was submitted to the IRB to add this individual to the project, however, this individual began consenting subjects prior to approval being obtained.

Please explain why Dr. Mammen was administering and obtaining informed consent of participants prior to IRB approval.

Several consent documents were signed by Dr. Han Liang who was not found to be affiliated with the study on any study staff form or listing of individuals authorized to administer informed consent.

Please explain why Dr. Liang was administering and obtaining informed consent of participants.

2.6 9 of the 31 subjects' medical records that were reviewed lacked a progress note documenting the informed consent process.

Please explain why subjects did not have a progress note documenting the informed consent process in their medical record as required by VHA Handbook 1200.05. Please implement corrective measures to ensure that future subjects have the appropriate progress note placed in their medical records.

2.8 The consent form signed by subject 211061 was not the most recent IRB-approved consent form. Subject 209342 signed a University of Pittsburgh consent even though the subject was confirmed by Mr. Hakim to be a VAPHS recruited participant.

Please explain why the correct version of the ICF was not used and outline corrective measures that will be implemented to ensure that all future subjects will sign the correct form. If you are unsure which is the most recently approved version you are encouraged to contact the IRB Office prior to consenting subjects.

3.0 INCLUSION CRITERIA

	Criteria	Criteria Met? Yes/No/Comments
3.1	Age between 18 and 60 years old, inclusively	Yes.
3.2	Able to read and write English	Yes.
3.3	If currently treated with psychotropic or neurological medications, medications and dosages will remain unchanged for the duration of the study.	Yes.
3.4	A score of 3 or greater on the 2 CAPS sleep items	Yes.

	Criteria	Criteria Met? Yes/No/Comments
	(nightmares and insomnia)	
3.5	Psychotropic or neurological medication and dosage have not been changed for the past two months if they were originally prescribed for psychiatric or neurological reasons	Yes.
3.6	Participants will remain in ongoing counseling services they may be receiving prior to study entry.	Yes.
3.7	Participants must have served or are currently serving in the military	Yes.

4.0 EXCLUSION CRITERIA

	Criteria	Criteria Absent? Yes/No/Comments
4.1	Current, extremely severe PTSD as determined by a score of >80 on the CAPS, and associated with severe functional impairment and distress (also determined on the CAPS)	Yes.
4.2	Current, severe, untreated Major Depressive Disorder as determined by the Structured Clinical Interview for DSM-IV (SCID)	Yes.
4.3	Must be randomized >28 and < 90 days after initial visit (initial visit is considered Day 0)	Yes.
4.4	Current history of suicidality requiring hospitalization (past 6 months)	Yes.
4.5	Current history (past 6 months) of substance or alcohol abuse as determined by the SCID, or by a positive drug screen at the physical examination	Yes.
4.6	Currently actively psychotic or bipolar disorder (past year)	Yes.
4.7	Presence of an untreated Axis I disorder not deemed secondary to PTSD	Yes.
4.8	Resting BP < 90/60 at the screening physical examination	Yes.
4.9	Heart rate >100 beats/minute	Yes.
4.10	Use of a beta-blocker	Yes.
4.11	Use of an alpha-1 antagonist agent in the previous 3 weeks	Yes.
4.12	Refusal to follow safety measures in the case of use of a phosphodiesterase 5 inhibitor (Cialis, Viagra, Levitra)	Yes.
4.13	Unexpected, untreated or serious EKG findings	No. See comment 4.13
4.14	Psychotropic or neurological medications and/or dosage changed in the past two months	Yes.
4.15	Medications and/or dosage changed in the last two	No. See comment 4.15

	months	
4.16	Unstable medical condition	Yes.
4.17	Pregnant or breast feeding women	Yes.
4.18	Apnea-hypopnea index (AHI) >15	No. See comment 4.18
4.19	Refusal to provide information relevant to selection criteria for participating in this study.	Yes.

4.0 Based upon the information contained in the subjects research records, and the VA electronic medical records (CPRS) the RCO(s) were unable to confirm that the 5 subjects screened including the 2 enrolled subjects, met all inclusion/exclusion criterion. The eligibility checklist was the only documentation available. All subjects reviewed were missing documentation of one or more exclusion criteria.

4.13 The EKG report for subject 210858 shows a marked sinus bradycardia. No explanation could be located that this finding was allowable (not considered serious) or if a repeat EKG was conducted with a normal result.

4.15 Subject 210893 was on an alpha-1 antagonist (flomax) until 9-17-2008 at which time it was replaced with Avodart. The subject was randomized 3 weeks later despite the fact that exclusion criteria state no medications and/or dosage changes in the last two months.

4.18 Subject 210893 did not have a sleep report in his research file to verify that inclusion/exclusion criteria, specifically the apnea-hypopnea index, were met.

