AWARD NUMBER: W81XWH-14-1-0599

TITLE: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

PRINCIPAL INVESTIGATOR: Giulio Maria Pasinetti MD., PhD

CONTRACTING ORGANIZATION:
Icahn School of Medicine at Mount Sinai
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Fort Detrick, Maryland 21702-5012

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Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

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6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Icahn School of Medicine at Mount Sinai
1 Gustave L. Levy Place
New York, NY 10029

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

There are no treatments for Gulf War Illness (GWI) and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications, particularly chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems. Recent evidence from our group and from others revealed that certain dietary flavonoids may promote cognitive function and/or alleviate chronic fatigue. We hypothesized that dietary supplementation with a Flavonoid Rich Preparation (FRP), a combination of Concord Grape Juice (CGJ) and Grape Seed Polyphenolic Extract (GSPE) may help alleviate clinical complications of GWI, particularly chronic fatigue and/or cognitive dysfunction. We propose to test the feasibility of dietary supplementation with FRP in Veterans with GWI, and to gather evidence supporting the efficacy of FRP in alleviating GWI-associated cognitive deficits and chronic fatigue.

Purpose: to conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP in improving cognition function and alleviating chronic fatigue in Veterans with GWI.

Scope: Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI.

Progress: We obtained FDA IND approval (IND 123889) for using FRP comprised of Concord grape juice and grape seed polyphenol extract to treat veteran GWI subjects. We also submitted IRB applications to our local institutions: the Icahn School of Medicine at Mount Sinai (ISMMS) in NY and the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS) at East Orange, NJ. Since submission of our initial IND and IRB documents, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have amended the SOW to reflect this modification. We have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment. We submitted to FDA an amendment for using only Concord grape FRP for our proposed studies in veterans with GWI. The amendment was approved by the FDA. We also submitted our amended protocol, using FRP with only Concord grape juice to the ISMMS IRB and the DVANJHCS IRB. The proposed amended protocol received ISMMS and DVANJHCS IRB approval (see appendices).

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	24	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION

An estimated 174,300 to 230,000 US military service members deployed to Iraq and Afghanistan are affected by Gulf War Illness (GWI). GWI is characterized by the persistent presentation of multiple functional symptoms involving a combination of diverse complaints centering on chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems that are not explained by established medical diagnoses. While the etiology of the GWI symptom complex is not known, GWI clinical complications typically persist over long-terms, cause significant pain and suffering, and interfere with the ability of affected Veterans to successfully integrate back into the civilian society. There are no treatments for GWI and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications. Recent evidence from our group and from others revealed/highlighted the potential value of flavonoids, a subclass of organic chemical called polyphenols that are abundantly found in some plants and common dietary preparations, may help alleviate chronic fatigue and preserve against cognitive functions. Based on this, our overall goal is to test the potential efficacy of dietary supplementation with a Flavonoid-Rich Preparation (FRP) to alleviate clinical complications in Veterans with GWI. In particular, we proposed to conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP (Concord grape juice) in improving cognition function and alleviating chronic fatigue in Veterans with GWI. Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI.

2. KEYWORDS

Gulf War Illness
Polyphenol
Flavonoids
Flavonoid-Rich Preparation
Chronic fatigue
Cognitive difficulties
Muscle pain
Mood disturbances
Sleep problems

3. ACCOMPLISHMENTS

- ***Major goals of the project***

Obtain IND/IRB approval (Year 0 to 0.5)

- obtain FDA IND approval
- Obtain local institutional IRB approval (from the Icahn School of Medicine at Mount Sinai and from the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS)
- Obtain approval from the U.S. Army Human Research Protection Office (HRPO)

Recruit 60 volunteers (Year 0.5 to 1.17)

- randomized volunteers into a treatment and a placebo arm, n=30 per arm
- complete baseline clinical assessments
- collect and bank baseline blood specimen

FRP treatment (Year 0.7 to 1.5)

- initial dose-escalation finding phase (6 weeks) followed by a stable treatment dose (18 weeks)
- complete clinical assessments during and post treatment
- collect and bank blood post treatment

Complete analysis of blood polyphenol contents (Year 0.5 to 1.7)

Complete data analysis and manuscript preparation (Year 1.8 to 2)

- ***Accomplishments under these goals***

We originally proposed to treat GWI subjects using a FRP comprised of combined Concord grape juice and a grape seed polyphenol extract. We obtained IND approval from the FDA (IND 123889) to conduct this trial using the FRP in veterans with GWI. Moreover, we submitted an IRB application to the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS) at East Orange, New Jersey for recruiting GWI cases for the study, treating and monitoring participant subjects, and collecting and banking de-identified plasma specimens from these subjects for subsequent biochemical analysis by investigators at the Icahn School of Medicine (ISMMS). We also submitted an IRB application to ISMMS for conducting biochemical analysis of banked de-identified blood specimen that will be provided by DVANJHCS.

