

AWARD NUMBER: W81XWH-14-1-0477

TITLE: Gulf War Illness Inflammation Reduction Trial

PRINCIPAL INVESTIGATOR: Ronald R. Bach, PhD

CONTRACTING ORGANIZATION: Minneapolis VA Medical Center
One Veterans Drive
Minneapolis, MN 55417

REPORT DATE: October 2022

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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

1. REPORT DATE OCTOBER 2022			2. REPORT TYPE Annual		3. DATES COVERED 29SEPT2021 - 28SEPT2022	
4. TITLE AND SUBTITLE Gulf War Illness Inflammation Reduction Trial					5a. CONTRACT NUMBER W81XWH-14-1-0477	
					5b. GRANT NUMBER GW130025	
					5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Ronald R Bach, PhD E-Mail: Ronald.Bach@va.gov					5d. PROJECT NUMBER	
					5e. TASK NUMBER	
					5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Minneapolis VA Medical Center Research Service (151) One Veterans Drive Minneapolis, MN 55417					8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development 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 Background: Gulf War illness (GWI) is a deployment-related chronic multisymptom illness impacting the health-related quality of life (HRQOL) of many U.S. Military Veterans of the 1990-91 Gulf War. A proinflammatory blood biomarker fingerprint was discovered in our initial study of GWI. This led to the hypothesis that chronic inflammation is a component of GWI pathophysiology. Objectives: The GWI inflammation hypothesis was tested in this Phase 2 randomized controlled trial by measuring the effects of prednisone, an anti-inflammatory drug, on the HRQOL of Veterans with GWI. ClinicalTrials.gov, Identifier: NCT02506192. Trial design and methods: Gulf War Veterans meeting the Kansas case definition for GWI were randomized to receive either prednisone or placebo. The Veterans RAND 36-Item Health Survey was used to assess HRQOL. The primary outcome was a change from baseline in the physical component summary score (PCS). PCS is a measure of HRQOL with respect to physical functioning and symptoms. Results: The 8 week prednisone treatment produced a statistically significant PCS increase from baseline. Conclusions: The improvement in physical HRQOL following prednisone-treatment supports the hypothesis that chronic inflammation of is a component of GWI pathophysiology. A Phase 3 RCT is required to determine the efficacy of prednisone as a treatment for GWI.						
15. SUBJECT TERMS NONE LISTED						
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER	19a. NAME OF RESPONSIBLE PERSON USAMRDC	
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER (include area code)	
Unclassified	Unclassified	Unclassified	Unclassified	8		

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

	<u>Page</u>
Introduction.....	4
Keywords.....	4
Accomplishments.....	5
Progress as of 30-09-2020.....	6
Impact.....	6-7
Changes/Problems.....	7
Products.....	7
Participants & Other Collaborating Organizations.....	7
Special Reporting Requirements.....	8
Appendices.....	8
References.....	8

Introduction

At least 25% of the 697,000 U.S. military personnel who served in the 1990-91 Gulf War, Operations Desert Shield and Desert Storm, meet the case definition for Gulf War illness (GWI). GWI is a deployment-related chronic multisymptom illness. Symptoms of the syndrome include musculoskeletal pain, chronic fatigue, cognitive impairment, gastrointestinal problems, skin rashes, and respiratory difficulties [1-3].

The mission of GWI research is to improve the health-related quality of life (HRQOL) of Veterans with GWI. To fulfill this mission, we employed a bench-to-bedside translational research strategy. The ultimate objective of this work is to discover an evidence-based treatment for GWI that will alleviate symptoms, stop progression, and mitigate the long-term health effects of the disorder.

The first step in the translational process was an observational study of blood from Gulf War Veterans who met a GWI case definition (GWI+) and those who did not (GWI-) [4]. Peripheral blood counts and plasma proteomic assays measured >100 parameters for each subject. Comparison of the GWI+ and GWI- data identified 12 biomarkers of GWI [5-7]. Evaluation of these biomarker biological functions revealed a proinflammatory biomarker fingerprint. Thus, chronic inflammation was identified as a therapeutic target.

The next step in the translational process was the clinical trial of an intervention aimed at the therapeutic target. The Gulf War Illness Inflammation Reduction Trial (GWIIRT), a randomized controlled trial (RCT), is a proof of concept study. Prednisone was selected as the evidence-based intervention for GWIIRT, because of its well-established efficacy as a treatment for inflammatory diseases. The hypothesis that chronic inflammation is a component of GWI pathophysiology was tested in this RCT by measuring the effects of prednisone on clinically relevant endpoints.