It is important that research documentation, particularly documentation that subjects met eligibility criteria, be accurate and complete. It is recommended that a note to file be placed in the subjects' files to state that they did meet the eligibility criteria.

5.0 SCREENING PROCEDURES

	Procedure	Procedure performed as indicated? Yes/No/Comments
5.1	Telephone Screening: Complete a brief telephone interview that includes demographic and basic clinical information	Yes.
5.2	Clinical Interview: A face to face interview will be conducted for eligible participants prior to informed consent	Yes.

	Procedure	Procedure performed as indicated? Yes/No/Comments
5.3	<u>Screening (after consent):</u> Participants who appear to qualify for the study from the face to face interview will then undergo the following diagnostic evaluation to determine eligibility, a total of three visits will be required to complete screening procedures; 1. Diagnostic interviews this includes: ➤ CAPS 1 (the time reference for completing the CAPS Part 1 is the month preceding the interview (1 week for CAPS 2) ➤ Trauma History questionnaire ➤ Combat Exposure Scale ➤ Interview for sleep disorders ➤ Pittsburgh Insomnia Rating Scale ➤ Interview for DSM-IV (SCID) ➤ Marital Satisfaction Questionnaires ➤ Attachment Questionnaire ➤ Interpersonal Support Evaluation List 2. Physical screening & routine lab tests includes: ➤ Self reports ➤ Medical history questionnaire (listing of all current medications and substance abuse) ➤ PE (height, weight) ➤ Routine lab tests (including blood count & chem., thyroid func, electrolytes, CBC, diabetes & liver func. ➤ EKG ➤ Urine drug screens for amphetamines, marijuana, heroin, barbiturate, PCP alcohol and other narcotics) ➤ Pregnancy test for women ➤ BP resting and then immediately after participant is asked to stand up <i>Findings from the above testing are to be reviewed by Dr Nofzinger or Moul.</i> 3. Sleep screenings (1 night diagnostic sleep study) including: ➤ Bilateral central and occipital EEG ➤ Bilateral anterior tibialis EMG ➤ Subjects will be videotaped	No. See comment 5.3

5.0 Comments and Recommendations

Subject 210675 research file lacked documentation of routine laboratory results or urine drug screen.

6.0 STUDY PROCEDURES—For PRZ or PLA

	Procedure	Procedure performed as indicated? Yes/No/Comments
6.1	<u>Baseline:</u> To be completed prior to randomization: ➤ Complete a sleep diary for 7 consecutive nights ➤ 2 nights of in lab sleep studies ➤ Pittsburgh Sleep Quality Index ➤ PSQI addendum for PTSD ➤ Pittsburgh Sleep Diary (short form) ➤ Insomnia Severity Index (ISI) ➤ Visually scored sleep latency, efficiency, duration ➤ Power spectral analysis (beta and delta power) ➤ Heart rate variability (high & low frequency) ➤ CAPS Part 2 ➤ PTSD symptom checklist (civilian version) ➤ Beck Depression Inventory ➤ Beck Anxiety Inventory ➤ Inventory of Complicated Grief ➤ QOL Enjoyment & Satisfaction Questionnaire ➤ Medical Outcome Survey (SF-36) ➤ Sheehan Disability Scale ➤ Treatment Expectation Form All participants will be randomized at to either prazosin, behavioral sleep intervention or placebo	No. See comment 6.1

	Procedure	Procedure performed as indicated? Yes/No/Comments
6.2	<u>RANDOMIZATION:</u> Must be randomized >28 and < 90 days after initial visit (initial visit is considered Day 0) All participants will be randomized at to either prazosin, behavioral sleep intervention (actigraph) or placebo Subjects randomized to the “medicinal” arm, will be randomized a second time to either prazosin or placebo If randomized to BSI did they receive actigraph? <u>Note:</u> The PRZ & PLA 2 conditions will also include minimal sleep education involving the distribution of pamphlet on sleep hygiene published by the American Academy of Sleep Medicine.	No. See comment 6.2
6.3	<u>Morning after 1st medication dose:</u> Participants are to be called by the study coordinator to verify that no unexpected event has occurred	No. See comment 6.3
6.4	<u>Week 1:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Insomnia Severity Index ➤ Clinical Global Improvement (both clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Drug administered	No. See comment 6.4
6.5	<u>Week 2:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Blood draw (stored appropriately in psychopharm. lab) ➤ Drug administered ➤ Drug accountability	No. See comment 6.5

