

Award Number: W81XWH-10-1-1045

TITLE: Enhancing Exposure Therapy for PTSD: Virtual Reality and Imaginal Exposure with a Cognitive Enhancer

PRINCIPAL INVESTIGATOR: JoAnn Difede, Ph.D.

CONTRACTING ORGANIZATION: Weill Medical College of Cornell University
New York, NY 10065-4805

REPORT DATE: October 2015

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; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE (DD-MM-YYYY) October 2015		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 27Sep2014 - 26Sep2015	
4. TITLE AND SUBTITLE Enhancing Exposure Therapy for PTSD: Virtual Reality and Imaginal Exposure with a Cognitive Enhancer				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-10-1-1045	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) JoAnn Difede, Ph.D. email: jdifede@med.cornell.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Weill Medical College of Cornell University 1300 York Avenue New York, NY 10065-4805				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 During this research period, three enrollment sites, Weill Cornell Medical College, the Southern California Institute for Research and Education (SCIRE) at the VA Long Beach Healthcare System ("Long Beach VA"), and the National Intrepid Centers for Excellence (NICoE) in Bethesda, Maryland have continued enrolling, assessing, and treating participants in accordance with the protocol. Extensive recruitment efforts are being undertaken at all sites, and site specific and study-wide recruitment strategies have been developed. As of this writing, across the three enrolling sites, 228 individuals have completed the telephone screen, 79 have completed the baseline assessment, 34 have completed treatment, 21 have completed the 3-month follow-up assessment, 12 people are currently in treatment, and 9 have dropped out of the study. New Virtual Iraq/Afghanistan virtual reality scenarios have been created, and cyclical quality assurance has been continuous throughout the research period.					
15. SUBJECT TERMS CRADA approval; Institutional Review Board and HRPO approval at NICoE; continued software development; online study database; recruiting participants; assessing and treating participants.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 18	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	1
Body.....	1
Key Research Accomplishments.....	13
Reportable Outcomes.....	14
Conclusion.....	14
References.....	15
Appendix.....	15

Annual Report

Enhancing Exposure Therapy for PTSD: Virtual Reality and Imaginal Exposure with a Cognitive Enhancer

1. INTRODUCTION:

We are conducting a multisite randomized clinical trial of an exposure therapy intervention for combat-related posttraumatic stress disorder (PTSD) delivered in two different formats – virtual reality exposure therapy compared to prolonged imaginal exposure therapy – combined with D-Cycloserine (DCS), a cognitive enhancer that has been found to facilitate the extinction of fear in exposure therapy. We also aim to determine whether a common human genetic single nucleotide polymorphism (SNP) in a growth factor, brain derived neurotrophic factor, BDNF (Val66Met), predicts treatment response to PTSD. This 2 x 2 design will allow several important comparisons to be made: a direct comparison of the efficacy of virtual reality versus imaginal exposure therapy, which has never been conducted for the treatment of PTSD; a direct test of DCS as a facilitator of exposure therapy allowing a brief effective treatment to be delivered even more efficiently; and a direct test of whether the effects of DCS differ across the modes of exposure therapy. Additionally, findings may lead to the development of the first human genetic test that could guide treatment, ultimately allowing for more tailored treatment plans in the future. This study will include 300 subjects diagnosed with PTSD related to Operation Iraqi Freedom and/or Operation Enduring Freedom participating at Weill Cornell Medical College in New York City, the National Intrepid Center of Excellence (NICoE) in Bethesda, MD for Emory University, and the Southern California Institute for Research and Education (SCIRE) at the VA Long Beach Healthcare System (“Long Beach VA”) for the University of Southern California.

2. **BODY:** *This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Provide data explaining the relationship of the most recent findings with that of previously reported findings. Appended publications and/or presentations may be substituted for detailed descriptions of methodology but must be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work must be approved by the Army Grants Officer’s Representative. This approval must be obtained prior to initiating any change to the original Statement of Work.*

Progress Toward Meeting the Goals Outlined in the Statement of Work

Study Set-up and Maintenance:

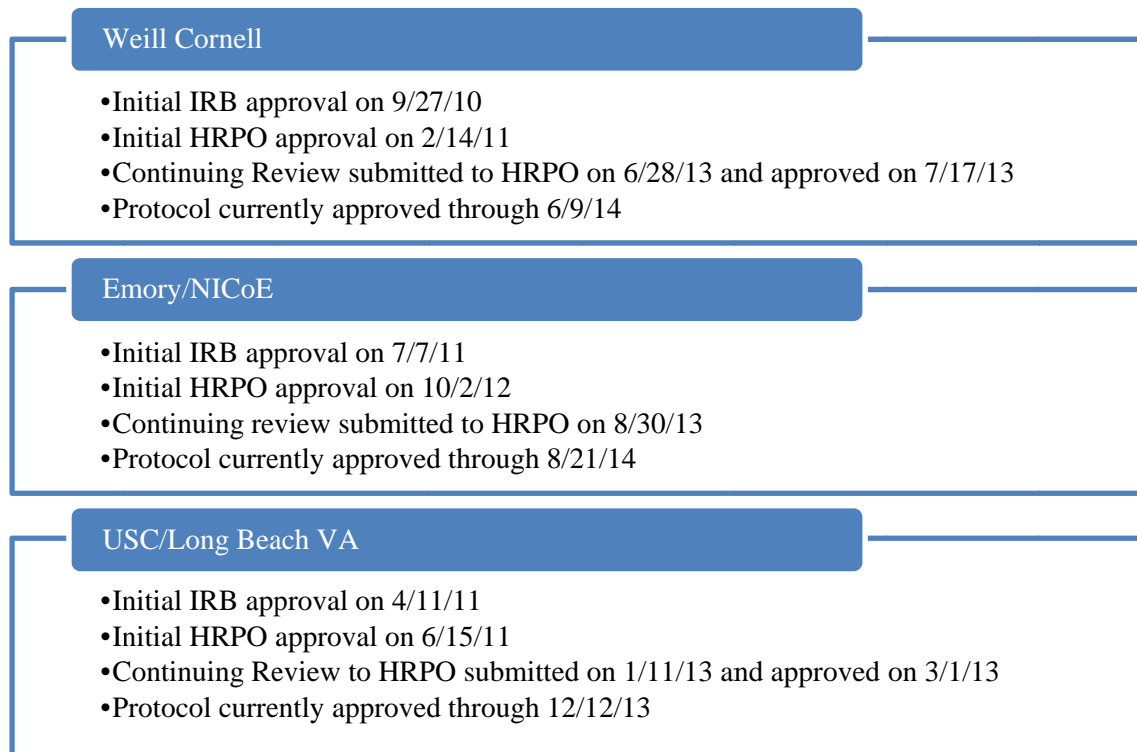
1) IRB Submissions and Approvals

Full IRB approval for Weill Cornell, Emory, and the Long Beach VA was attained in Year 1. USC agreed to be subsumed under the Long Beach VA's IRB. Additionally, the study was registered at the ClinicalTrials.gov website in Year 1.

Emory's enrollment site, the National Intrepid Center of Excellence (NICoE), was granted initial site IRB approval in July 2011. However, full IRB approval at NICoE was pending the adoption of the Cooperative Research and Development Agreement (CRADA). The CRADA was approved on 7/26/12. NICoE's Continuing Review received approval on 8/23/12 through the Department of Research Programs (DRP) at Walter Reed National Military Medical Center (WRNMMC). Final IRB approval for the sub-contract to Emory/NICoE has been received. The CRADA was finalized by DRP on 9/12/12. In addition, the data sharing agreement between NICoE/WRNMMC, Cornell, Emory, and USC was approved by the Navy Bureau of Medicine and Surgery (BUMED) on 9/11/12. The DoD Human Research Protections Office (HRPO) approved NICoE's site IRB protocol on 10/2/12.

Figure 1 provides an overview of IRB approvals for each site.

Figure 1. Summary of IRB approvals by site



We have submitted reports to Weill Cornell's Data and Safety Monitoring Board (DSMB) for periodic review on the following dates: 8/23/11, 11/19/11, 5/18/12, and 4/19/13. On 6/28/12, the DSMB requested that the review schedule be changed from semi-annual to annual or whenever the next 15 subjects have been enrolled. These changes were reflected in Cornell's subsequent IRB amendment, submitted on 10/15/12 and approved on 11/6/12. On 6/14/13, the DSMB requested that the review schedule be modified from annual review or review after the next 15 subjects are enrolled to annual review or in the case of an unexpected adverse event. These changes were reflected in Cornell's subsequent IRB amendment, submitted on 7/1/13 and approved on 9/26/13.

The protocol was also submitted to local IRBs for continuing reviews (Weill Cornell: submitted on 5/6/13 and approved on 6/17/13; Emory/NICoE: submitted 7/22/2013 and approved on 8/19/13; USC/Long Beach VA submitted on 11/13/12 and approved on 12/13/2012 as well as submitted on 9/20/13 and approved on 10/10/13). The recently approved USC/Long Beach VA documents will be forwarded to HRPO upon receipt.

2) Coordinating Between DoD, Weill Cornell, and All Study Sites

Weill Cornell's subcontracts with Emory, USC, and the Long Beach VA were all executed in Year 1 of the study and remain in effect. However, as discussed below, the contract between the Navy and the all other sites was delayed an additional year.