Since submission of our initial IND and IRB documents, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. The range of Concord grape juice doses proposed is within the range of efficacy for improving cognitive function in the elderly, as was discussed in the application. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have amended the SOW to reflect this modification. We have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment. We submitted to FDA an amendment for using only Concord grape for our proposed studies in veterans with GWI and the amended protocol received FDA approval (IND 123889). We also submitted our amended protocol, using only Concord grape juice to the ISMMS IRB and the DVANJHCS IRB. The proposed amended protocol received ISMMS and DVANJHCS IRB approval. In our 1st DoD Annual Report, we have submitted our amended SOW, as well as documents from the FDA and from ISMMS and DVANJHCS IRBs confirming approval of our amended protocol.

As stipulated by both local institutional IRBs, we have since applied for and received annual re-approval of our protocol. We attached a copy of the communication from the ISMMS IRB (Appendix 1) and the DVANJHCS (Appendix 2) confirming re-approval of our amended protocol.

We have since obtained USAMRMC HRPO approval to procure investigatory reagents and begin the initial subject recruitment. We attached a copy of the communication from the HRPO confirming approval of our amended protocol (Appendix 3).

All study logs, policies, procedures, and data collection tools are now in place. Neuropsychological assessment instruments have been delivered as well as all other necessary study items.

All study team personnel at the clinical site (VANJHCS) are also in place:
Principal Investigator: Drew Helmer, MD, MS
Study staff: David Litke PhD (Psychologist)
Jan Einhorn, RN (Study Nurse)
Yvette Blackbourne (Data Analyst)
William Van Doren (Research Assistant)
Evan Franks (Research Assistant - Back Up)

We have received the first shipment of Concord grape juice and placebo beverage from Welch.

Of the >400 potentially eligible Gulf War Veterans we identified, Will Van Doren (Research Assistant) has sent out recruitment letters to 137 potentially eligible Gulf War Veterans within a 75 mile radius of the clinical site (VANJHCS) and has actively follow-up with phone calls.

We have screened 10 Veterans total, with 7 of them being eligible for participation. Of these 7, 5 are currently consented/enrolled while the other 2 await consent/baseline appointments

Processed blood samples for the consented/enrolled participants are being stored securely within an ultra-low temperature freezer at the clinical site (VANJHCS). The first batch will be shipped to Mt. Sinai for analysis in the near future.

- ***Opportunities for training and professional development the project provided***
  Nothing to Report
- ***How were the results disseminated to communities of interest?***
  Nothing to Report
- ***What do you plan to do during the next reporting period to accomplish the goals?***

We now have in place all the necessary study personnel, study logs, policies, procedures and data collection and data management tools. We have also identified a large pool (137) of potentially eligible Gulf War Veterans who live within 75 miles of the clinical site. We have mailed recruitment letters to these Veterans and are actively making follow-up phone calls. Over the first six weeks of recruitment, we have consented/enrolled 5 participants, falling just short of our goal of one new participant enrolled per week.

During the next reporting period, we plan to reach out to neighboring VA facilities and other possible outreach sites to bolster our recruitment efforts in case we cannot draw 60 participants out of the pre-identified 137 Gulf War Veterans living within a 75 mile radius. Additionally, we will continue to strive toward our goal of one new enrollee per week to ensure we meet our enrollment quota.

We have been in contact/coordination with Welch regarding the next schedule shipment of grape juice / placebo.