	Procedure	Procedure performed as indicated? Yes/No/Comments
6.6	<u>Week 3:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Drug dispensed ➤ Drug accountability	No. See comment 6.6
6.7	<u>Week 4:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ Blood draw (stored appropriately in psychopharm. lab) ➤ Drug administered ➤ Drug accountability	No. See comment 6.7
6.8	<u>Week 5:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Drug dispensed ➤ Drug accountability	Yes.
6.9	<u>Week 6:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Blood draw (stored appropriately in psychopharm. lab) ➤ Drug dispensed ➤ Drug accountability	No. See comment 6.9

	Procedure	Procedure performed as indicated? Yes/No/Comments
6.10	<u>Week 7:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Drug dispensed ➤ Drug accountability	No. See comment 6.10
6.11	<u>Week 8:</u> ➤ Pittsburgh Sleep Diary Short Form ➤ Insomnia Severity Index ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ BP ➤ Heart Rate ➤ Blood draw (stored appropriately in psychopharm. lab) ➤ Drug accountability	No. See comment 6.11

	Procedure	Procedure performed as indicated? Yes/No/Comments
612	<u>Post Visit: (end of treatment assessment)</u> ➤ PSQI ➤ PSQI Addendum for PTSD ➤ Pittsburgh Sleep Diary ➤ Visually scored sleep (sleep latency, efficiency, duration) ➤ Power Spectral Analysis (beta & delta power) ➤ Heart rate variability (high & low frequency) ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ CAPS Part 2 (per protocol to be completed by a CNRC RN) ➤ PTSD symptom checklist (civilian version) ➤ Beck Depression Inventory ➤ Beck Anxiety Inventory ➤ Inventory of Complicated Grief ➤ QOL Enjoyment & Satisfaction Questionnaire ➤ Medical Outcome Survey (SF-36) ➤ Sheehan Disability Scale ➤ Marital Satisfaction Questionnaires ➤ Attachment Questionnaire ➤ Interpersonal Support Evaluation List ➤ Client satisfaction survey	No. See comment 6.12
6.13	<u>Blind Break</u>	Yes.
6.14	<u>Month 1:</u> Telephone contact	N/A
6.15	<u>Month 2:</u> Telephone contact	N/A
6.16	<u>Month 3:</u> Telephone contact	N/A
6.17	<u>F/U 4 TELEPHONE (i.e. 6 months after randomization):</u> PSQI PSQI Addendum for PTSD Insomnia Severity Index PTSD symptom checklist (civilian version) Beck Depression Inventory Beck Anxiety Inventory Inventory of Complicated Grief Medical Outcome Survey (SF-36) Sheehan Disability Scale	N/A

6.0 Comments and Recommendations

6.1 Subject 210675 research file lacked documentation for the 7 day sleep diary, ISI or Treatment Expectation form.

Subject 210893 research file lacked documentation for PSQI addendum for PTSD and CAPS Part 2 was completed.

6.2 Subject 210675 outpatient pharmacy profile documents that the subject was randomized to placebo, however, there is no documentation of the date randomization took place.

Subject 210893 research file lacked documentation of the randomization process

6.3 Subjects 210893 and 210675 research files lacked documentation that a telephone call was placed or received the morning after their first medication dose. Additionally, if the telephone call(s) were completed according to protocol, the research files lacked documentation of the calls outcome.

6.4 Subject 210893 research file lacked documentation that subject completed an Insomnia Severity Index.

6.5 Subject 210893 and 210675 research files lacked documentation that subjects completed the required blood draw.

6.6 Subject 210675 research file lacked documentation that BP and heart rate were measured.

6.7 See comment 6.5

6.9 See comment 6.5. Additionally, subject 210675 research file lacked documentation that BP or heart rate was measured.

6.10 See comment 6.6

6.11 See comment 6.5. Additionally, subject 210675 research file lacked documentation that the subject completed the Pittsburgh Sleep Diary Short Form.

It was difficult to ascertain the date of the Week 8 visit for subject 210893 as varying dates were noted on documents associated with the Week 8 visit. Specifically, the CGI, PGI, and Asberg Side Effects Rating Scale were dated 12/1/08, while other questionnaires/assessments were dated 12/2/08. Furthermore, one questionnaire which was listed in the protocol as being associated with the post-treatment visit was located within Week 8 visit section of the research folder- specifically the CSQ.

Please clarify the correct dates of visits and create a note to file for the discrepancies.

6.12 Subjects 210893 and 210675 research files lacked documentation that subjects completed the Post visit sleep study.

Subject 210893 research file lacked documentation of QOL Enjoyment and Satisfaction Questionnaire, attachment questionnaire and the Client Satisfaction Survey. It should also be noted however, that a CSQ was completed on 12/2/08 at the Week 8 visit. Furthermore, there is some discrepancy with respect to the dates of the Post-Treatment Visit, as study questionnaires have varying dates.

It was also noted that despite the fact that study medication treatment had ended, subject 210893 was dispensed 10 mg of Prazosin on 12-11-08, according to the pharmacy outpatient profile.