Weekly conference calls are in effect to facilitate coordination between sites and will continue for the duration of the study. The Principal Investigators at each site hold a weekly business call to discuss logistical issues, and other key personnel join the call as issues arise that are relevant to their study role. Separate supervision calls between the study therapists and between the study assessors are ongoing. Project coordinators at all sites hold a weekly conference call to discuss any site issues and recruitment efforts. Quarterly conference calls with all psychophysiological assessors began in October 2012 to ensure protocol adherence. Meeting agendas, when applicable, are available upon request. All study personnel are encouraged to contact each other between meetings should any issue arise that needs to be addressed immediately.

On June 6-7, 2013, Weill Cornell hosted the 3rd Annual Meeting, attended by thirty-six study personnel from all sites. Day 1 included breakout sessions for each study role, along with an overview of aggregate data, software development, and use of the online study database. Day 2 was dedicated to discussing recruitment and retention strategies and establishing goals for the upcoming year.

3) Hiring Study Personnel

Study personnel were assigned or hired at each site in Year 1, and new personnel are added as needed.

At Weill Cornell, Lucy Finkelstein-Fox was hired as a research assistant on 6/10/13. Ms. Finkelstein-Fox has replaced Brittany Mello, who has departed the study team to attend graduate school full-time. Ms. Mello was terminated on 8/2/13. Dr. Katarzyna Wyka has changed her involvement with the study to part-time, effective on 8/27/13.

At the Long Beach VA, Dr. Rachel Stewart (formerly Rachel Robertson) began an emergency medical/maternity leave on 8/19/13. At the present time, Dr. Stewart's return date is unclear. Dr. Marya Schulte, therapist at the Long Beach VA, left the study at the end of December 2012. Dr. Todd Adamson has since been hired part-time to fulfill her duties.

At NICOE, Dr. Suzanne Leaman returned from her maternity leave on 4/29/13.

At USC, Jack Mondonedo returned from leave on 10/12/12.

When needed, clinical positions are advertised locally and at relevant national meetings (e.g., Association of Behavioral and Cognitive Therapy), and applicants are reviewed and scored on a rolling basis by a coordinating committee consisting of key personnel at Emory and Weill Cornell.

4) Training Study Personnel in Study Methods

Dr. Adamson, the new therapist at the LBVA, travelled to Emory University on 1/11/13 to meet with Drs. Barbara Rothbaum and Maryrose Gerardi for therapist training and protocol orientation.

Consulting Drs. Kevin Holloway and David Riggs underwent the process of being credentialed at NICOE in December 2012 and January 2013, in order to fill in for Dr. Suzanne Leaman during her maternity leave. Drs. Maryrose Gerardi (Emory) and Judith Cukor (Cornell) participated in a conference call with Drs. Holloway, Riggs, and Adamson on 12/13/12 to review study materials and provide any necessary clarification of the therapists' role in the study.

Andrew Leeds from USC's Institute for Creative Technologies (USC ICT) visited the Long Beach VA recruitment site on 6/10/13 to install the new virtual reality "Bravemind" system, complete with the latest software developments and updated equipment. This updated VR system will be put into use once all study sites have ordered and installed Bravemind. The equipment was purchased at the Weill Cornell and NICOE sites in Year 3 of the study (September 2013), and will be online and functional early in Year 4 of the study (October 2013). A transition protocol will be implemented to insure standardized study procedures between sites.

All assessors and therapists continue to meet weekly with the assessment and therapy supervisors by conference call to ensure protocol adherence.

5) Maintaining Study Equipment and Supplies at All Sites

The virtual reality equipment and equipment for the startle and fear conditioning paradigms are installed at each of the enrollment sites. Additional study medication and supplies are ordered as needed and shipped to the appropriate personnel. The new virtual reality "Bravemind" system has been installed at the LBVA site, and is currently in the process of being installed at the Weill Cornell and NICOE sites as well. The Bravemind system is expected to be in use at all sites early in Year 4.

The randomization table and procedures are in place, and the randomization list has been provided to the necessary personnel at each site.

6) Preparing Study Assessment, Outcome Measures, and Participant Folders

All data are being collected in a secure HIPAA-compliant, internet-based data management program called REDCap (Research Electronic Data Capture). This database is available for our

use through the Weill Cornell Medical College Clinical and Translational Science Center (CTSC). The internet connections at each site have been configured to ensure that the data is transmitted in real time as it is entered by each clinician and study participant. All assessment and outcome measures are being submitted using the REDCap software.

REDCap is actively being used for data collection without incident. However, therapists and assessors have paper copies of self-report and clinical measures so that they are able to conduct their sessions should an error prevent the use of REDCap.

7) Setting up study database

The study database is linked to the REDCap data management system. The study coding system/ID scheme has been implemented at all enrollment sites. All study sites are completing tracking information (e.g., participant tracking spreadsheet, recruitment activity log, etc.) using a uniform spreadsheet in order to standardize data collection. These forms are uploaded into the REDCap database on a weekly basis for review.