Key Words

Gulf War Illness, Chronic Inflammation, Prednisone, Chronotherapy, Evidence-Based Treatment, Randomized Controlled Trial, Pain, Fatigue, Cognitive Dysfunction, Blood Biomarkers

Accomplishments

1st Quarter

- Started the analysis GWIIRT primary and secondary outcomes VR-36 data.. The primary outcome is a change from baseline in the physical component summary score (PCS). PCS is a measure of HRQOL with respect to physical functioning and symptoms. The secondary outcome is a change from baseline in the mental component summary score (MCS). MCS is a measure of HRQOL with respect to mental functioning and symptoms.

2nd Quarter

- Finished the VR-36 HRQOL data analysis. The primary outcome data demonstrated that the treatment with prednisone produced a statistically significant increase in physical HRQOL for Veterans with Gulf War Illness.
- Started the first draft of the manuscript describing the HRQOL data.

3d Quarter

- Finished the manuscript of the GWIIRT HRQOL data entitled :
Gulf war illness inflammation reduction trial: a randomized controlled trial of low-dose prednisone chronotherapy, effects on health-related quality of life
- Analysis of the blood biomarker data, the objective study data that is the key to understanding the subjective VR-36 results, was initiated.

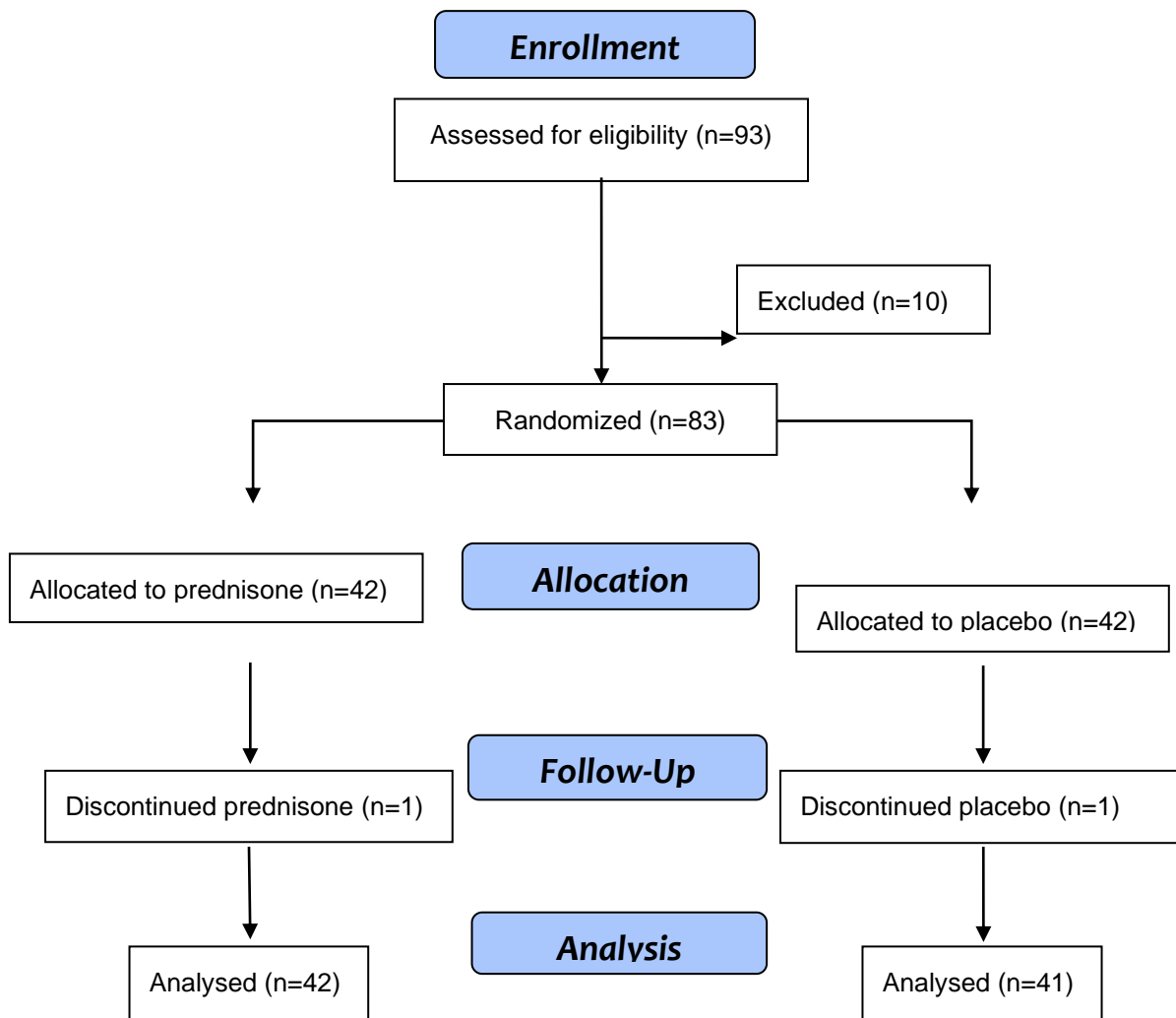
4th Quarter

- The manuscript describing the HRQOL data analysis was submitted for peer review and publication. Analysis of the blood biomarker data continued.
- A no cost extension for GWIIRT FY23 was requested on 17-08-2022 and approved on 14-09-2022.

Progress 30-09-2022

We have reached our accrual goal for Gulf War Illness Inflammation Reduction Trial (GW 130025). The study is now closed to further enrollment. The last subject had his last study visit on 09-04-2020. The active phase of the study has been completed, and we are now in the data analysis and reporting phase of the study.

	# Subjects
Telephone Screen (Kansas Case-Definition)	198
Consented/Enrolled	93
Randomized (Passed Safety Screen)	83
Withdrawn	2



IMPACT

After 8 weeks of low-dose prednisone chronotherapy, there was a significant improvement in the physical HRQOL of GWI+ Veterans with a baseline PCS <40. This result supports the hypothesis that chronic inflammation is a component of GWI pathophysiology. A Phase 3 RCT, measuring the

