

Award Number: W81XWH-11-2-0107

TITLE: Assessment of Chiropractic Treatment for Low Back Pain, Military Readiness and Smoking Cessation in Military Active Duty Personnel

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REPORT DATE: March 2016

TYPE OF REPORT: ANNUAL

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

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1. REPORT DATE March 2016		2. REPORT TYPE Annual		3. DATES COVERED 15Feb2015 - 14FEB2016	
4. TITLE AND SUBTITLE Assessment of Chiropractic Treatment for Low Back Pain, Military Readiness and Smoking Cessation in Military Active Duty Personnel				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-11-2-0107	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Ian Coulter, PhD, Christine Goertz, DC, PhD, Joan Walters, JD, PA E-Mail: coulter@rand.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The RAND Corporation P.O. Box 2138 1776 Main Street Santa Monica, CA 90407-2138				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 This study is comprised of three trials, referred to as the Assessment of Chiropractic Treatment (ACT). The following accomplishments have been made in each study during the reporting period of February 15, 2015 through February 14, 2016. ACT 1 is a randomized controlled trial of chiropractic for low back pain with a nested smoking cessation component in active duty military personnel. During this reporting period the study: Completed 100% (N=750) of ACT 1 trial recruitment; Long-term follow up assessments underway. ACT 2 is a randomized controlled trial of response and reaction times in Special Operations Forces at Ft. Campbell, KY; Expanded Special Operation Forces recruitment; Achieved ~75% (N=89/120) of recruitment goal. ACT 3 is a randomized controlled trial of strength, balance, and re-injury comparing standard care with standard care plus chiropractic treatment; Secured full command support for military study moving forward at Naval Hospital Pensacola; finalized addition of ACT 3 to the Cooperative Research and Development Agreement (CRADA) and pending final approval of Data Sharing Agreement (DSA) will launch study.					
15. SUBJECT TERMS Chiropractic, low back pain, tobacco cessation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 43	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION:

This annual report provides updates for the reporting period February 15, 2015 through February 14, 2016 on the study “Assessment of Chiropractic Treatment for Low Back Pain, Military Readiness and Smoking Cessation” (Grant Number W81XWH-11-2-0107). This program consists of three trials taking place at five military sites under the study. These trials have staggered start dates at multiple sites. Trial A is a randomized controlled trial of low back pain with nested smoking cessation for active duty personnel at Walter Reed National Military Medical Center (WRNMMC) in Bethesda, MD; Naval Hospital Pensacola (NHP), FL; Naval Medical Center San Diego (NMCS), CA) which was the first study to be initiated. This study is followed by consecutively run Trials B and C. Trial B is a randomized controlled trial of response and reactions times in Special Operations Forces at Blanchfield Army Community Hospital, Fort Campbell, KY. Trial C is a randomized controlled trial evaluating the effects of chiropractic care on strength and balance, in active duty military personnel at Naval Hospital Pensacola, FL.

BODY:

Clinical Trial A (ACT 1) Summary

Assessment of Chiropractic Trials Study A (called “ACT 1”) is a multi-site randomized controlled trial (RCT) for low back pain with nested tobacco cessation study at sites: Walter Reed National Military Medical Center in Bethesda, MD; Naval Hospital Pensacola, FL; Naval Medical Center San Diego, CA. The aim of ACT 1 is to conduct a multi-site, randomized controlled trial to test whether the combination of chiropractic treatment plus standard medical care is superior to standard medical care alone for relief of pain and the improvement in function in active duty military personnel (ages 18-50) with acute, sub-acute and/or chronic, non-surgical low back pain. A secondary aim is to assess success of tobacco cessation delivered by chiropractors. During this reporting period, 100% of the recruitment target has been met across all sites: a total of 750 participants have been recruited with 250 at Naval Medical Center San Diego (NMCS), 250 at Naval Hospital Pensacola (NHP), and 250 at Walter Reed National Military Medical Center in Bethesda (WRNMMC), MD.

Recruitment Overview

Study recruitment for ACT 1 has been successful throughout the last reporting period. Recruitment ended at Naval Medical Center San Diego on January 27, 2015; at Naval Hospital Pensacola on April 22, 2015; and at Walter Reed National Military Medical Center on November 20, 2015. At the end of this reporting period, long-term assessment data collection continues at the three sites (refer to Task 8). We conducted quarterly internal quality assurance visits at each site to maintain data integrity and ensure standardization of study procedures across all sites.

During this reporting period, the ACT 1 protocol at Walter Reed National Military Medical Center in Bethesda and Naval Hospital Pensacola was amended to include long-term follow up. This includes 3 additional online assessments that will measure outcomes at months 6, 9, and 12 from allocation. In addition, we are collecting data on a weekly basis via Short Message Service (SMS) to capture LBP status in this subset of participants from week 7 to week 52 (1 year). The addition of these outcome measures will provide important information on the trajectory of LBP in military personnel. These items were not added at Naval Medical Center San Diego since enrollment was almost completed at the time of the amendment submission.

Personnel changes during this reporting period:

- LTC Keith Myers, WRNMMC PI, was deployed from October, 2014 through February, 2015. During this time, MAJ Matthew Miller served as interim PI. LTC Myers resumed the role of PI in March, 2015. MAJ Matthew Miller remained on the protocol as an Associate Investigator.
- Julie Hartman, DC, assumed the role of Lead Project Manager August, 2015.
- Elissa Twist, DC, MS, CCRP assumed the role of Project Manager at WRNMMC August, 2015.
- Bridget Kane, MS, CCRC assumed the role of Project Consultant August, 2015.

Task 1: Submit quarterly technical progress reports to project officers

- In compliance with reporting requirements, quarterly reports were submitted in this reporting period on the following dates: May 13, 2015, August 17, 2015, and November 18, 2015.

Task 2: Annual reports have been sent to Defense Technical Information Center

- In compliance with reporting requirements, annual reports were submitted on March 14, 2012, March 15, 2013, March 13, 2015, and March 14, 2016.

Task 3: Finalized protocol and sites

- No changes in sites since end of last reporting period
- Added long-term follow up assessments to study protocol at Naval Hospital Pensacola and Walter Reed National Military Medical Center (October, 2014)

Task 4: Convened advisory panel for review of all study matters

- Convened advisory panel meetings to report progress and challenges on May 3, 2011, May 1, 2012, March 17, 2014, August 10, 2015.

Task 5: Prepared data collection systems

- Kept data collection systems updated during reporting period.
- Added long-term follow up web assessments at months 6, 9, 12; updated associated reports and timelines to reflect these additions
- Added online module to track screen failures/reasons for exclusion
- Added online module to track participant care received for LBP during study (includes providers visits for LBP and medications prescribed)

Task 6: IRB approval processes and other regulatory requirements

- During this reporting period, IRB amendments were submitted for all changes in staff, to update recruitment materials, protocol changes to include refinement of the 'contextual component' procedures and addition of long-term follow up assessments as well as changes to the informed consent document resulting from these protocol changes. The amendments were routed through all 5 IRBs (RAND, Palmer, NHP, NMCSO, and WRNMMC) prior to site implementation. Samueli Institute has a Federalwide Assurance (FWA) that stipulates RAND as the IRB on record for this program.
- There were a series of IRB approvals in sequence that were obtained, including local military scientific and IRB reviews, RAND, Palmer College, and second level Human Research Protection Office (HRPO) approvals, as follows:

Walter Reed National Military Medical Center in Bethesda, MD

- Initial submission October 18, 2012
- Amendment 01 February 4, 2013
- Amendment 02 May 21, 2013
- Amendment 03 September 24, 2013
- Amendment 04 February 4, 2014
- Amendment 05 April 29, 2014
- Amendment 06 August 4, 2014
- Amendment 07 May 15, 2014
- Reportable event September 17, 2014
- Amendment 08 September 18, 2014
- Amendment 09 November 10, 2014
- Amendment 10 March 24, 2015
- Amendment 11 August 17, 2015
- Reportable event October 9, 2015

Naval Hospital Pensacola, FL (IRB of record: Naval Medical Center Portsmouth)

*** Approval date indicates both Portsmouth approval as well as Commanding Officer of Naval Hospital Pensacola approval*

- Initial submission August 1, 2012
- Amendment 01 September, 17, 2012
- Amendment 02 January 31, 2013
- Amendment 03 April 12, 2013
- Amendment 04 September 6, 2013
- Data Sharing Agreement February 26, 2014 (renewal)
- Data Sharing Amendment July 24, 2015 (permission to use AHLTA data)
- Amendment 05 August 28, 2014
- Amendment 06 August 26, 2014
- Amendment 07 November 3, 2014
- Amendment 08 November 3, 2014
- Amendment 09 November 3, 2014
- Amendment 10 November 26, 2014
- Amendment 11 September 9, 2015

Naval Medical Center San Diego, CA

- Initial submission February 22, 2012
- Amendment 01 August 6, 2012
- Amendment 02 March 13, 2013
- Amendment 03 November 1, 2013
- Amendment 04 January 22, 2014
- Data Sharing Agreement February 26, 2014
- Amendment 05 April 14, 2014
- Amendment 06 July 21, 2015

- Data Sharing Amendment July 24, 2015 (permission to use AHLTA data)

RAND Corporation: ACT 1 gained initial approval on January 20, 2011 with continuing reviews and amendments to procedures approved on the following dates:

- Continuing reviews: Approved January 31, 2012, December 18, 2012, November 20, 2013, November 6, 2014, November 5, 2016.
- Amendment 01 July 28, 2011
- Amendment 02 August 9, 2011
- Amendment 03 January 31, 2012
- Amendment 04 April 12, 2012
- Amendment 05 May 15, 2012
- Amendment 06 September 16, 2012
- Amendment 07 January 2, 2012
- Amendment 08 August 21, 2013
- Amendment 09 November 7, 2013
- Amendment 10 April 3, 2014
- Amendment 11 September 15, 2014
- Amendment 12 October 21, 2014
- Amendment 13 December 16, 2014
- Event Report 01 March 4, 2013 - patient with gall bladder surgery that was deemed not connected to study
- Event Report 02 August 13, 2013 - an allocation algorithm error was corrected.
- Event report 03 October 3, 2014 – incorrect version of consent form utilized at WRNMMC, safety and welfare of participant was not compromised.
- Event report 04 December 11, 2015 – minor protocol deviation of mode of data collection

Palmer College of Chiropractic:

- Initial Submission January 18, 2011
- Amendment 01 March 9, 2011
- Amendment 02 March 16, 2011
- Amendment 03 June 6, 2011
- Amendment 04 December 7, 2011
- Amendment 05 February 7, 2012
- Amendment 06 March 19, 2012
- Amendment 07 May 4, 2012
- Amendment 08 May 11, 2012
- Amendment 09 July 26, 2012
- Amendment 10 January 11, 2013
- Amendment 11 November 15, 2013
- System Security Verification September 10, 2013
- Amendment 12 June 4, 2014
- Event report October 1, 2014
- Amendment 13 October 22, 2014

- Amendment 14 November 14, 2014
- System Security Verification November 26, 2014
- Amendment 15 August 12, 2015
- Event report October 7, 2015
- Amendment 16 December 10, 2015

Second Level Review at USAMRMC:

- During this reporting period, the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) provided official correspondence acknowledging HRPO receipt of continuing reviews for WRNMMC on April 7, 2015 and November 13, 2015, Palmer on March 2, 2015, RAND on March 31, 2015, and NMCS (closure report) on November 30, 2015.

Task 7: Hired and trained study coordinators for each site

- Developed standard employment contract
- Trained study personnel in standardized methods, including data entry and management
 - Site Project Manager – The new ACT 1 site PM, Elissa Twist, started on August 3, 2015 at the Palmer Center for Chiropractic Research (PCCR), Davenport, IA. The ACT 1 PM was oriented and trained by lead PM, Bridget Kane, during the week of August 3, 2015. The new ACT 1 PM was approved by the WRNMMC military IRB to conduct daily study operations and was then trained on site at WRNMMC from August 10, 2015 to August 14, 2015 by Abigail Roots, who departed from the site PM position on August 14, 2015.
 - Lead Project Manager – The new ACT 1 lead PM, Julie Hartman, started on August 3, 2015 at the PCCR Center for Chiropractic Research, Davenport, IA. The lead PM was oriented and trained by outgoing lead PM, Bridget Kane, August 3, 2015 to August 14, 2015. Ms. Kane then transitioned to the role of project consultant.
 - Long term follow-up Personnel – Study personnel involved with data collection for long term follow-up of participants at NHP and WRNMMC reviewed training procedures at the PCCR September 30, 2015.
- All study coordinators trained and certified for site-specific CITI
 - All human subject's protections certifications current through reporting period
- Obtained ID badges and security approvals for all on-site study personnel
 - Badges and security approvals current through reporting period
- Conducted administrative site visits to ensure all systems are in place and fully functional. Site visits for ACT 1 during this reporting period include:
 - *WRNMMC, Bethesda, MD* – No administrative site visits conducted during this reporting period. See quality assurance section.
 - *Naval Hospital Pensacola, FL – May 28-29, 2015* - Lead Project Manager, Bridget Kane, conducted a study-close out visit at NHP on May 29, 2015. During this visit, informed consent documents were given to Shirley Callan, Research Liaison, NHP to retain for CDR Penta, site PI. All other study documents were shipped to the Palmer Center for Chiropractic Research for retention. A final inventory of study supplies

and documents was conducted. All materials were accounted for and stored appropriately.