4. 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

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**
  As we have noted above, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. This amendment does not change

the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  As we have noted above, initiation of the study was delayed by the followings: i) submission to the FDA of an amendment to the previously approved IND 123889, to seek FDA approval to treat GWI subjects with only Concord grape juice, ii) submission of local institutional IRB amendments to the ISMMS and the DVANJHCS, seeking IRB approval to treat GWI subjects with only Concord grape juice. As we have discussed above, we received approvals for our amended protocol from the FDA, the ISMMS IRB, DVANJHCS IRB and the USAMRMC HRPO.

- **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**
  Removing grape seed polyphenol extract from the FRP formulation. GWI subjects will be treated with FRP comprised of only Concord grape juice.

- **Significant changes in use or care of human subjects**
  Removing grape seed polyphenol extract from the FRP formulation. GWI subjects will be treated with FRP comprised of only Concord grape juice.

- **Significant changes in use or care of vertebrate animals.**
  Not applicable

- **Significant changes in use of biohazards and/or select agents**
  Removing grape seed polyphenol extract from the FRP formulation. GWI subjects will be treated with FRP comprised of only Concord grape juice.

6. PRODUCTS

- **Publications, conference papers, and presentations**
  Nothing to Report
- **Journal publications.**
  Nothing to Report

- **Books or other non-periodical, one-time publications.**
  Nothing to Report

- **Other publications, conference papers, and presentations.**
  Presentation to the Gulf War Research Advisory Committee
  Presenter: Dr. Drew A. Helmer
  Date: September 29, 2015
  Presentation Title: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness
- **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

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**
  Dr. Giulio Pasinetti (PI, ISMMS): no change
  Dr. Drew Helmer (clinical PI, VA NJHCS): no change
  Dr. Lap Ho (co-investigator, ISMMS): no change

- **Has there been a change in the active other 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

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** N/A
- **QUAD CHARTS:** N/A

9. APPENDICES

Appendix 1 – ISMMS annual continuing approval for our amended protocol
Appendix 2 – DVANJHC annual continuing approval for our amended protocol
Appendix 3 – HRPO approval for our amended protocol

Gursahai, Susan

From: Deluca, Selina
Sent: Tuesday, January 19, 2016 9:52 AM
To: Pasinetti, Giulio
Cc: Gursahai, Susan
Subject: APPROVAL OF RESEARCH HS#: 14-01091/ Gulf War Grant

APPROVAL OF RESEARCH

Date: 1/19/2016

To: **Giulio Maria Pasinetti, MD, PhD (giulio.pasinetti@mssm.edu)**

On **1/16/2016**, an Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai's Federal Wide Assurances (FWA#00005656, FWA#00005651) to the Department of Health and Human Services approved the following human subject research from **2/3/2016** until **2/2/2017** inclusive:

Type of Review:	**Continuing Request for Approval**
Project Title:	**Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness**
Investigator:	**Giulio Maria Pasinetti, MD, PhD (Dept: PS - Psychiatry)**
Project Information:	**HS#: 14-01091** **GCO#1: 13-1398(0001) Department Of The Army/Department of Defense**
Sites:	**VA**
IND or IDE (if any):	**IND# 123889; No IDEs;**
Submission Details (if any):	**None**

Between **12/17/2015** and **12/22/2015**, or within 30 days prior to study close, whichever is earlier, you are to submit a completed FORM HRP-212: Continuing/Final Review Progress Report and required attachments, in order to request continuing IRB approval or study closure. If IRB continuing review approval is not granted before the expiration date of **2/2/2017**, IRB approval of this research expires on that date.

- The IRB has determined that this research involves no greater than MINIMAL RISK. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45CFR.46.102; 21CFR50.3k).
- The IRB approved this research under **expedited review procedure category(ies) 9**

In conducting this research you are required to follow the requirements listed in the **Investigator Manual**. If stamped approved consent forms are attached, use copies of these forms to document consent. IRB approval does not constitute or imply institutional support for the conduct of this research. Additionally, all required local committee approvals at each **research affiliate** site must be obtained prior to initiation.

cc: Study Contact(s): Susan Gursahai (susan.gursahai@mssm.edu)

Thank you,

Selina Deluca, MS, CIP

Senior IRB Analyst
Direct line: (212) 824-8207
Feel free to chat me using Lync: Deluca, Selina

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Department of Veterans Affairs

Memorandum

Date: September 14, 2016

From: ACOS, Research Service (15)

Subj: Approval – **Continuing Review**

To: Drew Helmer, MD

Your research project titled 01327 *Development of dietary polyphenol preparations for treating Veterans with Gulf War Illness* has been reviewed & approved by the appropriate Research Committee(s) and can continue.

