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TITLE: Curcumin, Resveratrol, and Stinging Nettle as Treatments for Gulf War Illness

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CONTRACTING ORGANIZATION: The University of Alabama, Birmingham, AL

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14. ABSTRACT This study is a randomized, placebo-controlled, blinded, longitudinal clinical trial of three anti-inflammatory botanicals (curcumin, resveratrol, and stinging nettle) that have shown promise as GWI treatments. This threeyear project will involve 300 Veterans with GWI. This project addresses the FY21 GWIRP Treatment challenge. It is solely designed to bring promising GWI treatments to patients as quickly, efficiently, and safely as possible. The project uses a decentralized clinical trial (DCT) design that opens the study to any Veteran of the Persian Gulf War living in the United States. It also maximizes efficiency by conducting three clinical trials in parallel and completing all trials in three years.					
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Introduction

Building upon previous research that identified three botanicals capable of alleviating GWI symptoms, namely curcumin, stinging nettle, and resveratrol, these three botanicals exhibited the most promising results and are selected for further investigation. This study aims to assess the efficacy of the three botanical agents for treating Gulf War Illness (GWI), to confirm initial findings, and gather essential information for their clinical application.

To streamline the trial process, all three botanical agents will be concurrently assessed in the same study, with a timeline of three years. This accelerated timeline seeks to provide effective treatments for GWI sufferers promptly. To ensure broad applicability, a Decentralized Clinical Trial (DCT) methodology will be employed, facilitating participation from Veterans across the United States. The trial can be conducted remotely, accommodating individuals with limited mobility.

Each botanical will be evaluated in a cohort of 100 GWI-afflicted Veterans, and the study will utilize a longitudinal design to yield robust statistical significance. Additionally, three distinct dosage levels (low, medium, and high) will be explored to offer dosing recommendations for future research and clinical implementation.

Keywords

Gulf War Illness, GWI, Decentralized Clinical Trial, DCT, Veterans, Gulf War, Persian-Gulf War, Curcumin, Resveratrol, Stinging Nettle, Supplements, Botanicals

Accomplishments

What were the major goals of the project?

The major goal of this work is to assess the efficacy of curcumin, resveratrol, and stinging nettle on GWI symptoms. Our milestones for the study activities are as follows:

Specific Aim 1: To determine if curcumin, resveratrol, and/or stinging nettle can reduce GWI symptom severity	Actual
Major Task 1 Study Preparation	Actual Completion Date or Percentage Complete
Subtask 1: Prepare Regulatory Documents and research protocol for study	March 2023
Define eligibility criteria, exclusion criteria, and screening protocol	August 2022

Develop and finalize consent form and human subject protocol	January 2023
Develop and finalize recruitment materials and recruitment strategy with NSU	January 2023
Submit all required regulatory documents to IRB for review	November 2022
Submit all required regulatory documents to USAMRDC for review (ORP/HRPO)	February 2023
Coordinate with Clinical Consortium coordinating site (Nova)	January 2023
Clinicaltrials.gov registration	November 2022
<i>Milestone Achieved: UAB IRB approval for study granted</i>	February 2023
<i>Milestone Achieved: HRPO approval for study granted</i>	March 2023
Submit amendments, adverse events and protocol deviations as needed	As needed
Submit necessary documents for IRB/HRPO continuing review	Annually
Subtask 2: Prepare materials for study design/enrollment	30%
Order, encapsulate, and package botanical supplements (curcumin, resveratrol, stinging nettle) and placebo	11%
Establish account with USPS for shipping	50%
Format and initiate symptom tracking software	February 2023
Format and initiate clinical trial monitoring software	January 2023
Format and initiate medication adherence monitoring software	February 2023
<i>Milestone Achieved: All supplements and placebo capsules encapsulated, packaged, and ready for shipment. All monitoring/symptom tracking software acquired</i>	30%
Major Task 2: Conduct clinical trials	Actual Completion Date or Percentage Complete
Subtask 1: Enroll GWI participants for study (first participant enrolled)	100%
25% of subjects enrolled (75 participants)	12.5%
50% of subjects enrolled (150 participants)	6.25%
75% of subjects enrolled (225 participants)	3.16%
100% of subjects enrolled (300 participants)	1.57%
<i>Milestone Achieved: 300 GWI participants enrolled in protocol</i>	1.57%
Major Task 3: Analyses	Actual Completion Date or Percentage Complete
Subtask 1: All data compiled, organized, and cleaned	0%
Subtask 2: Data analyses completed	0%
Subtask 3: Results reviewed by PI Dr. Younger	0%
<i>Milestone Achieved: Report full results from all analyses</i>	0%
Major Task 4: Preparation of final report and publications	Actual Completion Date or Percentage Complete
Subtask 1: Manuscripts #1, #2, and #3 submitted	0%
Subtask 2: Final report submitted to IRB for study closeout	0%
Subtask 3: Final report submitted to ORP/HRPO for study closeout	0%