- *NMCSD, San Diego, CA – March 16-20, 2015* – Lead PM, Bridget Kane, conducted a study-close out visit at NMCSD. During this visit, Lead PM met with a representative from the Clinical Investigations Department (CID) to review study closeout procedures as well as site PI, CAPT Rosenthal, to review document retention procedures. A final inventory of study supplies and documents was conducted.

Task 8: Study recruitment and data collection per site for reporting period:

- Tables and figures below display recruitment, accrual, retention and demographics for each site in ACT 1.

Table 1: Recruitment, Accrual and Retention

As of Feb 14 2016	NMCSD: San Diego	NHP: Pensacola	WRNMMC: Bethesda	Total
Baseline	273	260	273	806
# excluded	21	10	1	32
# chose not to participate	2	0	22	24
Allocated	250	250	250	750
Week 2 Assessment	250	250	250	747
# completed	232	195	233	660
# missed outcomes	17	52	15	84
% missed outcomes	7%	21%	6%	11%
# withdrawn	1	3	2	3
Week 4 Assessment	249	247	248	744
# completed	221	183	222	626
# missed outcomes	27	64	24	115
% missed outcomes	11%	26%	10%	16%
# withdrawn	1	0	2	3
Week 6 Assessment	248	247	246	741
# completed	237	208	238	683
# missed outcomes	10	35	7	52
% missed outcomes	4%	14%	3%	7%
# withdrawn	1	4	1	6
Month 3 Assessment	247	243	243	733
# completed	221	189	213	623
# missed outcomes	25	51	29	105
% missed outcomes	10%	21%	12%	14%
# withdrawn	1	3	1	5
# consented for long-term follow-up	N/A	57	97	154
Month 6 Assessment*	N/A	55	77	132
# completed		25	52	77
# missed outcomes		30	25	55
% missed outcomes		55%	32%	42%
Month 9 Assessment*	N/A	55	59	114
# completed		31	43	74
# missed outcomes		24	16	40
% missed outcomes		44%	27%	35%
Month 12 Assessment*	N/A	31	29	60
# completed		17	24	41
# missed outcomes		14	5	19
% missed outcomes		45%	17%	32%

Data for Walter Reed National Military Medical Center in Bethesda, MD

Table 2: Demographics for Annual Report of Project DoD ACT1*

As of Feb 14 2016

Questions	Values	Treatment 1 (n=125)		Treatment 2 (n=125)		Total (n=250)	
		n	%	n	%	n	%
Ethnic	Hispanic or Latino	16	13	9	7	25	10
	Not Hispanic or Latino	95	76	108	86	203	81
	Unspecified	14	11	8	6	22	9
Sex	Female	39	31	40	32	79	32
	Male	86	69	85	68	171	68
Race	American Indian or Alaska Native	0	0	0	0	0	0
	Asian	6	5	3	2	9	4
	Native Hawaiian or Other Pacific Islander	1	1	5	4	6	2
	Black or African American	41	33	42	34	83	33
	White	62	50	62	50	124	50
	Multi-racial	3	2	3	2	6	2
	Unspecified	12	10	10	8	22	9
Age	Mean SD	34.4	8.4	34.7	8.6	34.6	8.4
	Median	34.0		35.0		35.0	
	n	125		125		250	

* this table is for **Walter Reed National Military Medical Center in Bethesda**

percentages may not add up to 100 due to rounding

Figure 1: Walter Reed National Military Medical Center

Feb 14 2016

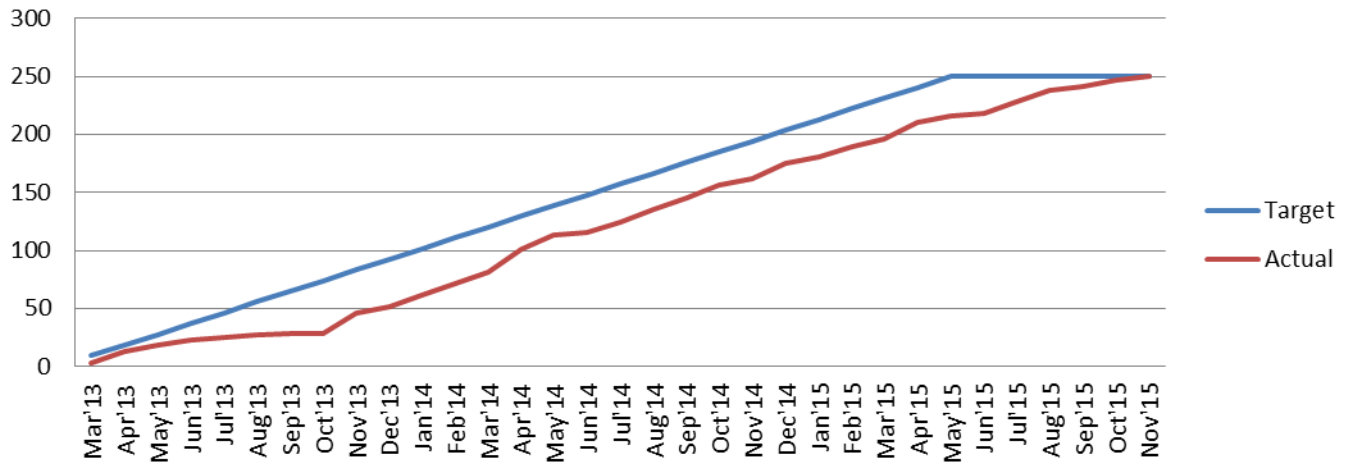
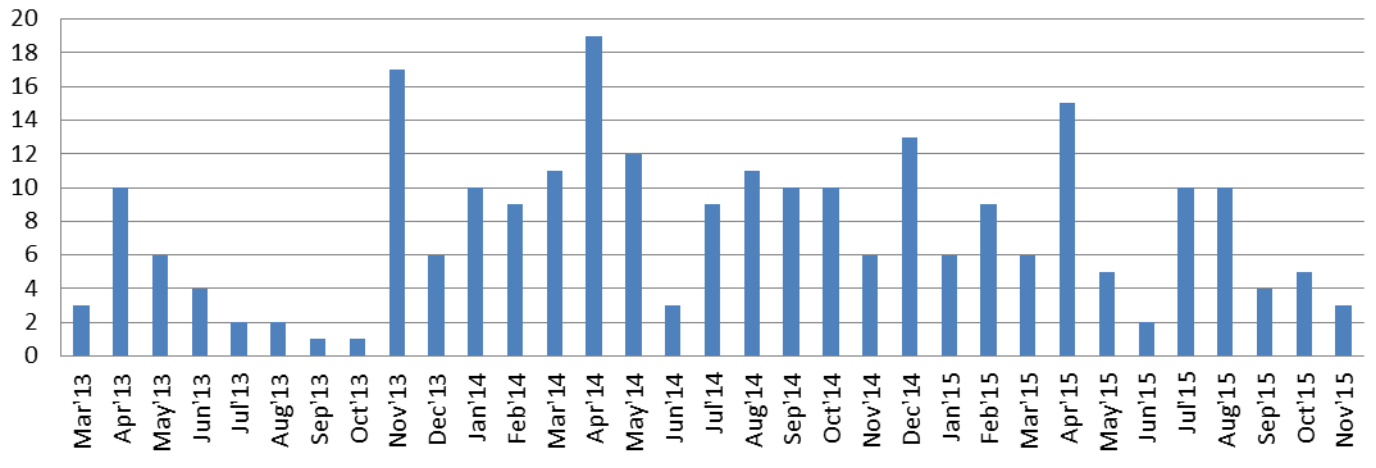


Figure 2: Walter Reed National Military Medical Center

Feb 14 2016



Data for Naval Hospital Pensacola

Table 3: Demographics for Annual Report of Project DoD ACT1*

As of Feb 14 2016

Questions	Values	Treatment 1 (n=125)		Treatment 2 (n=125)		Total (n=250)	
		n	%	n	%	n	%
Ethnic	Hispanic or Latino	29	23	12	10	41	16
	Not Hispanic or Latino	94	75	112	90	206	82
	Unspecified	2	2	1	0.8	3	1
Sex	Female	19	15	18	14	37	15
	Male	106	85	107	86	213	85
Race	American Indian or Alaska Native	0	0	0	0	0	0
	Asian	3	2	1	1	4	2
	Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
	Black or African American	17	14	15	12	32	13
	White	102	82	106	85	208	83
	Multi-racial	1	1	0	0	1	0
	Unspecified	2	2	3	2	5	2
Age	Mean SD	25.5	7.9	25.7	7.5	25.6	7.7
	Median	22.0		23.0		23.0	
	n	125		125		250	

* this table is for **Naval Hospital in Pensacola**

percentages may not add up to 100 due to rounding

Figure 3: Naval Hospital Pensacola

Feb 14 2016

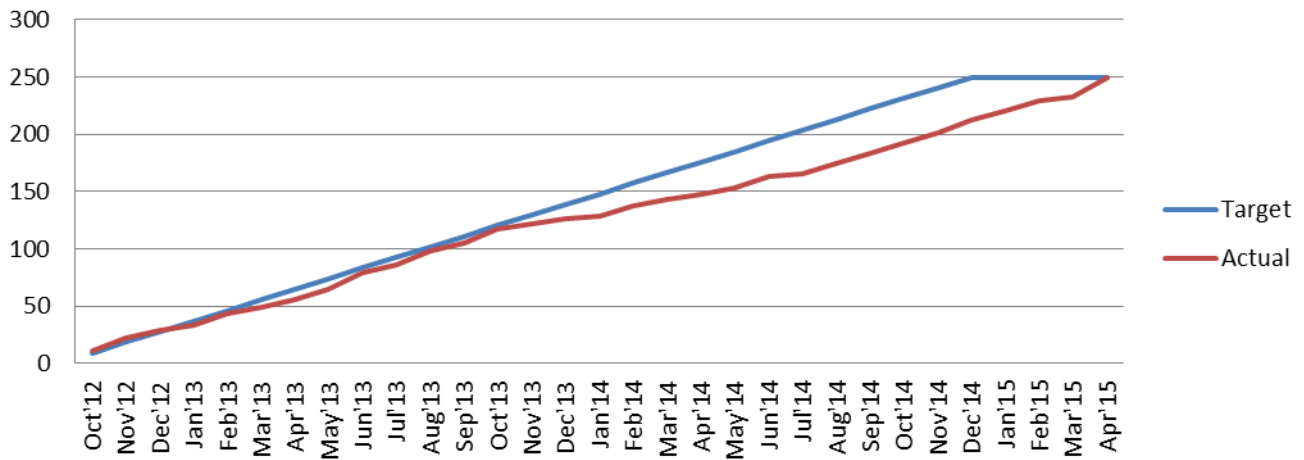
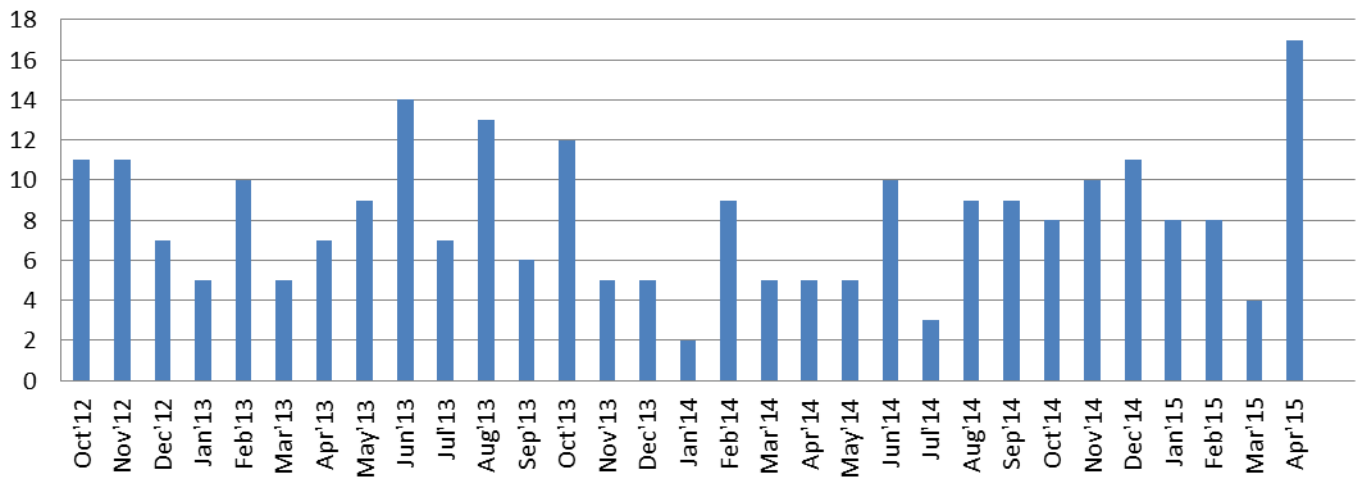