DoD Human Research and Protections Office (HRPO)

After NICOE completed the process of obtaining Cooperative Research and Development Agreement (CRADA) approval from the Walter Reed National Military Center (WRNMMC) last year, HRPO approved NICOE's site IRB protocol on 10/2/12. This allowed NICOE to begin enrolling participants at their site.

Recruitment Efforts:

Extensive recruitment is underway at all sites (see Figure 2 for a summary). Key personnel have reached out to local and national contacts within civilian and military settings to maximize referrals from our professional networks. Mass mailings via e-mail and postal mail have been sent over the course of the study period to community organizations (e.g., institutions of higher learning, religious groups, public libraries). We have scheduled and offered seminars to relevant military-related organizations (e.g., Iraq and Afghanistan Veterans of America, U.S. Army), and study investigators have been featured on programs such as CNN's "The Next List" and The Charlie Rose Show. Information about the study is available on each site's website and on Weill Cornell's, SCIRE's, and Emory's Facebook pages. IRB-approved recruitment materials are in place at each site, including a "dear colleague" letter explaining the study, multiple flyers, and online advertisement text (i.e., for Craigslist ads). A template for tracking all recruitment activities is in use at each site, and recruitment efforts are monitored and discussed with the PI's and study coordinator's weekly.

Figure 2. Examples of recruitment activity by type of outreach

Type of Recruitment Effort	Examples
Major Public Promotions	Featured in New York Presbyterian’s “Amazing Things” Campaign, CNN’s “The Next List,” The Charlie Rose Brain Series, the Boston Globe, Minnesota Public Radio
Intra-Institutional Outreach	Institution-wide broadcast e-mails, meeting with Department Chairs and academic collaborators, institutional grand rounds
Outreach to Military-related Organizations	Includes Iraq and Afghanistan Veterans of America, Veterans Mental Health Coalition of NYC, NYMetroVets, Real Warriors Campaign, Wounded Warrior Project
Attendance at Military-related Events	Includes US Army Ready and Resilient panel, Military Appreciation NY Mets Game, Army Week NYC, Fort Hamilton Wellness Retiree Fair, Veterans Mental Health Coalition meeting, Returning Warrior Workshop in Baltimore, College and Law Enforcement resource fairs
Outreach to Military Personnel	Identified contacts in the Army, Fort Hamilton, the U.S. Marine Corps, New York State Armory's Military Family Assistance Center, West Point Warrior Transition Unit, Navy Marine Relief Corps Travelling Nurses, National Guard, Uniformed Services University of the Health Sciences, ROTC units, Quantico, Andrews AFB, WRNMMC, Fort Meade, Pentagon, Langley AFB, Fort Belvoir
Online Recruitment Activities	Updating Facebook pages, Long Beach VA’s Twitter feed, posting study materials on program websites, Braveheart’s Google Words ad, regular postings on Craigslist, becoming listed on military and mental health-related resource pages
Outreach to Veterans’ Affairs	Traveling to local Vets Centers, meeting with senior VA leadership, scheduling presentations at VA Grand Rounds, the Long Beach VA's Mental Health Services Department, Region 8 Veterans’ Program Directors Consortium
Outreach to Community & Government Contacts	Includes NYC's Mayor’s Office of Veteran Affairs, Senator Gillibrand's office, LA County Department of Mental Health's Veteran Services, veteran liaisons and student groups at undergraduate institutions, personnel at the Fire and Police Departments, handing out flyers at the Annual 3 rd Avenue Community Street Fair and at NATW’s National Night Out, outreach to non-military hospitals, attendance at Research Week events

Weill Cornell Medical College Enrollment Site

Weill Cornell actively schedules events within the New York City military community to create awareness of our research study and build trust as a civilian provider. Our study personnel have given several presentations to inform groups and organizations about the study. For example, Dr. Melissa Peskin, study assessor, participated in a panel on Posttraumatic Stress at West Point Academy with SSG Ty Carter, a Medal of Honor recipient (8/30/13). Study personnel regularly attend local military-related events (e.g., Fort Hamilton Health Fair (10/27/12); the 6th Annual Army Appreciation Night at Citifield (5/26/13); a Ready and Resilient Panel, featuring the Army Vice-Chief of Staff, the Army Surgeon General, and Dr. Difede, held in honor of the Army's 238th birthday (6/13/13)). Personnel distribute our study flyers whenever possible, and are available to answer questions at these events.

We have built a strong relationship with the Veterans' Mental Health Coalition of New York City – a diverse organization consisting of over 300 individuals who represent veterans' services, advocacy, behavioral health organizations and local, state, and federal government agencies – and study personnel attend bi-monthly meetings to network within the coalition. Dr. Difede spoke to this group on 9/13/13 regarding PTSD and novel treatment modalities and distributed program information to those in attendance.