What was accomplished under these goals?

Progress in this reporting period (09/01/2022-08/31/2023) was focused on Major Task 1: Study Preparation. This narrative description of progress covers both Subtask 1 and Subtask 2.

Subtask 1 is: prepare regulatory documents and research protocol for study. Eligibility criteria, inclusion/exclusion forms, and the screening protocol were completed in August 2022. Following the establishment of the criteria, the clinicaltrials.gov registration was formed in November 2022. The consent form and human subjects protocol were completed for submission to IRB and HRPO in January 2023. The recruitment materials (physical and electronic flyers) and recruitment strategy were completed, with input from the Nova collaborators, in January 2023. With all of the forms and materials completed, the entire human subjects protocol was submitted to the IRB for review and approval. The IRB review/approval process required 4 months to complete. IRB approval was obtained in February 2023. This step was required before materials could be sent to HRPO. The draft protocol was sent to HRPO in September 2022, though the full IRB-approved protocol was not sent to HRPO until February 2023. After IRB approvals were obtained, final materials were submitted to OHRO/HRPO. Both milestones for Subtask 1 (IRB approval and HRPO approval) were completed by March 2023. Subtask 1 is 100% complete.

Subtask 2 is: prepare materials for study design/enrollment. Three of the five specific tasks were completed. First, the symptom tracking software (Qualtrics) was fully implemented and tested in February 2023. Second, the clinical trial monitoring software (Ripple) was fully programmed and ready to use in January 2023. Third, the medication adherence process was finalized and ready in February 2023. Two other specific tasks were not completed in the timeframe of this technical report. The capsulated botanicals were not obtained from Double Oak Mountain Pharmacy. The capsules had been ordered and the pharmacy was working on their preparation. Because no capsules had been received, this task was listed as 11% complete. Also, the United States Postal Service (USPS) process for shipping botanicals to participants was not fully approved and tested. The contract was already approved and mailing materials were received, but the package pickup and account billing details were still being finalized. This task was 50% complete at the end of the technical report timeframe. The overall subtask 2 was 30% complete.

A few other miscellaneous progress notes are: 1) the Clinical Trial Manager was hired and training, 2) the clinical coordinators were hired and trained, the LabCorp contract for remote blood tests was approved, the Nova subaward paperwork was finalized, and the first participant was consented on July 17, 2023.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to the communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

The first enrolled participant should start receiving study capsules in September 2023. We are actively working with High-Level Marketing to distribute study information on Facebook nationwide to aid in recruitment. Our goals for the next annual study period include enrolling over 175 participants and have three participants complete the protocol.

Impact

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

Changes/Problems

Changes in approach and reasons for change?

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them?

Regulatory approvals took longer than anticipated, though all approvals are now in place. We received IRB approval on 2/15/23. We received HRPO approval on 3/21/23. Contracts with LabCorp and Quest Diagnostics took longer than anticipated (8 months). Those contracts have now been approved. We now have all approvals

and contracts in place. We have finalized and trained the study team on the specific protocol. We foresee no adverse implications for the study or recruitment goals moving forward.