Figure 4: Naval Hospital Pensacola

Feb 14 2016



Data for Naval Medical Center San Diego, CA

Table 4: Demographics for Annual Report of Project DoD ACT1*

As of Feb 14 2016

Questions	Values	Treatment 1 (n=125)		Treatment 2 (n=125)		Total (n=250)	
		n	%	n	%	n	%
Ethnic	Hispanic or Latino	21	17	31	25	52	21
	Not Hispanic or Latino	97	78	80	64	177	71
	Unspecified	7	6	14	11	21	8
Sex	Female	30	24	29	23	59	24
	Male	95	76	96	77	191	76
Race	American Indian or Alaska Native	2	2	0	0	2	1
	Asian	11	9	6	5	17	7
	Native Hawaiian or Other Pacific Islander	1	1	2	2	3	1
	Black or African American	14	11	20	16	34	14
	White	88	70	87	70	175	70
	Multi-racial	4	3	3	2	7	3
	Unspecified	5	4	7	6	12	5
Age	Mean SD	32.4	7.4	32.4	7.5	32.4	7.4
	Median	31.0		32.0		31.5	
	n	125		125		250	

* this table is for **Naval Medical Center in San Diego**

percentages may not add up to 100 due to rounding

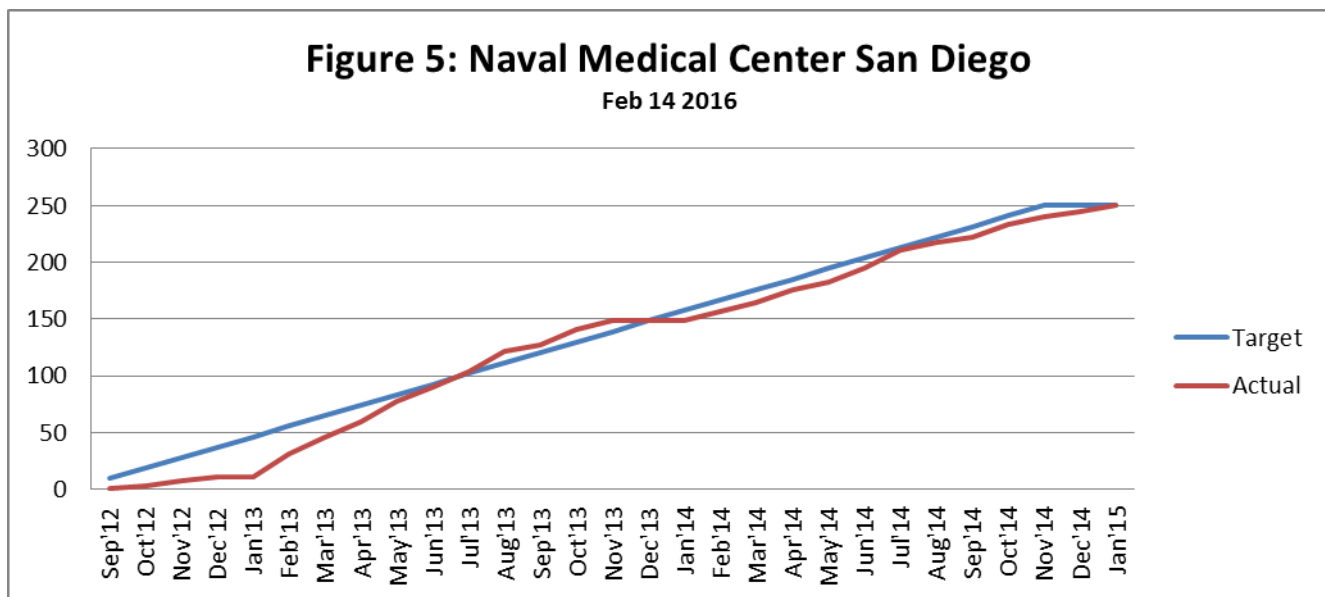


Figure 6: Naval Medical Center San Diego

Feb 14 2016

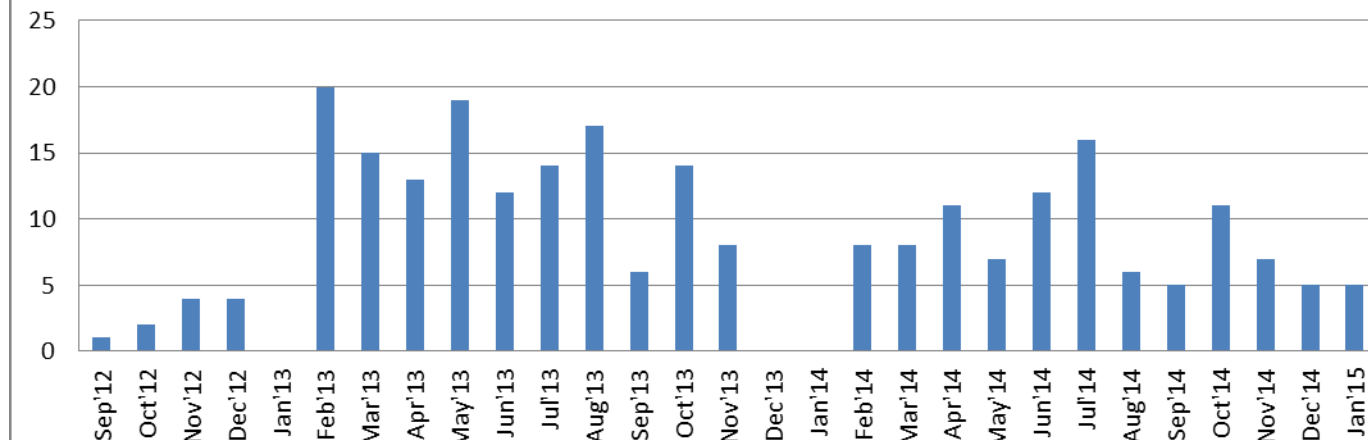


Table 5. Recruitment Summary Table

	Time Period					
	2/15/2013 to 2/14/2014		2/15/2014 to 2/14/2015		2/15/2015 to 2/14/2016	
Site	# enrolled	Avg # per mth	# enrolled	Avg # per mth	# enrolled	Avg # per mth
WRNMMC	67	5.6	119	9.9	64	5.3
NHP	94	7.8	96	8.0	22	1.8
NMCSD	129	10.8	96	8.0	0	0.0

Task 9: Quality assurance site visits conducted during this period included:

- Walter Reed National Military Medical Center in Bethesda, MD
 - *July 13-17, 2015* - Lead Project Manager, Bridget Kane conducted an internal quality assurance visit at WRNMMC- Bethesda on July 13-17, 2015. During this visit, informed consent documents were reviewed and found to be in order. Source documents were verified with the study electronic data capture system. In addition, Lead Project Manager met with Dr. Jasleen Shant, Chief, Department of Research Programs and Mr. Steven Ross, Grants Manager at WRNMMC to review the amendment to the NAVY CRADA for the addition of the ACT 3 study.
- Naval Hospital Pensacola, FL
 - *April 13-30, 2015* - Lead PM, Bridget Kane, went to Naval Hospital Pensacola to assist site PM in completing study recruitment. During this visit, an internal

quality assurance review was completed. Informed consent documents as well as site source documents were reviewed. Lead PM met with site PI, study DC, and OICs of branch clinics to discuss study status.

- Naval Medical Center San Diego, CA

No quality assurance site visits conducted during this reporting period. See administrative site visits section.

Task 10: Write methodology manuscript for submission

- ACT I methodology manuscript was submitted to journal during this reporting period.

Task 11: Submit annual continuing review documents for IRB. The following IRB continuing reviews have been processed on these dates:

- Walter Reed National Military Medical Center in Bethesda, MD received continuing review approval on October 8, 2015 and will expire on October 23, 2016.
 - Continuing review approval documents were submitted to MRMC for WRNMMC (per MRMC request) on April 7, 2015. MRMC HRPO acknowledged receipt of the current continuing review documents for WRNMMC on April 21, 2015.
 - Continuing review approval documents were submitted to MRMC for WRNMMC (per MRMC request) on November 13, 2015. MRMC HRPO acknowledged receipt of the current continuing review documents for WRNMMC on February 15, 2016.
- Naval Hospital Pensacola, FL received continuing review approval on September 9, 2015 and will expire on September 8, 2016.
 - Continuing review approval documents were submitted to MRMC for NHP (per MRMC request) on November 20, 2014. MRMC HRPO acknowledged receipt of the current continuing review documents for NHP on April 21, 2015.
 - Continuing review approval documents were submitted to MRMC for WRNMMC (per MRMC request) on November 15, 2015. MRMC HRPO acknowledged receipt of the current continuing review documents for WRNMMC on January 24, 2016.
- Naval Medical Center San Diego, CA was granted approval for completion of protocol August 19, 2015.
 - Protocol closure approval documents were submitted to MRMC for NMCS (per MRMC request) on November 16, 2015. MRMC HRPO acknowledged receipt of the current continuing review documents for NMCS on February 9, 2016.
- RAND Corporation gained continuing review approvals
 - January 31, 2012, December 18, 2012, November 20, 2013, November 6, 2014, and for this reporting period: November 5, 2015.
 - MRMC HRPO acknowledged receipt of continuing review documents from RAND Corporation on December 14, 2015,
- Palmer College received continuing review approval on December 1, 2015 and will expire on November 30, 2016.
 - Continuing review approval documents were submitted to MRMC for Palmer (per MRMC request) on March 2, 2015. MRMC HRPO acknowledged receipt of the current continuing review documents for WRNMMC on April 10, 2015.
 - Continuing review approval documents were submitted to MRMC for Palmer (per MRMC request) on January 14, 2016.

Task 12: Convene advisory board at yearly intervals and as needed (Annually)

- Created advisory panel and kick off meeting May 3, 2011.
- Convened advisory panel on May 1, 2012, March 17, 2014, and August 10, 2015.

Task 13: Close study recruitment

- NMCSO completed study recruitment on January 27, 2015 after meeting target goals.
- NHP completed study recruitment on April 22, 2015 after meeting target goals.
- WRNMMC completed study recruitment on November 20, 2015 after meeting target goals.

Task 14: Analyze data

- The Publications Committee approved the proposal and outline for a contextual evaluation paper to be written for peer-reviewed publication. The manuscript is in draft mode at this time.

Task 15: Write final study reports and manuscript

- ACT 1 protocol paper published <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4746780/>

Task 16: Convene publications committee at Month 18 and quarterly thereafter

- Recruited Publications Committee and initial meeting convened June 18, 2015
- Developed and approved charter and publication proposal form
- Convened publications quarterly: November 10, 2015, February 8, 2016.

Clinical Trial A (ACT 1) Summary of Tobacco Cessation Trial

The aim of this nested trial within Trial A is to measure changes in smoking and tobacco behavior between two treatment groups, in response to a tobacco cessation program delivered in the chiropractic arm of the study. Investigation of a smoking cessation program delivered by doctors of chiropractic will be imbedded in the low back pain trial. Those who wish to participate in the low back pain study but not the smoking cessation program will be allowed into the study.

Task 1: Finalized manual and other program materials

(Completed prior to this reporting period)

Task 2: Train chiropractors to deliver program in standardized fashion (Months 6-12) Palmer

(Completed prior to this reporting period)

Task 3: Finalized outcome parameters for tobacco cessation, loaded onto system

(Completed prior to this reporting period)

Task 4: Data Collection underway as follows:

Table 6: Tobacco Enrollment Report				
	<u>Tobacco User</u>	<u>Consented</u>	<u>Enrolled</u>	<u>Withdrawn</u>
Walter Reed National Military Medical Center	24	14	8	1
Naval Hospital Pensacola	49	40	16	2
Naval Medical Center San Diego	52	28	11	1

Task 5: Data Analysis (Not applicable during this reporting period)

Clinical Trial B (ACT 2) Summary

The Assessment of Chiropractic Treatment using reaction and response times in members of the Special Operation Forces (ACT 2) is a randomized controlled trial designed to evaluate changes in reaction and response times following chiropractic treatment compared to controls in the Special Forces population.

During this reporting period, the ACT 2 protocol was amended to broaden our eligibility criteria to include soldiers from the 160th Special Operations Aviation Regiment (SOAR) (Night Stalkers) and eliminate the upper limit age restriction. The operational tempo of the 5th group Special Forces Qualified (SFQ) unit at Ft. Campbell is quite high and many soldiers in the 5th group are not on post. By including the approximately 1000 flight status members (pilots/crew) in 160th SOAR regiment we are confident we will accomplish our recruitment goals and have recruited 89/120 participants to date.

Personnel changes during this reporting period:

- Julie Hartman, DC, assumed the role of Lead Project Manager August, 2015.
- Bridget Kane, MS, CCRC assumed the role of Project Consultant August, 2015.

Task 1: Make final selection of Special Forces site(s)

- Blanchfield Army Community Hospital, Fort Campbell, KY was identified as the single site for ACT 2.

Task 2: Finalized metrics for response and reaction times

- The protocols for the 5 different reaction time tests as well as the data collection forms were revised and finalized during a previous reporting period.
- Procedures for secure data transfer were finalized in previous reporting period.