We have an ongoing collaborative relationship with Fort Hamilton in Brooklyn, NY, the only military base in the New York metropolitan area, as well as the Lexington Armory for National Guard. Personnel at the West Point Warrior Transition Unit continue to refer service members to receive treatment through the study. Furthermore, study personnel regularly meet with military leadership whenever possible to inform them about our study, give a demonstration of the Virtual Iraq program, and discuss the mental health challenges facing Service Members. Over the past year, these meetings included Army officials Lt. Adams, Lt. Papandrea, and Lt. Charles at Fort Hamilton (10/10/12) as well as BG. Gary Volesky, Sgt. Mjr. Puckett, John Manley, and LTC TJ Rainsford (2/21/13); National Guard representatives on 10/10/12; and SSG Jon Morrison of Battery 258th Field Artillery Regiment Headquarters (5/14/13).

We have also extended our partnership with Weill Cornell's Clinical and Translational Science Center (CTSC) this year to further promote our recruitment efforts. Study personnel have worked together with personnel from the CTSC to distribute study fliers throughout the NYC community and at events such as National Night Out and the Third Avenue Street Fair.

Long Beach VA Enrollment Site and USC/ICT

At the Long Beach VA, study staff has continued outreach efforts at veterans' events, community colleges, local hospitals, and general mental healthcare-related events in the Long Beach Area.

Within the LBVA Hospital, there has been a recent focus on partnering with providers whose focus is outside of Mental Health while maintaining a high level of contact with individual referral sources from both Outpatient Psychiatry and Traumatic Stress Clinics. Dr. Reist, site PI, has been very active in this process and opened the LBVA's Grand Rounds presentation on 7/16/13 with a discussion of the DSM-5 PTSD diagnostic changes that highlighted this treatment study as a referral option for evidence-based treatment. Dr. Reist also lectured on the study at an event for all LBVA primary care providers on 8/7/13. The study team has additionally led in-services for the staff of nurse case managers within the Mental Health Treatment Clinic on 1/14/13 and 1/17/13 and for all Outpatient Mental Health care providers on

7/24/13, allowing all referrers to voice their questions and concerns related to the treatment study.

LBVA study personnel have also participated in several outreach activities within the area, serving as a community resource for veterans, active duty, and family members who may be interested in the study. The many events held at colleges and universities include organized fairs such as Azusa Pacific University's Military and Veteran Resource Fair (4/6/13), California State University Fullerton's "Women Veterans in Higher Education" event (3/19/13), the Saddleback College Veterans Resource fair (9/25/13), as well as presentations at El Camino College (6/18/13), Cypress College (7/24/13), Cerritos College (7/31/13), Santa Monica College (6/4/13, 8/27/13), and Long Beach City College (6/11/13, 8/20/13). We also plan to organize an event at Orange Coast College in the upcoming reporting period.

Study personnel have an ongoing relationship with local law enforcement agencies, such as the LA Sheriffs and Police Department, and have been working to cultivate such a relationship with the Long Beach Fire Department as well. This year, we have reached out to a West Los Angeles VA Vet Center (1/24/13) and two of its community-based outpatient clinics (2/14/13, 2/21/13), as well as the East Los Angeles VA Vet Center (3/28/13) in order to present the treatment study as a viable referral option. The study team also attended two local Region 8 Veterans' Program Directors Consortium staff meetings in early 2013 in order to present study information. The Long Beach VA Police Department's Annual Law Enforcement Day (5/8/13), as well as the Los Angeles Police and Sheriff's Departments' Peer Mental Health Program Training (6/19/13) and the U.S. Naval Hospital at Camp Pendleton's Research Day were additional opportunities for study personnel to distribute program information and provide general PTSD informational materials.

Additional community outreach events include the VA Long Beach Women Veterans' Educational Health Fair (3/21/13), a veteran reintegration and transition event hosted by Oakley and the Infinite Hero Foundation (5/14/13), LBVA's Research Week event (5/30/13) and the Community Providers Mental Health Summit on 8/8/13. Study staff also met with award-winning LA Times videographer Rick Loomis on 9/18/2013 at VA Long Beach to discuss the project and arrange an on-site photo shoot of the Virtual Iraq/Virtual Afghanistan setup (set for 09/30/2013). The LA Times story featuring one of VALB's study participants and his PTSD recovery process went to press on 10/6/13.

USC's recruitment efforts include study personnel presenting and demonstrating PTSD-related virtual reality scenarios to the Congressional Caucus on Veteran's Affairs on 7/8/13, public demonstrations of the new Bravemind system to Military personnel, as well as a considerable amount of media coverage.