Please clarify the correct date of the Post Treatment Visit and create a note to file for the discrepancies.

Please be aware that the IRB approves protocols to be implemented exactly as written. Please verify if subjects completed the study procedures. If the above procedures were not completed, please submit a protocol deviation report to the IRB.

In addition, please address corrective measures to be implemented to ensure that all procedures will be completed per protocol for future subjects.

7.0 STUDY PROCEDURES—BSI (subject 210858)

	Procedure	Procedure performed as indicated? Yes/No/Comments
7.1	Baseline: To be completed prior to randomization: ➤ Complete a sleep diary for 7 consecutive nights ➤ 2 nights of in lab sleep studies ➤ Pittsburgh Sleep Quality Index ➤ PSQI addendum for PTSD ➤ Pittsburgh Sleep Diary (short form) ➤ Insomnia Severity Index (ISI) ➤ Visually scored sleep latency, efficiency, duration ➤ Power spectral analysis (beta and delta power) ➤ Heart rate variability (high & low frequency) ➤ CAPS Part 2 (per protocol to be completed by a CNRC RN) ➤ PTSD symptom checklist (civilian version) ➤ Beck Depression Inventory ➤ Beck Anxiety Inventory ➤ Inventory of Complicated Grief ➤ QOL Enjoyment & Satisfaction Questionnaire ➤ Medical Outcome Survey (SF-36) ➤ Sheehan Disability Scale ➤ Treatment Expectation Form All participants will be randomized at to either prazosin, behavioral sleep intervention or placebo	No. See comments 7.1

7.2	RANDOMIZATION: Must be randomized >28 and < 90 days after initial visit (initial visit is considered Day 0) All participants will be randomized at to either prazosin, behavioral sleep intervention (actigraph) or placebo Subjects randomized to the “medicinal” arm, will be randomized a second time to either prazosin or placebo If randomized to BSI did they receive actigraph? Note: The PRZ & PLA 2 conditions will also include minimal sleep education involving the distribution of pamphlet on sleep hygiene published by the American Academy of Sleep Medicine.	No. See comment 7.2
7.3	Week 1: ➤ Pittsburgh Sleep Diary Short Form ➤ Intervention session (45 minute) ➤ Insomnia Severity Index ➤ Clinical Global Improvement (both clinician and self rated) ➤ Asberg Side Effects Rating Scale	No. See comment 7.3
7.4	Week 2: ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	Yes.
7.5	Week 3: ➤ Pittsburgh Sleep Diary Short Form ➤ Intervention session (45 minute) ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	No. See comment 7.5
7.6	Week 4: ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	Yes.

7.7	Week 5: ➤ Pittsburgh Sleep Diary Short Form ➤ Intervention session ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	No. See comment 7.7
7.8	Week 6: ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	Yes.
7.9	Week 7: ➤ Pittsburgh Sleep Diary Short Form ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	Yes.
7.10	Week 8: ➤ Pittsburgh Sleep Diary Short Form ➤ Insomnia Severity Index ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale	Yes.

7.11	Post Visit: (end of treatment assessment) ➤ PSQI ➤ PSQI Addendum for PTSD ➤ Pittsburgh Sleep Diary ➤ Visually scored 2 day (sleep latency, efficiency, duration) ➤ Power Spectral Analysis (beta & delta power) ➤ Heart rate variability (high & low frequency) ➤ Clinical Global Improvement (clinician and self rated) ➤ Asberg Side Effects Rating Scale ➤ CAPS Part 2 (per protocol to be completed by a CNRC RN) ➤ PTSD symptom checklist (civilian version) ➤ Beck Depression Inventory ➤ Beck Anxiety Inventory ➤ Inventory of Complicated Grief ➤ QOL Enjoyment & Satisfaction Questionnaire ➤ Medical Outcome Survey (SF-36) ➤ Sheehan Disability Scale ➤ Marital Satisfaction Questionnaires ➤ Attachment Questionnaire ➤ Interpersonal Support Evaluation List ➤ Client satisfaction survey	Yes.
7.12	Month 1: Telephone contact	N/A
7.13	Month 2: Telephone contact	N/A
7.14	Month 3: Telephone contact	N/A
7.15	F/U 4 TELEPHONE (i.e. 6 months after randomization): PSQI PSQI Addendum for PTSD Insomnia Severity Index PTSD symptom checklist (civilian version) Beck Depression Inventory Beck Anxiety Inventory Inventory of Complicated Grief Medical Outcome Survey (SF-36) Sheehan Disability Scale	N/A

7.0 STUDY PROCEDURES (BSI subject 210858)

7.1 The research file lacked the ISI and Treatment Expectation form.

7.2 The research file lacked documentation for the process of randomization.

The research file lacked documentation that the subject received an actigraph. Mr. Hakim has confirmed that due to the excessive travel of the subject, the subject did not wish to receive an actigraph monitor; however, the research file lacked documentation to this effect.