Task 3: IRB approval process

- Worked through sequences of IRB approvals, including local military scientific and IRB reviews, RAND, Palmer College, and second level Human Research Protection Office (HRPO) approvals. As follows:
 - Dwight D. Eisenhower Army Medical Center (Fort Campbell's IRB of record)
 - Initial submission December 12, 2013 (contingent approval)
Final approval received May 13, 2014
 - Amendment 01 May 16, 2014
 - Amendment 02 August 13, 2014

- Amendment 03 September 9, 2014
 - Continuing review November 13, 2014
 - Amendment 04 September 12, 2015
 - Continuing review November 20, 2015

- RAND Corporation
 - Initial submission December 6, 2012
 - Continuing reviews approved: May 31, 2013, May 19, 2014, MAY 8, 2015
 - Amendment 01 May 10, 2012 (Pilot approval)
 - Continuing review May 31, 2013
 - Amendment 02 August 21, 2013
 - Amendment 03 February 14, 2014 (re-design approved)
 - Continuing review May 19, 2014
 - Amendment 04 June 9, 2014
 - Amendment 05 August 18, 2014
 - Amendment 06 September 15, 2014
 - Amendment 07 September 23, 2015

- Palmer College (Military study)
 - Initial submission February 2, 2012
 - Amendment 01 May 1, 2012
 - Amendment 02 June 14, 2012
 - Amendment 03 January 9, 2013
 - Continuing Review 01 January 23, 2013
 - Continuing Review 02 January 24, 2014
 - Amendment 04 June 9, 2014
 - Amendment 05 August 6, 2014
 - Amendment 06 August 18, 2014
 - Continuing review 03 December 8, 2014
 - Amendment 07 August 15, 2015
 - Amendment 08 September 22, 2015
 - Continuing review 04 November 30, 2015

- USAMRMC: The ACT 2 protocol received HRPO and CIRO approval on May 2, 2014. The CRADA was executed on May 15, 2014. MRMC HRPO requested continuing review documents for Ft. Campbell (DDEAMC) and documents were sent to MRMC on January 14, 2016. MRMC HRPO acknowledged receipt of the current continuing review documents for DDEAMC on February 15, 2016. Continuing review for Palmer was sent to MRMC HRPO on January 16, 2016 with no acknowledgement received from MRMC to date.
- The ACT 2 protocol was selected for an audit during the Army Human Research Protections Office (HRPO) assessment. The audit took place via conference call on February 12, 2016 and was attended by site PI, Dr. Tom Jones, site PM, Ms. Darla Freehardt, and lead PM Dr. Julie Hartman. Auditors had no immediate concerns or

recommendations for improvement regarding this study. The study team is awaiting a formal report from HRPO which will be shared in the next review.

Task 4: Study recruitment and data collection

- Completed pilot study (previous reporting period)
- Launched main study September, 2014 at Blanchfield Army Community Hospital, Ft. Campbell, KY.
- Opened study enrollment to include pilots/crew from the 160th SOAR (Night Stalkers) September 2015.

Data for Ft. Campbell, KY

Table 1: Recruitment, Accrual and Retention*

As of Feb 14 2016	Ft Campbell
Screened	130
# screen failed	40
Baseline	90
# excluded	0
Allocated	89
Final Visit	80
# completed	79
# withdrawn	1

* As of the cutoff date for reporting 1 participant completed a baseline visit but was not yet allocated.

Table 2: Demographics for Annual Report of Project DoD ACT2*

As of Feb 14 2016

Questions	Values	Treatment 1 (n=44)		Treatment 2 (n=45)		Total (n=89)	
		n	%	n	%	n	%
Ethnic	Hispanic or Latino	4	9	3	7	7	8
	Not Hispanic or Latino	35	80	37	82	72	81
	Unspecified	5	11	5	11	10	11
Sex	Female	0	0	0	0	0	0
	Male	44	100	45	100	89	100
Race	American Indian or Alaska Native	0	0	0	0	0	0
	Asian	1	2	0	0	1	1
	Native Hawaiian or Other Pacific Islander	1	2	0	0	1	1
	Black or African American	3	7	1	2	4	4
	White	38	86	41	91	79	89
	Multi-racial	0	0	1	2	1	1
	Unspecified	1	2	2	4	3	3
Age	Mean SD	32.3	4.8	33.5	5.5	32.9	5.2
	Median	31.5		32.0		32.0	
	n	44		45		89	

* this table is for **Ft. Campbell, KY**

percentages may not add up to 100 due to rounding

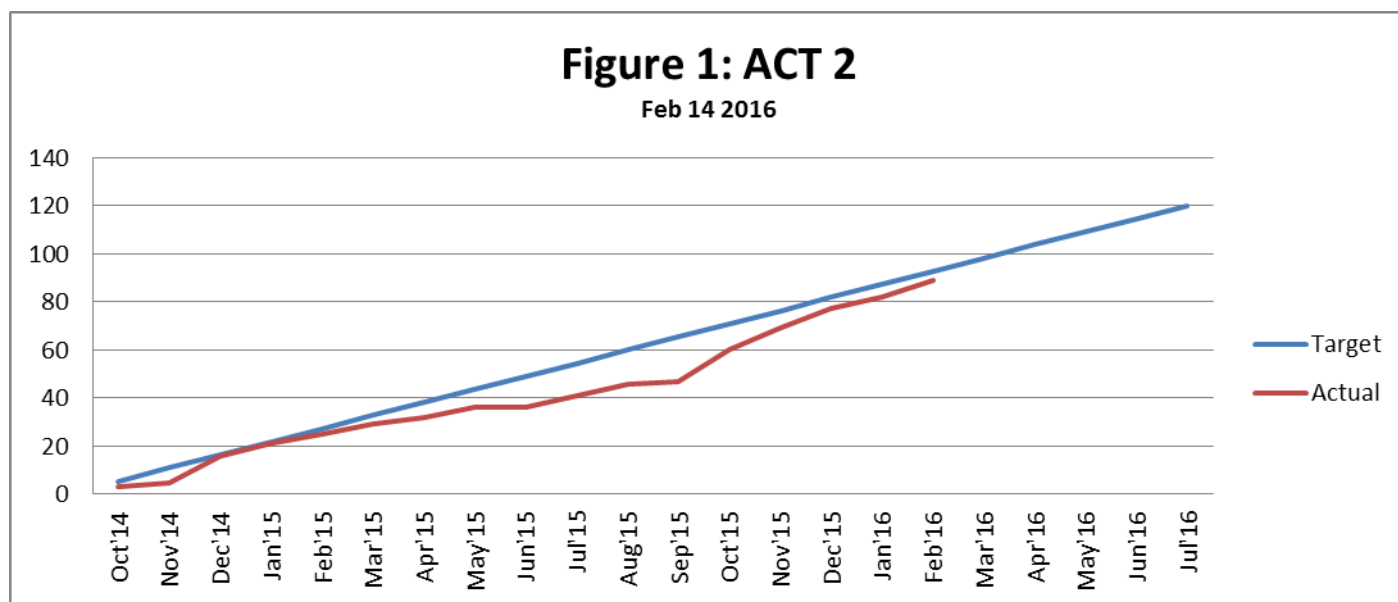
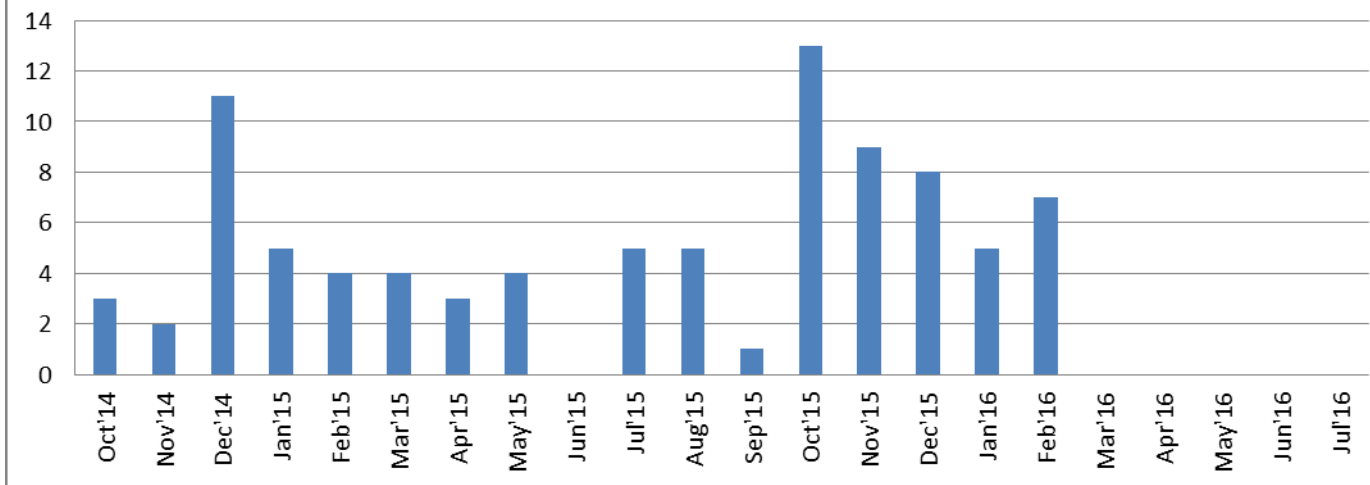


Figure 2: ACT 2

Feb 14 2016



Task 5: Quality assurance site visits

- Staff training
 - *August 3-14, 2015* – The new ACT 2 lead PM, Julie Hartman, started on August 3, 2015 at the PCCR Center for Chiropractic Research, Davenport, IA. The lead PM was oriented and trained by outgoing lead PM, Bridget Kane, August 3, 2015 to August 14, 2015. Ms. Kane then transitioned to the role of project consultant.
- Study logistics
 - *May 25-28, 2015* - Lead Project Manager, Bridget Kane, conducted an internal quality assurance visit at Ft. Campbell. During this visit, informed consent documents as well as site source documents were reviewed and found to be in order. Study status was also discussed with site PI and site Project Manager.
 - *August 19-20, 2015* - Principal Investigator, Dr. James DeVocht, conducted a site visit August 19-20, 2015 to evaluate the study testing equipment. Dr. DeVocht checked equipment function, made updates to equipment software, and provided a backup computer in the unlikely event of a problem with the main computer.
 - *November 2-6, 2015* - Lead Project Manager, Julie Hartman, conducted an internal quality assurance review on November 2-6, 2015. All regulatory documents were reviewed and source documents were verified. During this visit, Lead PM met with site PI Dr. Thomas Jones and discussed recruitment and study status.

Task 6: Analyze pre-post data (Not applicable during this reporting period)

Clinical Trial C (ACT 3) Summary

The ACT 3 pilot study, designed to refine the strength and balance testing procedures in participants with low back pain, launched at the Palmer Center for Chiropractic Research April 30, 2014. A total of 15 participants were enrolled in this study. Since the goals of this pilot study were

accomplished prior to enrolling 20 participants (original study goal), the investigators closed this study in December, 2014. This feasibility study allowed us to finalize protocols for the strength and balance testing, ensure integrity of data collection software, and evaluate the safety of implementing these protocols.

Military study regulatory updates: During this reporting period, the full study was submitted to the Naval Medical Center Portsmouth IRB on April 7, 2015. We received scientific review committee approval on June 4, 2015 and military IRB approval on June 10, 2015. The CRADA approval was finalized September 30, 2015. Full military IRB approval has not been granted through the Portsmouth IRB as it is contingent on the DSA; therefore, final IRB approval will be completed upon the approval of the DSA. This situation arose due to policy changes at BUMED. We were not able to amend the original DSA to include ACT 3 and were required to submit an entirely new application. This application was submitted on January 8, 2016 and is still being processed. The ACT 3 full study was approved by the Palmer and RAND IRBs. This protocol will be submitted for second level review at MRMC after all three IRB approvals are final and the amended CRADA and DSA are executed.

Personnel changes during this reporting period:

- Amy Minkalis, DC assumed the role of Lead Project Manager August, 2015.
- Bridget Kane, MS, CCRC assumed the role of Project Consultant August, 2015.
- Crystal Franklin, MPH assumed the role of Site Project Manager September, 2015.

Task 1: Established metrics for strength, balance, re-injury

- Tested and refined programs and procedures for evaluating strength and balance during the pilot phase of the study
- Moved the long-term follow up assessments to ACT 1 (re-injury)

Task 2: IRB approval process

- Worked through sequences of IRB approvals, including local military scientific and IRB reviews, RAND, Palmer College, and second level Human Research Protection Office (HRPO) approvals. As follows:
 - Madigan Army Medical Center IRB: (not applicable during this reporting period; no longer applicable)
 - RAND Corporation:
 - Pilot approval March 19, 2013
 - Main study approval October 1, 2013
 - Continuing review approvals: February 14, 2014, February 13, 2015, February 11, 2016.
 - Amendment 01 June 3, 2013
 - Amendment 02 November 15, 2013
 - Amendment 03 December 5, 2013
 - Amendment 04 March 7, 2014 withdrawn
 - Amendment 05 April 4, 2014
 - Amendment 06 September 22, 2014
 - Amendment 07 July 22, 2015
 - Amendment 08 November 13, 2015

- Palmer College
 - Main study ** *Per the direction of the Palmer College IRB, since there have been multiple changes to the military study including site and study design, we will be submitting an entirely new protocol and closing out the study protocol listed below.*
 - o Initial approval August 17, 2012
 - o Amendment 01 January 10, 2013
 - o Continuing review approval August 19, 2013
 - o Continuing review approval July 23, 2014
 - o New protocol approval September 1, 2015
 - o Amendment 01 October 21, 2015
 - Pilot study
 - o Initial approval January 11, 2013
 - o Amendment 01 May 10, 2013
 - o Amendment 02 June 24, 2013
 - o Amendment 03 July 10, 2013
 - o Amendment 04 October 7, 2013
 - o Continuing review January 16, 2014
 - o Amendment 05 April 2, 2014
 - o Amendment 06 September 8, 2014
 - o Study close out December 19, 2014
- Naval Hospital Pensacola, FL (IRB of record: Naval Medical Center Portsmouth)
 - o Initial approval June 10, 2015
 - o Amendment 01 September 8, 2015
 - o Amendment 02 October 14, 2015
- Second level review at USAMRMC: (not applicable during this reporting period)

Task 3: Prepared data collection system:

- Updated web-based functional assessments and questionnaires
- Updated paper and web-based data collection forms

Task 4: Consulted advisory panel on validity/relevance of selected outcomes measures: Addressed issues with advisory panel last reporting period during convened panel on May 1, 2012.