Dr. Skip Rizzo's work at USC's Institute for Creative Technologies (ICT) has been featured by prominent news sources such as the Boston Globe (9/16/13), The New Yorker (7/8/13), and CNN's Next List (1/27/13; 5/4/13). Dr. Rizzo and the ICT have additionally supported recruitment efforts by demonstrating the study equipment to individuals such as Medal of Honor recipient Staff Sgt. Ty Carter (9/7/13) and by supporting an off-Broadway play that features the study therapy tool "Virtual Iraq" (running from June 5-22, 2013).

NICoE Enrollment Site

The NICoE site received approval to begin recruitment efforts at the beginning of Year 3 on 10/2/2012. Throughout Year 3, we have continued to work on establishing a referral line through NICoE patients. Members of the NICoE team have reached out to several providers that

refer patients to NICOE and are hoping to establish referral relationships with them as well. We are also in the process of having the study added to the WRNMMC research website and are working to schedule talks and site visits at Reserve Centers, VA/Vet Centers, and within WRNMMC. Study personnel continue to do follow-up visits to sites where PI Dr. Roy has spoken. Within USUHS, administrators from NICOE met with the Brigade Commander to discuss our research who also passed the information along to the Command Master Chief. They will be putting up flyers around USUHS as well.

Dr. Leaman, study therapist at the NICOE site, has completed an in-service as a follow-up to Dr. Roy's talk with the Psychiatry Continuing Service and Trauma Recovery Program at WRNMMC. She has also done a talk with Behavioral Health Team in Primary Care and continues to work with CDR McGuire on speaking with case managers at the Warrior Rounds. Dr. Roy has given a talk with the Wounded Warriors and we have reached out to Outpatient Behavioral Health in order to set up a time to talk with the staff.

NICOE continues to maintain contact with the Behavior Therapy Center of Greater Washington, as they expressed this summer that they would like to refer eligible individuals to the study. We have continued to reach out to local synagogues, churches, family resources, and support organizations and will be following up with contacts at those locations in the coming weeks. Representatives from NICOE also had a table at the Returning Warrior Workshop, which took place on July 20-21 in Baltimore.

We are in the process of sending follow-up emails to the twelve vet centers, the D.C. VAMC and Baltimore VAMC, ten university counseling centers and eleven veterans services centers at universities, eight ROTC units, twenty-three student affairs veterans chapters, twenty targeted private practice clinicians, and six nonprofits that NICOE personnel have established contact with over the summer. We will also be reaching back out to the recovery care coordinators at Andrews AFB, WRNMMC, Fort Meade, Pentagon, Langley AFB, Ft. Belvoir and Quantico in order to address any questions they might have and share more information about our research. We are additionally working to establish contacts in the various Warrior Transition Units (WTU) at Ft. Meade, Ft. Belvoir, WRAMC, as well as the Community-Based WTU in Virginia.

We have begun reaching out to the various police stations around D.C., Maryland, and Virginia. We are contacting commanders for each of the districts/precincts in these areas and are providing information about our study. Currently, we have direct contact information for the Commanders of the various districts/precincts in Baltimore City, Baltimore County, Howard County, Harford County, Montgomery County, Prince George's County, Fairfax County, DC Metro, and the Capitol Police.

We are also looking into local non-military hospitals and are working on establishing referral relationships with individuals at Georgetown University Hospital, Washington Hospital Center, MedStar National Rehabilitation Hospital, Franklin Square Medical Center, Good Samaritan Hospital, Harbor Hospital, Montgomery Medical Center, Southern Maryland Hospital Center, St. Mary's Hospital, Union Memorial Hospital, and the MedStar National Rehabilitation Network. We will also be exploring potential referral relationships with local and psychiatric hospitals and institutes. We will be reaching out to staff at The Sheppard and Enoch Pratt Hospital, The Psychiatric Institute of Washington, and St. Elizabeth's Hospital. We are hoping to establish relationships with members of the staff at these locations that would be interested in referring potential participants to us.

On 9/10/13, NICOE held an all-hands meeting to discuss recruitment ideas and get input from all team members on ways to make recruitment efforts even stronger. In moving forward, study staff will continue to maintain contact with previously established connections while also continuing to build our network on potential referral resources.

Recruitment efforts are discussed during the weekly conference calls between the Principal Investigators and study coordinators, with all sites sharing successful strategies in order to improve results. Site specific and study-wide recruitment strategies continue to be developed and implemented as new resources and opportunities come to light.

Participant Enrollment and Treatment:

The tables below summarize participant enrollment and treatment. Specifically, Table 1 lists the statistics for enrollment and treatment in Year 3 alone, and Table 2 lists the cumulative statistics for enrollment and treatment.