1. Institutional Review Board – 9/12/2016
2. Research and Development Committee - NA
3. Subcommittee on Research Safety – 6/13/2016
4. IACUC Subcommittee - NA

All research must be conducted in accordance with federal regulations. The R&D Committee is responsible for establishing policy to ensure that all research in which the facility is to be engaged has been reviewed and approved for the ethical use of human subjects, animals, and biohazards.

In fulfilling the responsibilities for oversight of the VA NJHCS Research Program; the R&D Committee may make appropriate recommendations to the Medical Center Director for suspension of a research study or remedial or restrictive action regarding a principal investigator who fails to comply with local and federal regulations.

Kevin Beck, PhD

Digitally signed by Kevin Beck, PhD
DN: cn=Kevin Beck, PhD, o=VANJHCS, ou=ACOS Research & Development, email=kevin.beck@va.gov, c=US
Date: 2016.09.14 12:14:53 -04'00'

Kevin Beck, PhD
ACOS, Research Service

IRB APPROVAL - Continuing Review

Date: September 14, 2016
From: Donna Geppner, M.S., CTTS, CIP
Investigator: Drew A. Helmer, MD, MS
Protocol: Development of dietary polyphenol preparations for treating Veterans with Gulf War Illness
ID: 01327 Prom#: 0016 Protocol#: N/A

The following items were reviewed at the 09/12/2016 meeting:
- Research Protocol - Version date - 8/11/16 (08/11/2016; 09/12/2016)
- Consent Form - Version 5 - 8/9/16 (08/09/2016; 09/12/2016)
- Continuing Review Application - No subjects enrolled (07/19/2016; 09/12/2016)
- Protocol History (08/22/2016; 09/12/2016)

The following items were Approved at the 09/12/2016 meeting:
- Research Protocol - Version date - 8/11/16 (08/11/2016; 09/12/2016)
- Consent Form - Version 5 - 8/9/16 (08/09/2016; 09/12/2016)
- Continuing Review Application - No subjects enrolled (07/19/2016; 09/12/2016)

The following items were Acknowledged (but do not require Approval) at the 09/12/2016 meeting:
- Protocol History (08/22/2016; 09/12/2016)

The anniversary date by which the continuing review must occur is retained. Approval is granted for a period of 12 months and will expire on 10/04/2017. Your Continuing Review is scheduled for 09/11/2017, and the requirements are attached.

The protocol was determined to have the following level of risk:
Greater than Minimal Risk

The protocol was determined to have the following level of benefit to participants:
No prospect for direct benefit to participants, but likely to yield generalizable knowledge

The following other committee reviews are scheduled:
Subcommittee on Research Safety (SRS) [06/12/2017]

VA New Jersey Health Care System IRB operates under the HHS Federal Wide Assurance FWA00001281. Investigator files must be retained for 6 years post study closure date. Such records include: research records maintained by the investigator that span the entire lifecycle of the project and the records required by regulations such as the investigator's regulatory file.

Conditions of IRB Approval

What Are the Conditions of IRB Approval?

1. Adhere to ethical principles: (1) Respect for persons - consent, privacy, confidentiality, (2) Beneficence - maximize possible benefits to the subject and minimize possible harms, and (3) Justice - equitable selection.

2. Obtain informed, written consent from each human subject or his legally qualified guardian or next-of-kin, unless specifically waived by the IRB. If the subject lacks decision making capacity or has been declared incompetent, surrogate consent is required. You are required to place the original, signed consent form in the medical record (and document it in the electronic record), provide a copy to the subject, provide a copy to the Research Office (if applicable), and keep a copy for your files.

3. Promptly report all Serious Adverse Events or Serious and Unexpected Events to the IRB (both events at the VA and sponsor reports of events at other sites). The FDA defines Serious Adverse Events as: (1) death, (2) life-threatening, (3) hospitalization - initial or prolonged, (4) disability, (5) congenital anomaly, (6) required intervention to prevent permanent impairment/damage, or (7) serious and unexpected severity or frequency of expected events.