efficacy and safety of prednisone versus placebo, is required for FDA approval of low-dose prednisone chronotherapy as a treatment for GWI. According to the power analysis, if baseline PCS <40 is added to the inclusion criteria, then each arm of the Phase 3 RCT will require at least 231 subjects. Also, the effects of a longer treatment are unknown. Therefore, the treatment phase of the Phase 3 RCT should be extended beyond 8 weeks. The success of this Phase 2 RCT opens the path to FDA approval of an evidence-based treatment for GWI. Also, it provides the basis for objective diagnosis of GWI using blood biomarkers of inflammation. The GWIIRT results demonstrate that translational research is a path to discoveries that can improve the health and well-being of Gulf War Veterans. Fulfilling that promise will require the funding of the Phase 3 RCT.

Changes/Problems

A no cost extension was and approved with the effective date of 14-September-2022. The purpose of this modification is to extend the period of performance by 12 months, at no additional cost to the Government. Quarterly reports and submission of SF-425s shall continue during the no-cost extension period. All terms and conditions of the award remain unchanged.

Products

None

Participants & Other Collaborating Organizations

Name:	Ronald R. Bach, PhD
Project Role:	P.I.
Nearest person month worked:	12
Contribution to Project:	As PI, Dr. Bach is fully engaged in the efforts to finish the final data analysis and reporting phase of GWIIRT.
Name:	Rebecca Rudquist, BSN
Project Role:	Study Coordinator
Nearest person month worked:	0
Contribution to Project:	Ms. Rudquist participates as co-author in the GWIIRT manuscript preparation and submission process.

Special Reporting Requirements

None

Appendices

None

References

1. Research Advisory Committee on Gulf War Veterans' Illnesses. Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations. Washington, D.C.: U.S. Government Printing Office, 2008.
2. Institute of Medicine of the National Academies Committee on Gulf War and Health. Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War. Washington, DC: The National Academies Press. 2009.
3. White RF, Steele L, O'Callaghan JP, et al: Recent research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment. *Cortex*. 2016; 74: 449-475.
4. Fukuda K, Nisenbaum R, Stewart G, et al: Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA*. 1998;280(11):981-988.
5. Johnson GJ, Slater BC, Leis LA, Rector TS, Bach RR: Blood Biomarkers of Chronic Inflammation in Gulf War Illness. *PLOS ONE*. 2016 Jun 28;11(6).
6. Butterick TA, Trembley JH, Hocum Stone LL, Muller CJ, Rudquist RR, Bach RR: Gulf War Illness-associated increases in blood levels of interleukin 6 and C-reactive protein: biomarker evidence of inflammation. *BMC Res Notes*. 2019; 12: 816.
7. Johnson GJ, Leis LA, Slater BC, Bach RR: Elevated platelet count, C-reactive protein, and thromboxane analog-induced platelet aggregation in patients with Gulf War Veterans' illnesses: evidence of a chronic inflammatory state? *Blood coagulation & fibrinolysis: an international journal in haemostasis and thrombosis*. 2013;24(7):736–41.