Table 1. Study enrollment figures by site for Year 3 only

	Weill Cornell	Long Beach VA	NICOE	Total Across Sites
Completed the Telephone Screen	27	56	19	102
Number of Patients Assessed	16 ^a	16	7 ^b	39
Number of Patients Eligible and Enrolled in Treatment	9	16	5	30
Number of Treatment Sessions Held	94	177	64	335

^a 7 assessed were ineligible

^b 1 assessed was ineligible and 1 chose not to enroll

Table 2. Study enrollment figures by site (Cumulative to date 10/25/13)

	Assessed and Enrolled				Current	Completed Treatment			
	Completed Baseline Assessment	Assessed and Not Eligible for the study	Enrolled in the Study	Enrolled in study but did not enter Treatment	Currently In Treatment	Completed Post-treatment Assessment and 3-month Follow-Up	Completed Post-treatment Assessment and Awaiting 3-month Follow-Up	Awaiting Post-treatment Assessment and 3-month Follow-Up	Dropped Out During Treatment
Overall	79	22	55	2	12	21	12	1	9
Site:									
WCMC	32	13	17	2	3	8	3	1	2
LBVA	40	7	33	0	9	13	5	0	6
NICoE	7	2	5	0	0	0	4	0	1

Sample description:

Across the three sites currently enrolling participants, 228 individuals have completed the telephone screen, 79 have completed the baseline assessment, 34 have completed treatment and 21 have completed the 3-month follow-up assessment, 12 people are currently in treatment, and 9 have dropped out of the study.

Of the 5 women (6.3%) and 74 men (93.8%) assessed, the majority were Caucasian (47%), followed by Hispanic/Latinos (26%), African/Americans (14%), Asians (8%) and Other (5%). The mean age was 33.40 (SD=7.49, range 21-58) and 46% were married or living with a significant other, 37% were single and 18% were separated/divorced. The education level was as follows: High School or GED -17%, Some College or Training -60%, College Graduate -10% and More Than College -13%.

Participants represented three branches of the Armed Forces: Army -62%, Marines -28%, Navy -10%, with the following history of deployments: one deployment -37%, two deployments -32%, three deployments -14%, and four or more deployments -17%. Seventeen percent were Active Duty at the time of their baseline assessment and 64% reported prior PTSD treatment.

Treatment Adherence and Inter-rater Reliability:

As part of treatment adherence monitoring in Year 3, the study independent monitors reviewed and provided feedback for 47 therapy sessions across sites. This feedback is routinely discussed during weekly therapist supervision calls. Likewise, the inter-rater reliability ratings of study assessments are used to provide training and feedback to study assessors. In Year 3, 24 assessment videos have been reviewed and rated across sites.

Collection and processing of Biological Samples:

Saliva samples collected both as part of the psychophysiological assessments as well as for genetic testing are shipped in batches to Weill Cornell for storage and processing. In Year 3, 180 salivate tubes have been delivered for processing to the Weill Cornell Clinical &

Translational Science Center (CTSC). In addition, Dr. Glatt's lab has processed additional 6 genetic samples, totaling in 34 processed samples to date.

Software Development:

The following contains a list of the deliverables proposed for this work and the status of achievement on the software development components of this project.

1) Hire Software/Art Personnel

- a) The team is continuing the work proposed on schedule

2) Create new scenarios

- a) Developed an Afghan Forward Operating Base level, including an often-requested new type of encounter: dynamic mortar attack. This feature has started to make its way in additional levels as well
- b) Developed Afghan City Market level
- c) Developed Iraqi Industrial level
- d) Added the ability to drive in an MRAP, in addition to the Humvee. These two vehicles can now be swapped at will in relevant levels.
- e) Added foot control encounter in Afghan village level
- f) Added Afghan helicopter patrol encounter
- g) Added fog and sand storm weather effects in most levels
- h) Added ability for clinician to load up custom sounds

3) Refine single computer system approach

- a) Updated the underlying game engine, Unity, to the latest version, 4

4) Cyclical Quality Assurance

- a) Continued provision of QA services
 - i) JIRA defect database maintenance and organization
 - ii) Confluence wiki weekly build status reports
 - iii) Authoring and execution of test cases and checklists
 - iv) Assessment of build release candidates for demonstrations and clinical use
- b) Focused test passes on binary builds related to areas of risk: Unity 4.0 updates, pruning of asset files, significant features and logic modifications
- c) Technical support as needed to maintain and optimize systems at DCS study sites

5) Documentation

- a) Overhaul and expansion of User Manual contents for ease of setup and operation by non-technical clinical staff
- b) Revised the required specifications for PC desktop and laptop systems
- c) Detailed a complete list of necessary components to assemble the VRET system, including hyperlinks for recommended vendors
- d) Step-by-step instructions provided to connect all hardware and peripherals
- e) Created four new device connection diagrams that utilize actual photos of the equipment for clarity