Per the protocol, actigraphy will provide objective estimates of sleep-wake patterns to determine whether subjects adhered to sleep restriction instructions. Additionally, subjects will be asked to push the event marker to indicate the beginning and end of imagery rehearsal practice sessions.

Please explain why subject 210858 was enrolled after refusal of actigraph monitoring.

Please be aware that the IRB approves protocols to be implemented exactly as written. Please submit a protocol deviation report to the IRB.

7.3 The research file lacked documentation that the subject intervention was audio taped.

7.5 See comment 7.3

7.7 See comment 7.3

Mr. Hakim confirmed subject's week 1 intervention was audio taped. However, week 3 and 5 interventions were conducted by telephone and not audiotaped.

Please be aware that the IRB approves protocols to be implemented exactly as written. Please submit a protocol deviation report to the IRB.

It is important that research documentation, be accurate and complete. It is recommended that a note of explanation be placed in the subject's file summarizing why week 3 and 5 interventions were not conducted in person or audio taped as described in the VAPHS IRB approved protocol.

8.0 DATA AND SAFETY MONITORING PLAN

Per the protocol, the data safety and monitoring plan (DSMP) will address the following areas: progress of the research study (including assessment of data & timeliness and participants recruit, accrual & retention) review of outcome and adverse event data to determine if changes should be made to protocol or ICF 3) assessment of external factors or relevant information 4) review study procedures for protection of research participants privacy. Each of the above will be addressed in weekly to monthly meetings with research staff. All study data in these areas will be summarized on a yearly basis. Reports of the DSMP will be submitted to the IRB at the time of annual renewal.

Dr. Germain noted there is an independent DSMB to review the validity and integrity of the data. The Board meets by teleconference bi-annually. Per the protocol, minutes will be kept for each meeting and submitted at continuing review or more often as requested by the IRB.

The RCO reviewed the IRB file and found that although there are not 2 separate reports (DSMP and DSMB) per the protocol, the above information was submitted to the VAPHS IRB at continuing review. It is recommended that in the future the investigator clearly delineate the DSMP from the DSMB report.

9.0 RECORD-KEEPING AND STUDY DOCUMENTATION

Mr. Hakim retains current IRB approval letters and related IRB and R&D documents. Mr. Hakim maintains hard copies of this information in a Regulatory Binder as well as creating a Desktop folder to where he places scanned copies of IRB, R&DC and other regulatory documents. The RCO considered this a Best Practice.

9.0 Comments and Recommendations

9.1 Each subject (screened and enrolled) had a research file with the subject's identification code. All subject research files are maintained in a locked cabinet in Mr. Hakims WPIC office.

9.2 For subjects randomized to the BSI treatment, subjects audio taped interventions are maintained in Robin Richardon's WPIC office.

General comment: All subject research files lacked documentation of one or more study procedures. It is important that research documentation be accurate and complete.

10.0 VA DATA SECURITY AND PRIVACY

As part of the audit, there is discussion regarding VA Data Security and Privacy Policies. This interview was conducted with Dr. Germain, Abdul Hakim and the VAPHS Research Compliance Officer (Ms. Caroff). The findings of that interview and other audit findings are below.

10.1 Hard copies of research subject's records and informed consent documents are maintained in folders in a locked cabinet at the WPIC office of Abdul Hakim.

10.2 Per protocol, the blood samples collected from subjects randomized to the medication treatment arm are to be deidentified and stored in the WPIC psychopharmacology laboratory. The RCO(s) were unable to visit the lab and confirm that the storage of samples meet VA and VAPHS policy.

10.3 Subjects randomized to the BSI treatment arm are to have the interventions on visits 1, 3 and 5 audio taped. These recordings are deidentified and stored in Robin Richardon's private office at WPIC. The RCO(s) were unable to verify the deidentification and storage of the tapes as Ms. Richardon was not in the office the day of the audit.

10.4 The Research Compliance Officer has verified that all research staff members documented on IRB approved study staff form or listed as individuals authorized to administer informed consent are current with VAPHS research education and training.

10.5 Despite the fact that Dr. Han Liang was noted to have administered informed consent and carried out various other research processes, has not completed VA Office of Research and Development (ORD) mandated human subjects' training.

11.0 GENERAL AUDIT FINDINGS

11.1 The protocol states that all subjects will have routine laboratory tests (blood samples) drawn on baseline visit. Subjects randomized to the medication treatment (PRZ or PLA) arm will have blood samples drawn on visits Week 2, 4, 6 and 8. These samples will be stored at the WPIC psychopharmacology laboratory. However, the protocol does not state how long the samples will be stored or a process for the destruction of the samples.