Task 5: All systems prepared and awaiting DSA to execute full study

Task 6: Quality assurance site visiting and training

- Staff training
 - *August 3-14, 2015* – The new ACT 3 lead PM, Amy Minkalis, started on August 3, 2015 at the Palmer Center for Chiropractic Research, Davenport, IA. The lead PM was oriented and trained by outgoing lead PM, Bridget Kane. Ms. Kane then transitioned to the role of project consultant.

- *September 28-October 9, 2015* – Crystal Franklin was hired as the ACT 3 on-site Clinical Project Manager for Naval Hospital Pensacola and started September 28, 2015. She was oriented to the protocol and trained at the PCCR in Davenport, IA by lead PM Amy Minkalis and research clinic staff.
- Study logistics
 - *October 19-23, 2015* - Lead PM, Amy Minkalis, conducted a site visit with Associate Investigators Dr. Robert Vining and Dr. James Boysen. Visit activities included equipment assembly and testing as well as additional training for site project manager, study doctor of chiropractic and chiropractic assistant.
 - *February 24-25, 2015* – Lead PM, Bridget Kane and Associate Investigator Dr. Robert Vining conducted a site visit to Naval Hospital Pensacola to meet with military site PI, CDR Joseph Penta and study DC, Dr. Greg Lillie, to review study logistics prior to protocol IRB submission. Lead PM also met with OIC and Senior Medical Officer of branch clinics to obtain support statements for the ACT 3 study.

Task 7: Analyze data and write final study reports

- Evaluated feasibility and safety of functional testing protocols of following completion of pilot study

KEY RESEARCH ACCOMPLISHMENTS ACROSS ALL STUDIES:

Key research accomplishments are as follows:

ACT 1:

- Achieved 100% of ACT 1 trial recruitment (N=750)
- Completed study recruitment at NMCS, NHP, WRNMMC
- Completed contextual component of ACT 1 protocol
- Added long-term follow up assessments at NHP and WRNMMC
- Published ACT 1 protocol manuscript

ACT 2:

- Launched ACT 2 study at Ft. Campbell, KY
- Expanded recruitment to broader Special Operation Forces with command support
- Achieved 74% (N=89) of recruitment goal

ACT 3:

- Completed pilot study at the Palmer Center for Chiropractic Research
- Secured full command support for military study at Naval Hospital Pensacola
- Hired and trained site project manager
- Submitted new DSA application; all systems prepared and ready to launch once approved

REPORTABLE OUTCOMES ACROSS ALL STUDIES:

Not applicable during this reporting period.

CONCLUSIONS:

The significance of this research is high. Low back pain is a prevalent public health problem in both the military and civilian populations. Currently a clear “gold standard” medical treatment for low back pain does not exist and studies show that evidence-based guidelines are rarely used in general practice. Thus, there is a need to consider innovative treatment options for chronic diseases such as low back pain. Our preliminary data suggested that chiropractic treatment in addition to standard medical care may be superior to standard medical care alone in active duty service members. In addition, doctors of chiropractic are well positioned to provide information to support smoking cessation. The results from this set of trials will provide critical information regarding the health and mission-support benefits of chiropractic health care delivery for active duty service members.

REFERENCES: No references.

APPENDICES:

Appendix A. Newsletter from reporting period.

Appendix B. Published manuscripts.

SUPPORTING DATA:

Not applicable during this reporting period.

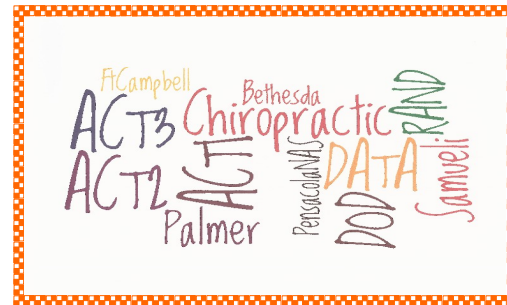


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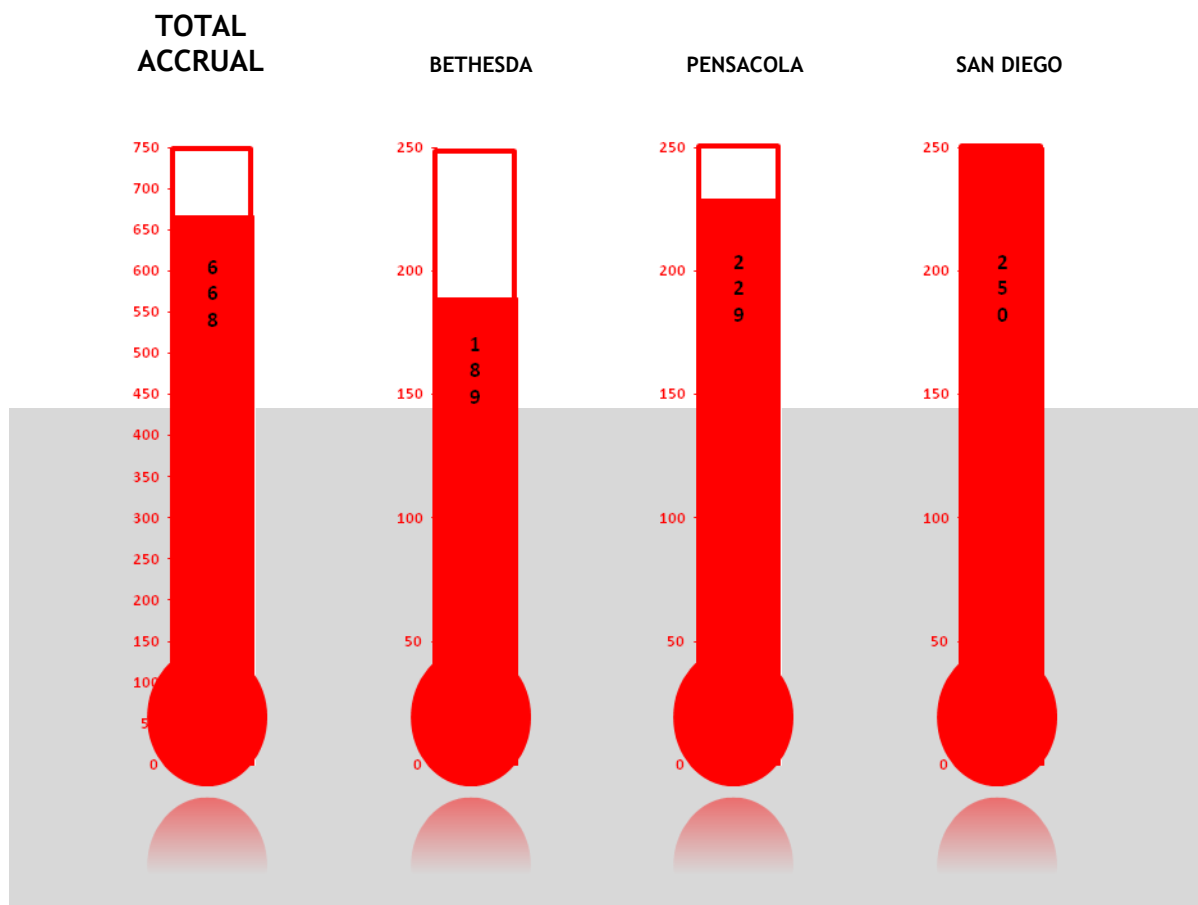
March, 2015

Inside This Issue:

- Message from the PI, Joan Walter, **Qualitative Component, ACT1**
- Main Article: **San Diego Completes Enrollment**
- Spotlight on Team Member:
Fort Campbell, KY Project Manager:
Darla Freehardt, BS, LPN, CCRP



ACT1 Enrollment Reach 89%





Message from the PI...

Joan Walter

We are in the home stretch to complete ACT1, which is comparing the outcomes of low back pain patients who are randomly assigned to be treated by a chiropractor in addition to usual medical care for LBP, with those who are randomly assigned to be treated for their back pain by others providing usual care. One of the challenges of interpreting and generalizing data from randomized controlled trials (RCT's) is that every clinical setting has its own unique environment of care. Many of the factors that promote healing are in the background, and their impact, both positive and negative, can be missed. That may mean that some of the differences in outcomes between the two treatment arms may be partly due to the environment of care in which the study was conducted.

The research plan for ACT1 therefore includes a qualitative portion to address these factors. In order to document and assess the practice environment or context in which care is provided, the ACT1 research team has conducted site visits to collect observations and stakeholder descriptions of how the study is being conducted at each site. Qualitative data was collected and is being analyzed, so that the study's 3 sites can be characterized and outcome results can be better understood, once the study has been completed.

Some general observations that are common to the 3 sites demonstrate some of the progress that has been made in integrating chiropractors and chiropractic care into the military medical system, at these successful sites. At this stage, with the RCT ongoing, we cannot yet address the key outcome questions; but we can describe some of the culture and practice environments that foster integrative care for low back pain, and make these clinical settings good sites for the research.

It is important first to note that all of the study Chiropractors were already embedded as clinicians at each of the 3 study sites. They readily agreed to participate in the research, and each of them demonstrated very strong commitment to successfully conducting the research project at the outset, and have continued to be highly engaged. Collaboration among all of the providers (Chiropractors, physicians, PA's, etc.) is evident in the 3 clinic environments, in the form of joint morning report, and weekly staff meetings and also cross-consultations. The Study Chiropractors at these sites are generally acknowledged as valuable members of the treatment team, by primary care and specialty providers, and by patients. The Chiropractors and their teams work effectively to schedule appointments to optimize care for the patients, many of whom have very demanding work schedules and obligations.

These are just some of the notable positive findings made during our ACT1 site visits. More detailed observations and stakeholder interview results will be presented as part of the larger research report at the end of the study. We look forward to sharing that information, and to continuing to explore the many aspects of effective integrative pain care in the military. Thanks for following!

Naval Medical Center San Diego

ACT1 Reaches Enrollment!

We are very excited to announce that on January 27, 2015, Project Manager Erin Cesario enrolled the site's 250th participant. This herculean feat would not have been possible without the dedication and commitment of every person at NMCS D who contributed to these efforts. Thanks to CPT Rosenthal for taking on the role of site Principal Investigator and overseeing the ACT1 project at NMCS D. The project would still be in the early stages of recruitment if it were not for the help of CDR Christopher Chisholm, Head of the North Island Branch Clinic, during the early stages of recruitment. CDR Chisholm found us a space to work and our

presence in the clinic on a daily basis proved to be key to the project's success. CDR Chisholm also assisted with study logistics by allowing the clinic's Independent Duty Corpsman (IDC), HM1 Douglas McLaughlin, to conduct initial study examinations. The IDC's, similar to a physician extender, can see patients and conduct physical exams. Thank you HM1 McLaughlin!



Dr. Goertz (PI), Dr. Ward (study chiropractor), and Erin Cesario (Site PM).

Site Project Managers Amy Engel and Erin Cesario were invaluable to study recruitment. They discovered that visiting busy clinic waiting rooms, handing out flyers, and stimulating small discussions about the study generated awareness of the ACT1 study and yielded the most study phone calls. In fact, the majority of enrollees were individuals who responded to

these flyers. While everyone's contribution to study logistics was significant, we could not have conducted the study without the support and care of Dr. David Ward, our study chiropractor at NMCS D. Dr. Ward was able to accommodate our chiropractic study participants even when his schedule was overflowing with patients. It is truly remarkable to be able to look back and recall the various intricacies of conducting a new research study in a military setting. We could not have navigated this process without our entire team! Congratulations to the staff at NMCS D and to the entire ACT1 team! One down – two more sites to go!



HM1 Douglas McLaughlin and PM Erin Cesario.

Spotlight:

Darla Freehardt, BS, LPN, CCRC ACT2 Project Manager, Ft Campbell

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Darla Freehardt BS, LPN, CCRP joined the Palmer Center for Chiropractic Research July 2014 as the Clinical Project Manager for the ACT2 study at Blanchfield Army Community Hospital Chiropractic Clinic, Fort Campbell, Kentucky. As a spouse of a retired Army helicopter pilot, Darla is patriotic to the core and thrilled with the opportunity to work with the military community.