Changes that had a significant impact on expenditures?

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents?

Nothing to report.

Products

Publications, conference papers, and presentations?

Nothing to report.

Website(s) or other Internet site(s)?

Nothing to report.

Technologies or techniques?

Nothing to report.

Inventions, patent applications, and/or licenses?

Nothing to report.

Other products?

Nothing to report.

Participants & Other Collaborating Organizations

What individuals have worked on the project?

<u>Name:</u>	Jarred Younger, PhD
<u>Project Role:</u>	Principal Investigator
<u>Researcher Identifier (ORCID ID):</u>	0000-0003-3616-9919
<u>Nearest Person Month Worked:</u>	4

<u>Contribution to Project:</u>	Dr. Younger has overseen study start-up procedures and the initial stages of the study protocol. He has reviewed patients' screeners and medical questions about trial participation.
<u>Funding Support:</u>	R01NS109529, R01HL147603, R01MD010441

<u>Name:</u>	Paige Palenski
<u>Project Role:</u>	Lab Manager
<u>Researcher Identifier (ORCID ID):</u>	0000-0001-5628-8013
<u>Nearest Person Month Worked:</u>	3
<u>Contribution to Project:</u>	Paige briefly handled the regulatory and financial aspects of this study. She also helped develop the study protocol.
<u>Funding Support:</u>	Nothing other than this award

<u>Name:</u>	Regan Gaskin
<u>Project Role:</u>	Researcher IV
<u>Researcher Identifier (ORCID ID):</u>	0000-0003-3504-5447
<u>Nearest Person Month Worked:</u>	9
<u>Contribution to Project:</u>	Regan has handled this project's regulatory and financial aspects. Additionally, she has worked on the study start-up procedures, including sub-awards, subcontracts, system management setup, and study logistics. She has overseen the work of the clinical researcher coordinators working on the study.
<u>Funding Support:</u>	Nothing other than this award

<u>Name:</u>	Oliva Haskin
<u>Project Role:</u>	Clinical Research Coordinator
<u>Researcher Identifier (ORCID ID):</u>	N/A
<u>Nearest Person Month Worked:</u>	2
<u>Contribution to Project:</u>	Oliva has recruited, screened, and consented participants for the study.
<u>Funding Support:</u>	Nothing other than this award

<u>Name:</u>	Nathan Dewberry
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<u>Project Role:</u>	Clinical Research Coordinator
<u>Researcher Identifier (ORCID ID):</u>	N/A
<u>Nearest Person Month Worked:</u>	2
<u>Contribution to Project:</u>	Nathan has recruited, screened, and consented participants for the study.
<u>Funding Support:</u>	This award and funding from the UAB Center for Clinical and Translational Science

<u>Name:</u>	Chanel Mason
<u>Project Role:</u>	Clinical Research Coordinator
<u>Researcher Identifier (ORCID ID):</u>	N/A
<u>Nearest Person Month Worked:</u>	1
<u>Contribution to Project:</u>	Chanel has recruited, screened, and consented participants for the study.
<u>Funding Support:</u>	This award and funding from the UAB Center for Clinical and Translational Science

<u>Name:</u>	Pat Stokes
<u>Project Role:</u>	Clinical Research Coordinator
<u>Researcher Identifier (ORCID ID):</u>	N/A
<u>Nearest Person Month Worked:</u>	1
<u>Contribution to Project:</u>	Pat was trained on the study protocol and interacted with participants, however, she is no longer a part of the study team
<u>Funding Support:</u>	This award and funding from the UAB Center for Clinical and Translational Science

Has there been a change in the active support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to report.

Special Reporting Requirements?

Collaborative Awards?

Nothing to Report/Not applicable.

Quad Charts?

Nothing to Report/Not applicable.

Appendices

Nothing to Report