11.2 Per WPIC pharmacy outpatient profile, subject 210893 had 10mg of Prazosin dispensed by Dr. Han Liang. As previously noted, Dr. Liang has not been found to be affiliated with the study on any study staff form or listing of individuals authorized to administer informed consent. VAPHS Department of Human Resources has confirmed that Dr. Han Liang currently has no affiliation with the VAPHS.

11.3 Per the protocol, to minimize assessment bias to the non-blind BSI, a CNRC RN will perform the clinician administered post-treatment assessments (e.g. CAPS-2). Mr. Hakim confirmed he administered the post treatment assessments on all subjects.

Please explain why the post treatment assessments were not performed by CNRC RN as described in the VAPHS IRB approved protocol. Please submit a Protocol Deviation report to the IRB.

Research file for subject 211030 documents on 10-23-2008 that subject was taking Timolol (beta-blocker). However, subject continued with additional screening procedures including the blood draw.

Please explain why this subject continued with screening procedures, specifically the blood draw, when there was a clear medicinal exclusionary criterion identified.

Mr. Hakim stated that some subjects preferred to do the pencil and paper version of the Pittsburgh Sleep Diary while others preferred the PDA. However, the RCO(s) were unable to determine which subjects utilized the PDA and were unable to locate PDA results/reports.

It is important that research documentation, be accurate and complete. It is recommended that a note be placed in each of the 2 subject's files summarizing the event and the outcome or a note to file that the information can be retrieved from CPRS.

The audit staff would like to thank Dr. Germain and Mr. Hakim for their cooperation during this audit.

Germain, Anne

From: Germain, Anne
Sent: Thursday, January 08, 2009 8:53 AM
To: Steinhauer, Stuart
Subject: Witness signature in VA consent forms

Stuart,

After our discussion on the phone on Monday about whether signature of the consent by a witness is always mandatory or not, I thought you would be interested in what was taken right out of the report we received yesterday:

Note: VAPHS Standard Operating Procedures do not permit an individual listed on the research staff form to serve as a witness to the participant or the legally authorized representative's signature.

This is indeed consistent with the SOP's we have from the VA, which my coordinator follows. I thought I should let you know if directives are not consistent across SOPs. I would also appreciate if you could forward to me the SOP from Central Office you were referring to so that we can make sure our procedures here are consistent with the latest directives.

Anne

Germain, Anne

From: Germain, Anne
Sent: Tuesday, January 13, 2009 7:33 PM
To: Hakim, Abdul N
Subject: FW: Question of who can be a witness to consent

Abdul,
Please append the correspondence below to the compliance report response.
Anne

-----Original Message-----

From: Sonel, Ali F [mailto:Ali.Sonel@va.gov]
Sent: Thursday, January 08, 2009 1:24 PM
To: Germain, Anne; Steinhauer, Stuart; Squeglia, Nicholas L; Capozzoli, Tammy J; Caroff, Krissa J; Hakim, Abdul N
Subject: RE: Question of who can be a witness to consent

Witnesses do not need to be VA staff nor credentialed. The witness does not carry out study procedures for research purposes. That is no different than an individual who serves as a witness for an invasive procedure carried out in the VA.

Any person otherwise authorized to operate in the location that the consent is administered can serve as a witness as long as they are not affiliated with the specific study.

-----Original Message-----

From: Germain, Anne [mailto:germax@UPMC.EDU]
Sent: Thursday, January 08, 2009 10:35 AM
To: Sonel, Ali F; Steinhauer, Stuart; Squeglia, Nicholas L; Capozzoli, Tammy J; Caroff, Krissa J; Hakim, Abdul N
Subject: RE: Question of who can be a witness to consent

Dr. Sonel,
Thank you for your response.
Can you advise on how we can remain compliant given the IRB directive that non-study personnel are not allowed to be in contact with VA-recruited participants? The difficulty is that my staff is credentialed by the VA for VA-related study, but the rest are Pitt/UPMC credentialed only. Including one of the on the study requires that they become study-staff and VA approved, which then exclude them as potential witnesses.

Thank you,
Anne Germain, PhD

From: Sonel, Ali F [Ali.Sonel@va.gov]
Sent: Thursday, January 08, 2009 10:15 AM
To: Steinhauer, Stuart; Squeglia, Nicholas L; Capozzoli, Tammy J; Caroff, Krissa J
Cc: Germain, Anne
Subject: RE: Question of who can be a witness to consent

Currently it is the same standard as it had been for clinical consent forms, which is that it has to be an individual who is not affiliated with the study team. The witness is only witnessing that the signature belongs to the subject and not the consent process.