Darla began her medical career as a LPN in Pennsylvania and then obtained a BS in Psychology at the University of Maryland. She has worked in many diverse areas with experiences in hemodialysis, in-patient hospital care, home health, long term care, First Steps parenting program, and running an Internal Medicine practice. Prior to working at Palmer, Darla worked as a research nurse at Vanderbilt University Medical Center. She helped to develop and coordinate investigator-initiated trials and managed sponsored trials and multi center trials in Oncology and Cardiovascular research. Darla has a special place in her heart for Cardio Oncology and the work being done to identify and prevent the cardio-toxic effects of chemotherapy. She has contributed to several publications concerning breast cancer and heart disease as well as chemotherapy related heart failure.



Darla loves to travel; she met her spouse in Colorado and they raised their family in 7 different states and in Europe. Today the majority of her travel time is spent in her "Nana-mobile" as she drives to Indiana and western TN to visit her 8 grandchildren.

The journey of research is one of challenge and discovery. Darla is immersed in ACT2 and enjoys working with the exceptional staff at Fort Campbell and Palmer in the pursuit of the effects of Chiropractic care on reaction and response times.

STUDY PROTOCOL

Open Access



Assessment of chiropractic treatment for active duty, U.S. military personnel with low back pain: study protocol for a randomized controlled trial

Christine M. Goertz^{1*}, Cynthia R. Long¹, Robert D. Vining¹, Katherine A. Pohlman⁴, Bridget Kane¹, Lance Corber¹, Joan Walter³ and Ian Coulter²

Abstract

Background: Low back pain is highly prevalent and one of the most common causes of disability in U.S. armed forces personnel. Currently, no single therapeutic method has been established as a gold standard treatment for this increasingly prevalent condition. One commonly used treatment, which has demonstrated consistent positive outcomes in terms of pain and function within a civilian population is spinal manipulative therapy provided by doctors of chiropractic. Chiropractic care, delivered within a multidisciplinary framework in military healthcare settings, has the potential to help improve clinical outcomes for military personnel with low back pain. However, its effectiveness in a military setting has not been well established. The primary objective of this study is to evaluate changes in pain and disability in active duty service members with low back pain who are allocated to receive usual medical care plus chiropractic care versus treatment with usual medical care alone.

Methods/design: This pragmatic comparative effectiveness trial will enroll 750 active duty service members with low back pain at three military treatment facilities within the United States (250 from each site) who will be allocated to receive usual medical care plus chiropractic care or usual medical care alone for 6 weeks. Primary outcomes will include the numerical rating scale for pain intensity and the Roland-Morris Disability Questionnaire at week 6. Patient reported outcomes of pain, disability, bothersomeness, and back pain function will be collected at 2, 4, 6, and 12 weeks from allocation.

Discussion: Because low back pain is one of the leading causes of disability among U.S. military personnel, it is important to find pragmatic and conservative treatments that will treat low back pain and preserve low back function so that military readiness is maintained. Thus, it is important to evaluate the effects of the addition of chiropractic care to usual medical care on low back pain and disability.

Trial registration: The trial discussed in this article was registered in ClinicalTrials.gov with the NCT01692275 Date of registration: 6 September 2012

Keywords: Low back pain, Chiropractic, Comparative effectiveness, Military, Spinal manipulative therapy, Pragmatic clinical trial

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Background

Low back pain (LBP) is well recognized as a prevalent and burdensome health problem in both military and civilian populations [1, 2]. It is also one of the most common reasons why members of the U.S. armed forces seek medical care [3, 4]. LBP, common in both deployed and non-deployed military personnel [5], is also among the most likely conditions to interrupt combat duty [2, 6]. In army personnel, LBP represents the highest 5-year risk factor for permanent disability [7].

Because of the combined costs associated with personal suffering, healthcare, and disability expenditures, and the resulting impaired capacity of personnel to conduct military operations, LBP has been characterized as “the silent military threat” [8, 9]. Development of a more effective, early treatment that prevents chronicity and reduces recurrence is likely to mitigate some of the deleterious effects of LBP on individuals and the military healthcare system.

In the United States, the chiropractic profession contains more than 70,000 actively licensed practitioners [10] who specialize in conservative treatment for musculoskeletal conditions with a special focus on spinal health [11]. At least 7.5 % of the U.S. population seeks chiropractic care each year, representing over 190 million patient visits annually [12, 13]. The care offered by doctors of chiropractic (DCs) is consistently rated highly by patients in studies assessing satisfaction [14–17]. Randomized controlled trials (RCTs) have demonstrated that chiropractic care and its signature treatment, spinal manipulation, is an effective conservative care option for patients with LBP [18–21]. Chiropractic care or spinal manipulation is also endorsed as an evidence-based, cost effective, conservative treatment option in the clinical practice guidelines for patients with acute, subacute, and chronic LBP [22–24].

DCs provide care in private practice and in multidisciplinary healthcare settings, including Veterans Affairs and military health treatment facilities [25, 26]. Currently, chiropractic care is available at 65 military health treatment facilities within the United States and internationally [27].

Goertz et al. conducted a pilot RCT comparing the effectiveness of chiropractic care plus standard medical care with standard medical care alone for active duty military personnel with acute LBP [28]. This study reported clinically and statistically significant greater improvement in pain and disability in the group including chiropractic care. However, the study was conducted at a single military installation with a relatively small sample ($n = 91$). This paper describes a larger scale, multisite, comparative effectiveness study at three geographically and demographically diverse U.S. military medical treatment facilities. Because chiropractic care for LBP in

the military is delivered within a multidisciplinary framework of care, rather than as a single system of care, the study is focused on the comparative effectiveness of chiropractic care plus usual medical care with usual medical care alone, in a pragmatic design.

Specific aims

The primary aim of this pragmatic comparative effectiveness study is to compare pain and disability of active duty military personnel with LBP who are treated with chiropractic care and usual medical care compared with those treated with usual medical care alone. We hypothesize that those allocated to receive both chiropractic care and usual medical care will show greater reduction in pain and disability than those receiving usual medical care alone.

Secondary aims explore the effects of adding chiropractic care to usual medical care on healthcare utilization, medication use, and quality of life.

Methods

Overview

The Assessment of Chiropractic Treatment for LBP in Active Duty Military Personnel (ACT 1) is a pragmatic, prospective, multisite, parallel group comparative effectiveness study with adaptive allocation [29–31]. ACT 1 is being conducted at Naval Medical Center San Diego, California (NMCS), Naval Hospital Pensacola, Florida (NHP), and Walter Reed National Military Medical Center (WRNMMC), Bethesda, Maryland. Two hundred and fifty participants with chronic, subacute, or acute non-surgical LBP are being enrolled at each site (total of 750).

Participants meeting eligibility criteria are allocated to one of two treatment groups: usual medical care (UMC) plus chiropractic care and UMC alone. The active care phase of the study is 6 weeks from group allocation. Patient-reported outcomes (PROs) are assessed at baseline (prior to randomization) and at 2, 4, 6, and 12 weeks from allocation with the primary endpoint at 6 weeks (Fig. 1).

The trial is managed through the Submission Tracking and Reporting System (STaRS), a comprehensive web application developed by the Palmer Center for Chiropractic Research (PCCR) with a dual purpose of collecting outcome assessments for study participants and serving as a secure electronic data capture and clinical trial management system for study personnel. The STaRS application is available for participants to access 24 hours a day throughout the duration of the trial. Study staff use STaRS for data entry, confirmation of participant eligibility, and study event reporting. STaRS also provides real-time reports for study management.

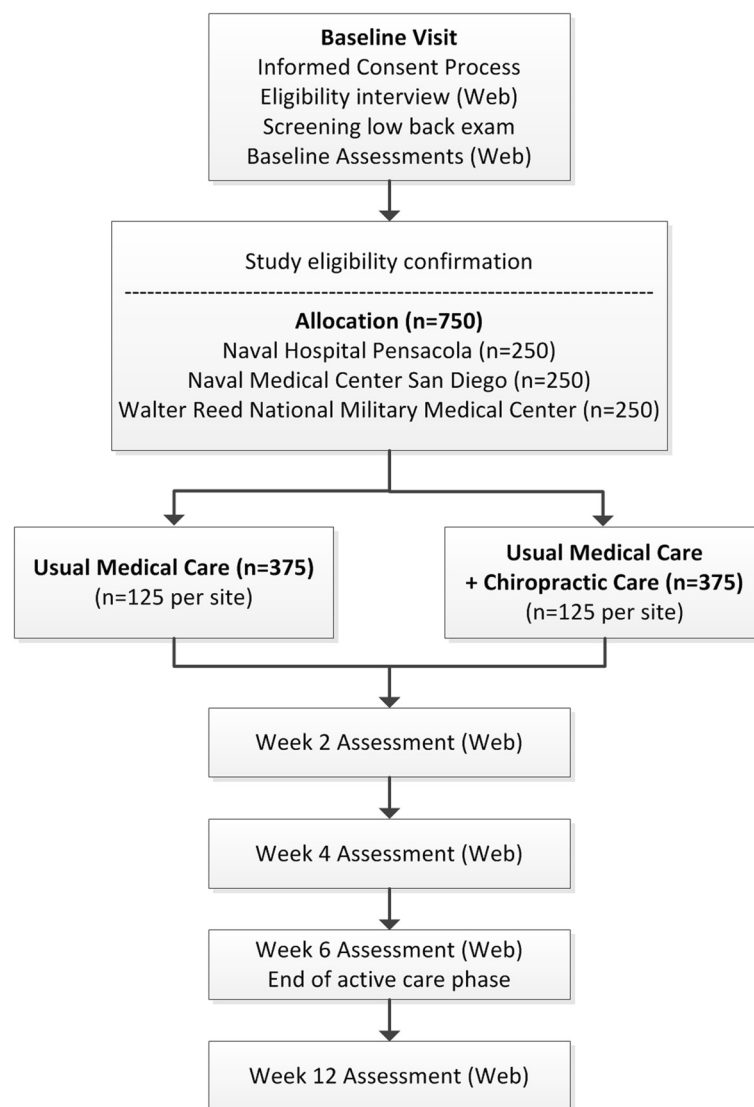


Fig. 1 ACT 1 study flow chart

Trial organization

The research team comprises individuals from three collaborating institutions: the RAND Corporation, the PCCR, and the Samueli Institute. The RAND Corporation manages the financial aspects, overall administration, and Institutional Review Board (IRB) issues of the grant award, as well as required deliverables to the Department of Defense (DoD) program officer. The Samueli Institute advises on processes for conducting research within the military and ensures compliance with the entities that regulate the conduct of human subjects' clinical research within the DoD to include the U.S. Army Medical Research and Material Command Human Research Protection Office and the Army's Clinical Investigation Regulatory Office.

Investigators from the PCCR are responsible for developing, implementing, and managing the trial at each of the three sites. Each trial site includes an active duty United States Naval or Army medical officer serving as principal investigator (PI), one or two DCs, and one PCCR site Project Manager (PM) locally stationed at the military treatment facility (MTF). The PM is responsible for day-to-day trial implementation at the respective MTF including the conduct of recruitment activities, participant tracking, and communication. A lead PM oversees trial operations at all three sites, acts as a liaison between the sites and trial co-investigators, and ensures protocol adherence and fidelity across sites. A central trial clinician reviews and monitors all adverse events.

Clinical sites

Participating clinical sites are MTFs that had an already established chiropractic program. DCs delivering patient care for trial participants are civilians who were contracted on a full-time basis by the DoD within the MTF 15–20 years prior to initiation of the study. Further information about each site is briefly described below.

Naval Hospital Pensacola (NHP)

NHP and its nearby associated naval branch clinics provide healthcare services to active duty military personnel in the Pensacola, Florida region. Chiropractic care is available to active duty personnel at the Naval Branch Health Clinic Naval Air Technical Training Command. Chiropractic services are part of the Sports Medicine and Rehabilitative Therapy Clinic and have been available since September 2003. A single DC provides care for trial participants at the Naval Air Technical Training Command branch clinic.

Walter Reed National Military Medical Center (WRNMMC)

WRNMMC, located in Bethesda, Maryland, is the largest U.S. military medical center, providing services to over 1 million beneficiaries per year [32]. The chiropractic clinic at WRNMMC is located within the Department of Orthopedics and Rehabilitation and provides care to active duty service members with musculoskeletal conditions including service members with combat-related injuries. WRNMMC established chiropractic services in 1998. Two DCs provide care to trial participants at this site.

Naval Medical Center San Diego (NMCSD)

NMCSD is a large military healthcare system located in coastal southern California serving U.S. military personnel stationed at several surrounding military bases. NMCSD provides chiropractic care for active duty personnel as a special service of the Physical Therapy Department. Chiropractic services have been available at NMCSD since 2003. A single DC provides care to trial participants within the branch clinic at North Island, on Naval Base Coronado.

Regulatory approvals

The trial protocol received ethics approvals from the following five Institutional Review Boards: Palmer College of Chiropractic (#2010G137), RAND Corporation (#2010-0782), NMCSD (#NMCSD.2012.0022, IRB of record: Naval Medical Center San Diego, California), NHP (#NHPC.2012.0002, IRB of record: Naval Medical Center Portsmouth, Virginia), and WRNMMC (#369462, IRB of record: Walter Reed National Military Medical Center Bethesda, Maryland). The study protocol was also approved by the U.S. Army Medical Research and

Material Command Human Research Protection Office and the Clinical Investigation Regulatory Office. All study investigators have completed training in the protection of human subjects as required by the respective collaborating institutions.