- f) Created three new audio connection diagrams that utilize actual photos of the equipment for clarity
- g) Step-by-step instructions provided for installation and uninstallation of VRET software and all dependencies
- h) Clinician Controller section with up-to-date descriptions of each button command found within all panel scenario layouts
- i) Updated visual guides for mounting of tracker devices
- j) Added reference maps of all 14 scenarios with top-down and isometric views that detail ambushes, teleport zones, NPC placement, etc.
- k) General edits and formatting changes throughout development for accuracy and clarity

6) Hardware development and evaluation

- a) Minimum and recommended computer system specifications determined for desktops and laptops
- b) All peripherals and ancillary components to complete a desktop/laptop VRET system itemized
- c) Decision to move to 64-bit Windows 7 Operating System to be in-line with the current market and allow for enhanced visual content; removed imposed memory (RAM) limitation of 32-bit OS
- d) Continued tracking of ordering options and model availability of target HMD, the Sony HMZ
- e) Created prototype build of Bravemind compatible with “Future of VR” Oculus Rift HMD
- f) Integrated lower-cost tracking device alternatives Hillcrest FSM-6 and InterSense InertiaCube4
- g) Added support for InertiaCube 4 tracking hardware, as well as improved support for Sony HMZ-T1 Head Mounted Display

7) DCS 3-site system upgrades

- a) Finalized setup of new VRET system and its components at VALB DCS study site; successful litmus test of the new software and system hardware with actual patients
- b) Weill Cornell and Emory/NICoE sites purchasing of new system and components complete; expected setup and rollout for clinical use in Q1 2014

3. KEY RESEARCH ACCOMPLISHMENTS: *Bulleted list of key research accomplishments emanating from this research.*

- Obtained IRB approval for study protocol at all sites.
- Obtained CRADA approval between sites.
- Held two-day Annual Meeting in Years 1, 2 and 3 for all study personnel to receive training on study protocol and procedures.
- Hired and trained personnel for their study role at each site, as needed.
- Finalized study methods and implemented standardized procedures at each site.
- Created confidential online database (REDCap) with all assessment materials available for subjects.
- Purchased and installed all necessary equipment for virtual reality treatment and psychophysiological assessments.

- Developed and implemented site specific and study-wide recruitment strategies.
 - Continued enrolling, assessing, and treating participants in accordance with the approved protocol.
 - Developed beta version of Virtual Iraq/Afghanistan Enterprise Level exposure therapy system.
 - Developed prototype of Bravemind system, to be integrated into the treatment protocol at all study sites in Year 4.
4. **REPORTABLE OUTCOMES:** *Provide a list of reportable outcomes that have resulted from this research to include: (manuscripts, abstracts, presentations; patents and licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; infomatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award)*
- 1) Development of the beta version of Virtual Iraq/Afghanistan Enterprise Level exposure therapy system.
5. **CONCLUSION:** *Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.*

The 2008 and 2012 Institute of Medicine (IOM) Reports on the treatment of posttraumatic stress disorder noted a paucity of effective, empirically validated treatments for combat-related PTSD. This study is using the one treatment noted by the IOM reports to have substantial evidence in other trauma populations, exposure therapy, and enhancing it with virtual reality and a novel pharmacologic agent, D-Cycloserine. Thus, this study is poised to provide several valuable contributions to the understanding of combat-related posttraumatic stress disorder. Improving the effectiveness of therapy through the use of virtual reality would have far-reaching, positive consequences for our wounded warriors. Results of this clinical trial will directly influence the future delivery of services, and may help disseminate a standardized treatment protocol as is being done for other psychiatric disorders. If D-Cycloserine, a benign pill, proves to be an effective way to enhance the effects of psychotherapy, the result would have a tremendous impact at very little cost. Additionally, there are currently no genetic or non-genetic biomarkers for assessing treatment response to any psychiatric disorder. Findings from this study may lead to the development of a human genetic test that could guide treatment of patients with PTSD with the BDNF SNP to therapeutic strategies, such as imaginal exposure therapy with DCS, prior to a trial of an SSRI. The BDNF SNP would be the first biomarker that would inform treatment strategy decisions for clinicians in the treatment of PTSD. The capability of predicting the best treatment for the individual would make treatment efforts more effective and efficient, and would decrease suffering and the costs associated with a PTSD diagnosis and treatment.

6. REFERENCES: *List all references pertinent to the report using a standard journal format (i.e. format used in Science, Military Medicine, etc.).*

- 1) Rizzo A, Buckwalter JG, Forbell E, Reist C, Difede J, Rothbaum B, Lange B, Koenig S, Talbot T. Virtual Reality Application to Address the Wounds of War. *Psychiatric Annals*, March 2013, 43(3): 123-138.
- 2) Difede J, Cukor J, Wyka K, Olden M, Hoffman H, Lee FS, Altemus M: D-cycloserine Augmentation of Exposure Therapy for Posttraumatic Stress Disorder: A Randomized Clinical Trial.

7. APPENDICES: *N/A*