That said, it looks like there may now be a new policy coming out that may

allow us to rereview our position but that can not happen immediately and current policy must be followed in the interim.

From: Steinhauer, Stuart R [mailto:sthauer@pitt.edu]
Sent: Thursday, January 08, 2009 9:42 AM
To: Sonel, Ali F; Squeglia, Nicholas L; Capozzoli, Tammy J; Caroff, Krissa J
Cc: 'Germain, Anne'
Subject: Question of who can be a witness to consent

This issue just came up again, and we need a clarification for investigators. While a witness is required other than the person providing consent, and it is preferably not a member of the same research team, there had been some discussion that it could still be a team member when no other witness is available. However, Tammy pointed out that the need for a non-team member is in the current SOP. We need to clarify this for all investigators (including me) - can this be discussed at the next HRPP meeting?

Stuart R. Steinhauer, Ph.D.
Director, Biometrics Research Program
VA Pittsburgh Healthcare System
and
Research Associate Professor of Psychiatry University of Pittsburgh School of Medicine
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web: <http://www.wpic.pitt.edu/research/biometrics>



University of Pittsburgh

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January 16, 2009

George G. Dougherty, Jr., M.D., Chairperson
Institutional Review Board (IRB)
VA Pittsburgh Healthcare System #646
7180 Highland Drive
Pittsburgh PA 15206

Dear Dr. Dougherty:

Please find enclosed the responses to questions raised by the VAPHS Research Compliance Committee following the on-site audit conducted on December 18, 2008, for the protocol entitled, *"Efficacy of Adjunct Sleep Interventions for PTSD"* (IRB # 02386). Items raised and associated responses are provided below.

CONSENT FORM REVIEW

Please explain why all of the 31 subjects reviewed lacked the signature of a witness to the subject's signature.

Eleven of the 31 consent forms are not VA participants based on their recruitment method, and ten individuals were not recruited from the VA, although they did signed a VA consent form study previously accepted by the University of Pittsburgh IRB. Thus, total of eleven VA-recruited participants did not have a witness signature as now requested.

Based on your prior directives indicating that my non-VA credentialed personnel on my staff could not be in contact with any VA-recruited participants, and on the VAPHS Standard Operating Procedures which do not permit an individual listed on the research staff form to serve as a witness to the participant or the legally authorized representative's signature, I specifically instructed my staff not to obtain signature of a non-VA credentialed member of my team.

In light of the new clarifications about from Dr. Sonel (see appended correspondence), we will now obtain a witness signature from other personnel of the NCTRC in future consents.

Please explain why Dr. Mammen was administering and obtaining informed consent of participants prior to IRB approval.

Dr. Mammen completed his training in obtaining informed consent for this study with Dr. Moul prior to Dr. Moul's departure. Dr. Mammen conducted informed consent process under Dr. Nofzinger supervision after Dr. Moul's departure, to ensure the continuity of the study process. Dr. Mammen thus conducted informed consent process under direct supervision, while his paperwork was being processed at the VA for credentialing. Please note that Dr. Mammen is an experienced practicing psychiatrist with extensive research experience, and who has served on the University of Pittsburgh IRB in the recent past. He is abundantly qualified.

Please explain why Dr. Liang was administering and obtaining informed consent of participants.

The four consents that were signed by Dr. Liang signed occurred during the unexpected absence of Dr. Moul or Mammen. Dr. Liang was asked to be present during the consent process, which was soon after revisited by Dr. Moul or Mammen.

Please explain why subjects did not have a progress note documenting the informed consent process in their medical record as required by VHA Handbook 1200.05. Please implement corrective measures to ensure that future subjects have the appropriate progress note placed in their medical records.

The eleven individuals who do not have a progress note were not VA-recruited participants, and thus, we do not have permission to access to their electronic medical records.

Please, note that we are awaiting your instructions on how to enter progress notes for participants who are assigned to another VA (e.g., Butler VA) and for which we do not have access to electronic medical systems. This is the case for one current participant. My coordinator has asked how this issue should be addressed, but has not yet received an answer as of yet.

Please explain why the correct version of the ICF was not used and outline corrective measures that will be implemented to ensure that all future subjects will sign the correct form. If you are unsure which is the most recently approved version you are encouraged to contact the IRB Office prior to consenting subjects.

That a participant (209342) signed a University of Pittsburgh Consent Form rather than a VAPHS form was an oversight of Dr. Moul who pulled a different chart than that assigned to this participant. He was scheduled to return to sign the correct one at a subsequent visit, but the participant no-showed for all scheduled appointments, not allowing us to correct this mistake. Please, be assured that only the latest and current the University and VAPHS consent forms are readily available.