Prior to study commencement, the collaborating investigative institutions also established a Cooperative Research and Development Agreement (CRADA) with each of the three participating MTFs. Final approval of the CRADA occurred in June 2012 and was renewed in April 2015. A data sharing agreement and systems security verification, under the auspices of TRICARE Management Activity, were established between the MTFs and the ACT 1 collaborating institutions (RAND Corporation and PCCR).

Recruitment procedures

Active duty participants aged 18–50 years (inclusive) reporting acute, subacute, or chronic LBP who are able to provide voluntary written informed consent are eligible for this trial. Participants are ineligible if they have knowledge of a pending absence through the 6-week active treatment phase. Such absences could include a planned leave, deployment, temporary duty assignment, or permanent change of station. Participants unwilling to be allocated to either intervention arm are also ineligible. A detailed description of the inclusion/exclusion criteria is summarized in Table 1.

Patients with LBP enter the military healthcare delivery system through multiple pathways. Thus, the investigative team identified department clinics likely to diagnose or manage patients with LBP within each MTF and requested their assistance with recruitment efforts. Command support (permission) was obtained prior to study recruitment, from each respective department, to post IRB-approved study advertisements and recruit study participants. At WRNMMC, command support was obtained from the internal medicine, physical therapy, neurosurgery, and physical medicine and rehabilitation departments. At NHP, command support was received from the Department of Family Medicine, the Department of Orthopedics, and three branch clinics: Naval Air Station Pensacola branch clinic, Naval Air Technical Training Center, and Corry Station. At NMCSD, command support was obtained from the Department of Orthopedics, Naval Branch Health Clinics Miramar, Naval Base San Diego and Coronado, and the NMCSD Military Health Center.

Participant screening

Trial participants are recruited via either self-referral or referral from a healthcare provider. IRB-approved recruitment materials are placed in patient waiting rooms and other approved areas within each MTF. In

Table 1 Eligibility criteria

Inclusion criteria	Rationale
Age ≥ 18 and ≤ 50	Age range of most active duty U.S. military personnel
Acute, subacute, or chronic low back pain	Low back pain commonly treated by primary care and chiropractic providers
Ability to provide voluntary written informed consent	Able to comprehend study details; able to make decisions without limitations or impairment
Active duty status at one of the three participating military treatment facilities	Chiropractic care available only to active duty personnel at U.S. military treatment facilities
Exclusion criteria	
LBP from a non-musculoskeletal source (pain from a visceral condition[s])	Care outside study scope needed; potential to confound health outcomes
Co-morbid pathology that may directly impact spinal pain	Care outside study scope needed; potential to confound health outcomes
Recent spinal fracture (within the last 8 weeks)	May influence ability to measure pain-related health outcomes; safety concern
Recent spinal surgery (within the last 12 weeks)	Potential to confound health outcomes due to natural history or from potential complications
Spinal or paraspinal tumor(s)	Care outside study scope needed
Spinal or paraspinal infection(s)	Care outside study scope needed
Spinal inflammatory arthropathy (rheumatoid arthritis, enteropathic spondyloarthropathy)	Potential to confound health outcomes
Contraindication(s) for spinal manipulation of the lumbar spine and pelvis (unstable spinal segments, cauda equina syndrome)	Care outside study scope needed
Pregnancy or plans to become pregnant within active treatment period	Potential to confound health outcomes
Diminished/altered mental capacity	May prohibit informed consent or compromise safety or compliance with study procedures
Use of spinal manipulative care for any reason within the past month	Prevent carryover effects from recent chiropractic care
Significant/severe osteoporosis	Potential to confound health outcomes; care outside study scope may be needed
Unwilling to provide phone and electronic contact information	Compromises ability to adhere to study protocol
Unable to confirm availability during the active treatment period due to known deployment, orders for a distant duty assignment, or other absence	Compromises ability to adhere to study protocol
Does not agree to be enrolled regardless of group assignment	Compromises ability to adhere to study protocol
Post-traumatic stress disorder diagnosis	Potential to confound health outcomes

either recruitment method, participants must meet all clinically related eligibility criteria determined at exam and general criteria confirmed by the PM during the baseline interview. Individuals who do not meet all study eligibility criteria are excluded. Responses to the baseline eligibility interview and eligibility criteria obtained from the examining clinician are entered and electronically stored in STaRS.

Interested participants meet with the PM, who initiates the informed consent process in a private setting. The PM reviews the informed consent document, study flow chart, and specific visit activities with the participant. Individuals have the opportunity to read the informed consent document and ask questions about participation. Those wishing to participate sign the written informed consent document. Following the consent process, a baseline interview is conducted to obtain basic demographic information to screen for non-clinically determined eligibility criteria. After the baseline interview is submitted, STaRS assigns each participant a unique study number. Eligible participants are also assigned a temporary password to complete online assessments.

Initially eligible participants undergo a clinical evaluation of their low back by the healthcare provider who manages the condition (that is, a neurologist, physiatrist, or internist), a primary care provider, or an Independent Duty Corpsman. During the evaluation, the provider renders a professional opinion regarding clinically determined eligibility criteria such as whether or not the LBP is related to the musculoskeletal system, the need for additional diagnostic testing, and the existence of conditions posing a contraindication to spinal manipulation (such as acute spinal fracture or cauda equina syndrome). Eligibility information obtained from the clinical evaluation is documented by the provider on a paper form and provided to the PM, who enters the information into STaRS to determine eligibility. Alternatively, the LBP evaluation may be performed prior to an individual's meeting with a PM as part of the patient's standard of care.

Baseline assessment

Prior to allocation, all eligible participants complete a baseline assessment consisting of demographic information, expectations of care, and a series of PRO questionnaires that measure current pain intensity, the impact of the current LBP on functional status and quality of life, and self-reported medication use for LBP. The baseline assessment is conducted on dedicated study computers.

Participants access the baseline assessment questions by logging into STaRS using their email address as their username and the temporary password assigned by STaRS. STaRS requires all participants to change their

password upon initial login, which is used to complete future online assessments.

Allocation

Participants remaining eligible after completing: 1) the consent process, 2) baseline interview, 3) clinical evaluation, and 4) baseline assessment are allocated to a treatment group. Allocation occurs within STaRS via an adaptive computer-generated minimization algorithm programmed to balance group assignment on the factors of sex (M, F), age (18 to <30, 30 to 50), LBP duration (<1 month, 1–3 months, >3 months), and baseline Numeric Rating Scale (0–5, 6–10) measurement (worse pain in past 24 hours). Participants are allocated to one of two groups: 1) UMC or 2) UMC plus chiropractic care. PMs, participants, and all study personnel are unable to influence the group assignment, and future allocations are concealed.

Study interventions

Usual medical care

In this pragmatic trial, UMC includes any care recommended or prescribed by a non-chiropractic military healthcare provider for the purpose of managing/treating LBP. UMC may include education about a condition, self-management advice, and pharmacologic pain management. Physical therapy and referral to a pain clinic may also be prescribed as a component of UMC. UMC providers report prescription medication class, referrals, and/or self-care recommendations. Participants allocated to the UMC group are asked by study personnel to avoid receiving chiropractic care for 6 weeks unless otherwise directed by their healthcare provider.

Usual medical care plus chiropractic care

Participants allocated to this group continue with prescribed UMC as described above and also receive up to 12 chiropractic visits during the 6-week active care period. Chiropractic treatment frequency, duration, and procedures are determined individually based on the participant's condition, response to care, scheduling availability, and other factors pertinent to the case.

The primary therapeutic procedures delivered by DCs for LBP are thrust or non-thrust spinal manipulation in the low back and adjacent regions [33]. Treatment decisions regarding manipulation type, location, and direction are based on the LBP diagnosis and concurrent diagnoses. Other factors that inform treatment decisions include patient preference, prior response to care (if known), the presence or absence of local tenderness, paraspinal muscle hypertonicity, spinal joint hypomobility, positions of relief and/or provocation, and imaging findings (for example, spinal curvatures, congenital anomalies). Other therapeutic procedures delivered by

the DC may include rehabilitative exercise, manual manipulation of upper and lower extremity joints and other spinal regions, interferential current therapy, ultrasound therapy, cryotherapy, heat therapy, and manual myofascial therapies.

Outcome measures

PROs are collected at 2, 4, 6, and 12 weeks from allocation (Table 2). The primary endpoint is at 6 weeks and the secondary endpoint is at 12 weeks.

Primary outcome measures

The co-primary outcome measures are the Numeric Rating Scale (NRS) for average pain intensity during the past week and the Roland-Morris Disability Questionnaire (RMDQ). The NRS has excellent metric properties, is commonly used in RCTs studying LBP [34, 35], and has been demonstrated as a valid and reliable measure [36]. Participants are asked to rate their average level of LBP during the past week on an ordinal 11-box scale (0 = no LBP; 10 = worst possible LBP). The RMDQ is a reliable and valid LBP-related disability assessment instrument commonly used in clinical research [37, 38]. Containing 24 questions, it is considered sensitive to disability-related changes in patients with LBP [39–41].

Secondary outcome measures

Secondary outcome measures include the NRS of the worst LBP intensity during the past 24 hours, the Back Pain Functional Scale, bothersomeness of symptoms, Patient Reported Outcomes Measurement Information System (PROMIS)-29 variables, medication use, and healthcare utilization.

The Back Pain Functional Scale is a 12-question survey assessing functional status. Each question is answered using a 6-point scale (0 = unable to perform activity and 5 = no difficulty), resulting in scores ranging from 0 to 60 where the higher scores are equal to better functional status [41]. Bothersomeness of symptoms associated with LBP is measured by asking the patient to rate the bothersomeness of LBP during the past week, measured on a 1 to 5 scale (1 = not at all bothersome and 5 = extremely bothersome) [42, 43].

The PROMIS-29 is a set of questions that measure depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and satisfaction in social roles [44]. The PROMIS-29 instrument contains 29 questions; 4 items from each primary domain plus a single pain intensity rating. This outcome instrument is administered at baseline and at weeks 6 and 12 [45–47]. Perceived global LBP improvement is assessed using a question adapted from a study investigating the effect of expectations on patients with LBP [48]. Participants are asked to rate their perceived LBP improvement on a 7-point

Table 2 Data collection schedule

Outcome measure	Assessment time point				
	Baseline (+/- 3 days)	Week 2 (+/- 3 days)	Week 4 (+/- 3 days)	Week 6 (+/- 7 days)	Month 3 (+/- 7 days)
Demographics	X				
Numeric Rating Scale for pain intensity	X	X	X	X	X
Roland-Morris Disability Questionnaire	X	X	X	X	X
Back Pain Functional Scale	X	X	X	X	X
Bothersomeness of symptoms	X	X	X	X	X
PROMIS-29	X			X	X
Global improvement measure		X	X	X	
Healthcare utilization and medication use	X	X	X	X	X

scale (0 = completely gone to 6 = much worse) at weeks 2, 4, and 6.

Participants are asked to indicate the type of health-care providers who have treated their current episode of LBP and indicate how often they took pain relieving medication (both prescription and/or over-the-counter) during the past week. Choices are 0 days, 1–2 days, 3–4 days, 5–6 days, or 7 days.

Data collection and management

Data collection

This trial uses paper data collection forms, electronic data capture through STaRS, and data abstracted from the participant's electronic medical record.

The STaRS home page provides all users the same login that, upon validation, directs them to the appropriate section of the application according to login credentials. PMs enter baseline data, including the exam screening form, into customized logic-based electronic forms that provide validation checks to ensure participant eligibility prior to allocation.

Electronic data capture is used to collect PROs at 2, 4, 6, and 12 weeks from allocation (Table 2). Participants are directed to the outcome assessments. Many features were implemented to provide participants with a self-managed experience while collecting study data at respective intervals over the 12-week study period. Participants may complete the assessment from any device capable of supporting an internet connection and web browser. If a participant forgets or would like to change their password, a link is provided that sends them a temporary password to their email address. At the time of the next login with the temporary password, STaRS will prompt the user to define a new password for future use. Within the STaRS application, participants may also update their contact information at any time.

Outcome measures are collected in a linear manner across all time points. Primary outcome measures are required variables and must be completed as a whole,

whereas secondary outcome measures may be skipped by the participant. Programmatic review prompts the users after each assessment for any missing variables and asks them to review and complete them before moving onto the next measure. A visual progress bar is provided at the bottom of the page to inform users of overall percent completed.

STaRS sends an email at pre-programmed intervals to remind participants to complete the online assessments. Outcome assessments are available to complete for a window of 6 days for weeks 2 and 4, and 14 days for weeks 6 and 12. Automated emails are programmed to be sent the day the window opens for the respective time point. An additional email will be sent by STaRS if the participant has not completed the assessment by the actual due date. To augment STaRS automated emails, the PM personally contacts each participant by text message, email, or telephone during the window for each assessment. Participants can inform the site PM if they are unable to access STaRS or complete the assessment for various reasons. All contact with participants is documented by the site PM within STaRS.

If a participant does not complete an assessment within the designated window (Table 2), a PM will attempt to collect the primary outcome measures using a computer-assisted telephone interview. A PM will attempt to collect the week 2 and 4 assessments within 3 days, and the week 6 and week 12 assessments within 7 days of the assessment expiration dates.