It is important that research documentation, particularly documentation that subjects met eligibility criteria, be accurate and complete. It is recommended that a note to file be placed in the subjects' files to state that they did meet the eligibility criteria.

We use the medical and the consensus forms to document that status of a participant. Dr. Mammen conducts a thorough medical evaluation of all participants' medical issues and places the results in the medical section of their red binders. The AHI data is all electronically stored under the participants study IDs, and it is emailed to the coordinator, the study physician, and me within 48 hours of the study.

Note: Should the compliance officers request to review these files in the future, we can easily provide access to these procedures and files on site, during the review process to answer these questions. Several comments in this report indicated that pieces form of documentation were lacking in the participants' file. I want to respectfully disagree with this statement. Some information may not have been included in the participants binder if it was not de-identified, or because information is logged in the intervention binders, rather than the evaluation binders for each participants. Some of the documentation is kept and filed electronically. Evidence of complete documentations and study forms as approved by the IRB can be consulted on site when required. The officers did not require indicate that they were looking for this information. We will be glad to review of documentation they did not request while on site.

Please, clarify the correct dates of visits and create a note to file for the discrepancies.

Study procedures may be completed over more than one contact or visit. For instance, the Asberg, CGI, and PGI must be conducted the day before the treatment visit by the study

physician and the Coordinator in order to request the medications for the face-to-face visit. These instruments are reviewed during the visit again, as an internal safety procedure.

Please clarify the correct date of the Post Treatment Visit and create a note to file for the discrepancies.

Please, see previous response.

Please be aware that the IRB approves protocols to be implemented exactly as written. Please verify if subjects completed the study procedures. If the above procedures were not completed, please submit a protocol deviation report to the IRB.

All procedures were completed as approved by the IRB. Deviations are logged and reported as required.

In addition, please address corrective measures to be implemented to ensure that all procedures will be completed per protocol for future subjects.

We will carefully review the protocol to determine whether the time frame as specified in the current protocol is inconsistent with actual ongoing procedures and revise as appropriate.

Please explain why subject 210858 was enrolled after refusal of actigraphy monitoring.

The participant did not "refuse" the actigraphy. After careful review of this participant's chart, we could not find evidence suggestive of refusal by this individual. Additional information regarding the source of this statement would be greatly appreciated.

Actigraphy could not be used as proposed in this participant because of scheduling conflicts that would have prevented the storage of actigraphy data, even if the data had been collected. Knowing that the actigraphy would not be usable in this participant, I instructed the coordinator that this measure should be omitted, as I have ethical concerns about collecting a measure from a participant knowing that it would not be usable.

Please be aware that the IRB approves protocols to be implemented exactly as written. Please submit a protocol deviation report to the IRB.

This report is attached.

The RCO reviewed the IRB file and found that although there are not 2 separate reports (DSMP and DSMB) per the protocol, the above information was submitted to the VAPHS IRB at continuing review. It is recommended that in the future the investigator clearly delineate the DSMP from the DSMB report.

These are delineated in the IRB approved protocols. The DSMP is conducted weekly by the PI and her research team. The DSMB is a bi-annual activity that involves a review of data and relevant study material by three external reviewers, not affiliated to the study in order to have additional and impartial monitoring of data and safety issues.

Please explain why the post treatment assessments were not performed by CNRC RN as described in the VAPHS IRB approved protocol. Please submit a Protocol Deviation report to the IRB.

Administrations of post-treatment evaluation are not to be conducted exclusively by the RN. It is in the event that the person conducting the post-treatment evaluation was the BSI therapist.

The protocol will be modified to more accurately reflect this point.

Research file for subject 211030 documents on 10-23-2008 that subject was taking Timolol (beta-blocker). However, subject continued with additional screening procedures including the

blood draw. **Please explain why this subject continued with screening procedures, specifically the blood draw, when there was a clear medicinal exclusionary criterion identified.**

Beta-blockers prescribed for high blood pressure are and exclusionary criteria, as indicated in the protocol. This participant was prescribed a beta-blocker for glaucoma, administered through eye drops. During the screening procedure, Dr. Mammen did extensive research (documented in the participant's chart) about potential risks associated beta-blockers used for glaucoma. As no evidence was found regarding potential risk, and corroborated by Dr. Marroquin, a cardiologist and consultant on our studies, the participant was allowed to proceed in the study.

It is important that research documentation, be accurate and complete. It is recommended that a note be placed in each of the 2 subject's files summarizing the event and the outcome or a note to file that the information can be retrieved from CPRS. IRB-approved template notes for CPRS are being used. Data collected fm the PDA's is electronic data stored directly in our database. This was showed to the RCO's during their visit by my coordinator.

Please, do not hesitate to contact me if you have questions. I can be reached at (412) 246-6436.



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