For participants in the group that also receive chiropractic care, the DC completes a paper data collection form for each study visit that details the type of spinal manipulation performed including the anatomical region, and other therapeutic procedures used with the corresponding diagnosis (ICD-9) and procedural (CPT) codes. The PM carefully tracks the number of study visits per patient that occur in the 6-week period and manages documentation for study visits. During the active care phase of the trial, PMs enter data from the

study treatment forms into customized electronic forms. Data entry errors and change requests are submitted through a module within STaRS that provides an audit trail of who altered specific data elements and when they were altered.

To document UMC received for LBP and to explore healthcare utilization for LBP, information from healthcare provider visits for LBP that occur during the 12-week study period is abstracted from the participant's electronic medical record. Data abstracted includes reason for visit, provider type(s), diagnoses, procedures conducted, and prescribed medications.

The dual purpose of the STaRS application allows for trial management tools. STaRS is programmed to produce reports to allow study staff to monitor participants through all phases of the study. Specific reports available to study staff include a screening report, which provides the number of participants screened as well as the reasons for exclusion, and a tracking report, which allows the user to view individual participant information such as date of important study visits, allocation, and the status of each outcome assessment. PMs can monitor trends with respect to missed outcomes. PMs also enter adverse events and protocol deviations into STaRS, which is programmed to provide emails to specific study investigators as well as research staff. This feature allows for central investigator oversight, which is especially important given the multiple site locations.

Data management and security

The STaRS application is 21 CFR part 11 compliant and integrated with a Central Participant Database and a Project/Users Permissions System to control project personnel access to web modules. PCCR registered the backtoaction.org site secured with Certified Secure Socket Layers (SSL) 128-bit encryption, hosted (IIS V6.0), and maintained by Palmer College of Chiropractic Information Services department. The web programmer developed the application in ASP.NET v4.0 in C# and Structured Query Language (SQL) using Microsoft Visual Studio 2010. All data are stored on an internal Microsoft SQL Server 2014. Only select study personnel have access to data via Microsoft SQL Server Management Studio 2014. All PCCR servers reside behind a stateful firewall with permissions determined by Active Directory.

The data core manager will perform a soft lock of the database (Microsoft SQL Server) and write programs in SAS System for Windows (Release 9.3) using SAS ACCESS in order to perform data cleaning procedures of range and consistency checks. Once all data edits are recorded and performed, the data core manager will coordinate with the programmer to perform a final lock removing all access to the database to ensure that no

further changes to the data can be made. Final analyzable dataset(s) and the data dictionary will be created from the final locked database.

Statistical methods

The data will be analyzed using an intention-to-treat approach in which participants will be analyzed according to their original treatment allocation. All observed data will be used in the analyses. Data analyses will be performed using SAS/STAT (Release 9.3) (SAS Institute Inc., Cary, NC).

Primary data analysis and sample size

The co-primary outcome variables (RMDQ and the NRS for LBP intensity) will be modeled with linear mixed effects regression over baseline and weeks 2, 4, 6, and 12. We will assume group means are the same at baseline, and include terms in the model for time (as a categorical variable), site, site-by-group, time-by-group, and site-by-time-by-group interactions, and the variables in the minimization algorithm. The covariance structure will be chosen by comparing the maximized log-likelihoods and the Bayesian information criteria for several covariance pattern models against the unstructured covariance. Diagnostics of the conditional predicted values and conditional residuals will be used to assess the assumption of normality and fit for each model.

The main results will be based on the final models for the co-primary outcome variables at the end of the active care phase (6 weeks). If the site-by-time-by-group interaction is significant at the 0.05 level, results will be reported by site. A p -value ≤ 0.025 will be used to determine if between group differences are statistically significant.

Because the patient populations at the three sites are different, we calculated a sample size of 106 per group for each site to provide adequate power to detect clinically important differences between groups at each site. The sample size estimates were obtained using a significance level of 0.025 to account for 2 primary outcome variables. The estimates of standard deviation (5.4 for the RMDQ and 2.0 for the NRS for average pain intensity over the past week) come from our pilot study [28]. This provides 80 % power to detect a 2.4 between group difference on the RMDQ and 92 % power to detect a 1.2 difference on the NRS. In the pilot study, there was 13 % and 11 % missing data in the UMC plus chiropractic care group at the week 2 and 4 assessment periods, respectively, but 39 % and 37 % in the UMC alone group. We increased the sample size to 125 per group at each site, assuming we would be able to keep our loss to follow-up at the week 6 endpoint at or below 15 %, due to the implementation of intensive follow-up procedures.

Secondary evaluations of the final models will compare group differences at week 12 to ascertain if the pattern seen at week 6 remains after the active care phase. Group differences will also be reported for week 2 and 4 to compare to the results of the pilot study. Secondary analyses will compare the percentage of patients with clinically meaningful improvement of at least 30 % relative to baseline at the week 6 endpoint on the co-primary outcome variables [49]. General estimating equations with a working covariance matrix will be used to estimate the differences in proportions between groups at each time point, with terms in the model for time (as a categorical variable), group, site, site-by-group, and time-by-group interactions, and the minimization variables. Consistent with the recent NIH Task Force recommendations [50] for a minimum dataset for chronic LBP, we will conduct an exploratory analysis over a range of improvement levels.

Two approaches to sensitivity analyses will be used to examine the possible effects of missing data on the results obtained from using all observed data for the co-primary outcome variables. Prior to conducting the sensitivity analyses, baseline variables that are predictive of missing outcomes will be identified with logistic regression models. The first approach will be under the assumption that data are missing at random and will use the Markov chain Monte Carlo method to impute missing values for each of the primary outcome variables based on the final mixed model covariates, the observed outcome variable at baseline and weeks 2, 3, 6, and 12, and the baseline variables predictive of missing data. The resulting datasets for each of 20 imputations will be analyzed with the linear mixed effects models that are fit with all observed data and the results will be combined. The second approach will be under the assumption that data are missing not at random. It will follow the pattern mixture approach described by Carpenter and Kenward [51] by first imputing missing values as described above for the missing at random approach and then for each participant in each treatment group for each imputation. The imputed observation will be decreased by different amounts representing different patterns of responses. The resulting datasets for each pattern will be analyzed and the estimates combined as described above. If results differ between the analysis of the observed data and that based on imputed full datasets under different missingness assumptions, multiple sets of results will be reported.

Secondary data analysis

The continuous secondary outcome variables will be analyzed with linear mixed effects regression as described above, but p -values ≤ 0.05 will be used to determine if between group differences are significant. The ordinal

categorical variable representing the number of days that participants reported using medications for LBP over the past week will be analyzed over baseline and weeks 2, 3, 6, and 12 with a proportional odds model. Generalized estimating equations using all observed data with a working covariance structure will be used to fit the model.

Protocol fidelity and quality assurance

Protocol fidelity

We are carefully tracking intervention and protocol adherence. Using the Armed Forces Health Longitudinal Technology Application, or patient electronic medical record, we are tracking all care received for LBP during the 3-month study duration. This includes both UMC visits, as well as chiropractic visits. Instances where participants who are allocated to receive UMC only but do receive chiropractic care during the 6 weeks of active care, as well as participants who are allocated to receive chiropractic care but do not will be classified as unanticipated events and documented in STaRS.

Internal quality assurance process

The lead PM conducts an internal quality assurance audit at each site on a quarterly basis for the purpose of maintaining data integrity, ensuring study protocol fidelity, and standardizing study operating procedures across all three sites. During the audit, the lead PM reviews regulatory documentation and informed consent documents. Electronic data are verified by comparing the paper source documents to the data entered in STaRS. Any errors discovered during the quarterly audits are documented, corrected by the site PM, and reported to the site PI, collaborating investigators, and appropriate regulatory bodies, if applicable.

During these site visits, the lead PM also meets with site PMs, PIs, DCs, and/or clinic command to facilitate communication about overall study status and discuss study timelines, as well as address site concerns or barriers interfering with study conduct. Information gathered during the site visits is conveyed to study co-investigators. In addition, the PCCR PI has a monthly conference call with study personnel at each clinical site to monitor study progress.

Study event monitoring and reporting

Adverse events

We have defined an adverse event as any untoward medical occurrence presenting during the active study period (6 weeks) that may or may not have a causal relationship with study procedures [52]. A serious adverse event is defined as an event resulting in a condition considered as life-threatening, a congenital anomaly or birth defect, in-patient hospitalization, disability, permanent damage,

death, or an occurrence that requires intervention to prevent death or significant disability. Adverse event information is being collected via 1) direct report to PM and/or 2) self-report during online assessments.

Participants are encouraged to contact the PM if there are any unplanned hospitalizations/procedures or for any other health-related events whether or not the participant considers them related to the study. When participants report adverse event information directly to a PM, the PM enters the adverse event information into STaRS, which generates an auto-notification message to the lead PM, designated trial clinician, and PI. Participants are also being prompted to answer questions about adverse events during the week 2, 4, and 6 online assessments. The lead PM and the central trial clinician review adverse event information received from online assessments on a weekly basis. The site PM will be asked to follow up with any participant who reports an adverse event to ascertain whether or not the event resulted in hospitalization or appeared to be an unexpected reaction or side effect from the study intervention. The lead PM facilitates the submission of any reportable adverse events to the respective IRBs, site medical monitor, and/or the Data and Safety Monitoring Committee (DSMC). Events not meeting the criteria for immediate reporting are submitted to the IRBs at the time of continuing review.

Each military study site has a medical monitor assigned to the study. The medical monitor is responsible for reviewing adverse events, as well as unanticipated events that may increase the risk to trial participants, any related serious adverse event, or related participant death. Events meeting these criteria are also submitted to the DSMC and the U.S. Army Medical Research and Materiel Command, Human Research Protection Office.

Study limitations

Given the nature of this trial, it is not possible to blind either the treating clinicians or participants to treatment assignment. This is an important limitation to this study. However, all participants, clinicians, and study personnel are blinded to next treatment assignment, and all key study personnel and data analysts are blinded to group assignment. One could also argue that the pragmatic nature of this comparative effectiveness trial is a limitation given the resulting lack of homogeneity in treatment approach both within and across groups. The advantage of this approach is that the results are more applicable to “real world practice”; the disadvantage is that one must sacrifice the homogeneity inherent within an RCT.

We believe that a comparative effectiveness design is the best way to answer questions that will be meaningful to policy makers as they consider the appropriate role

for chiropractic care in active duty military populations. Further, our experience in the conduct of clinical trials in MTFs has shown us that this type of trial is feasible to conduct in busy clinical practice settings. We will address this limitation by collecting detailed data on the treatments rendered to participants, for both analysis and reporting purposes.

Discussion

Since LBP is one of the leading causes of disability among U.S. military personnel, it is important to find pragmatic and conservative treatments that will not only treat LBP, but could ultimately preserve low back function so that military readiness is maintained. In this trial, we will evaluate the effects of the addition of chiropractic care to UMC on LBP pain and disability. A pilot study compared chiropractic care plus standard medical care with standard medical care alone for active duty military personnel with acute LBP [28]. Improvements in pain and disability were significantly greater in the chiropractic care group. This comparative effectiveness study will evaluate whether these prior findings can be reproduced in a larger sample, across multiple sites, and with varied populations including individuals with sub-acute and chronic LBP. The information gleaned from this large, multisite trial may assist military healthcare providers to more effectively treat a highly prevalent condition responsible for high healthcare costs, debilitating effects on patients, and military readiness.

Trial status

Recruitment began in September of 2012. As of November 20, 2015, 750/750 participants were allocated and recruitment was closed.

Abbreviations

ACT: Assessment of Chiropractic Treatment; CRADA: Cooperative Research and Development Agreement; DC: Doctor of Chiropractic; DoD: Department of Defense; DSMC: Data and Safety Monitoring Committee; IRB: Institutional Review Board; LBP: low back pain; MTF: Military Treatment Facility; NHP: Naval Hospital Pensacola; NMCS: Naval Medical Center San Diego; NRS: Numeric Rating Scale; PCCR: Palmer Center for Chiropractic Research; PI: Principal Investigator; PM: Project Manager; PRO: patient-reported outcome; PROMIS: Patient Reported Outcomes Measurement Information System; RCT: randomized controlled trial; RMDQ: Roland-Morris Disability Questionnaire; SQL: Structured Query Language; SSL: Secure Socket Layers; STaRS: Submission Tracking and Reporting System; UMC: usual medical care; WRNMMC: Walter Reed National Military Medical Center.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CG, IC, and JW conceived the trial. CG, CL, KP, RV, LC, and BK participated in refining the design of the trial. CL, LC, and CG participated in plans for data analysis. RV, BK, CL, IC, JW, LC, CG, and KP drafted the manuscript. All authors read and approved the final manuscript.

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The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of Defense or the U.S. Government.

Acknowledgements

This trial was funded by Department of Defense Office of Congressionally Directed Medical Research Programs, Defense Health Program Chiropractic Clinical Trial Award (W81XWH-11-2-0107).

The identification of specific products or scientific instrumentation does not constitute endorsement or implied endorsement on the part of the author, the DoD, or any component agency.

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Received: 15 October 2015 Accepted: 21 January 2016

Published online: 09 February 2016

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