4. Promptly report all deviations (including error and accidents) from the approved protocol and do not initiate any unapproved changes (amendments, consent form modifications, advertisements) without IRB review and approval, except where necessary to eliminate apparent immediate hazard to human subjects.

5. Report Emergency Use of unapproved test articles to the IRB within 5 days.

6. If applicable, provide a copy of each subject's consent form and the Investigational Drug Information Record (VA Form 9012) to the Investigational Pharmacist prior to your request to receive, store, and dispense study medications. (The Investigational Pharmacist is responsible for the storage and dispensing of investigational drugs.)

7. Submit Continuing Review information to the IRB by the date specified and inform the IRB when your study is completed (federal law requires that every protocol must be reviewed a minimum of once per year). File a final report upon completion or termination of a study.

What Are the Penalties for Non-Compliance?

1. Non-compliance may result in suspension of approval or a particular project. Serious or continuing non-compliance may result in suspension of your privilege to conduct research at this VAMC.

INTRODUCTION

You are being invited to take part in a research study at the War Related Illness and Injury Study Center (WRIISC) at the Veterans Affairs New Jersey (VA NJ) Health Care System and the Icahn School of Medicine at Mount Sinai (ISMMS).

Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

BACKGROUND & PURPOSE

Gulf War Illness (GWI) is a multi-symptom illness that can persist over time and can cause as much disability as other major medical illnesses. It can interfere with the ability of Veterans to successfully integrate back into civilian society. There are currently no effective treatments to help alleviate the symptoms of GWI and there is a need to develop new treatments.

Recent studies have highlighted the potential value of a class of chemicals referred to as flavonoids that are found in a variety of plants and some common foods. These flavonoids may benefit GWI by improving chronic fatigue and thinking tasks.

You are being asked to take part in the research study because you are a Gulf War Veteran who was deployed to the Persian Gulf between August 1990 and August 1991 and you fit the definition of Gulf War Illness. The overall goal of this study is to test whether the daily consumption of Flavonoid-Rich Preparation (FRP), comprised of Concord grape juice (CGJ) may be effective in treating GWI, such as improving chronic fatigue and thinking tasks.

Information collected from the proposed study might also provide the basis for a larger, future study to further develop specific, readily available nutritional flavonoid rich supplements for Veterans with GWI.

This study is being sponsored by the Department of Defense (DoD). The DoD is paying for the VA NJ Health Care System to do this study. The non-profit Veterans Biomedical Research Institute will handle the money.

DVA NJHCS IRB
SEPT 12 2016
APPROVED

About 100 people will take part in this study at the VA NJ Health Care System.

DURATION OF THE RESEARCH

Your individual participation in this study will be for 6 months. This study will take approximately 14 hours of your time and you will need to make 9 visits to War Related Illness and Injury Study Center at the VA NJ Health Care System in East Orange.

STUDY PROCEDURES

If you decide to take part in this study, this is what will happen:

1. On the first day, you will come to the WRIISC (this visit should last approximately 2 hours of your time):
    a. Review the risks and benefits of participating.
    b. Sign this informed consent form.
    c. Fill out some questionnaires on paper or online.
    d. Complete some neuropsychological test; these consist of a series of questions and test that are done on paper and also on the computer to evaluate your thinking and memory skills.
    e. Be randomized (like flipping a coin) into one of the two study groups, (i) juice or the (ii) placebo group. You will have a 1 in 2 chance of receiving the juice instead of placebo.
        - Placebo is defined as a pretend treatment that is compared in a clinical trial with an active ingredient to test if the active ingredient has a real effect. In this case, placebo is defined as a liquid mix of water, sugar and artificial flavors and colors (with no juice in it) that is compared in a clinical trial with the juice to test if the juice has a real effect.
    f. You will be provided with a supply of juice or placebo together with log sheets on which you will need to keep a daily record of the juice you ingest and a food frequency questionnaire.
    g. A 9ml (approximately 2 tablespoons) blood sample will be drawn by a trained nurse.

2. This study is called a double blind study; neither you nor your study doctor will know which group you have been assigned to.

3. You will drink a total of 4 oz., 8 oz. or 16 oz. of CGJ or the placebo beverage per day. For comparison sake, the standard can of soda is 12 oz. CGJ (or the placebo beverage) will be supplied in 16 oz. bottles and a 4 oz. measuring cup. You will be instructed to consume one of these cups a day, one cup two times a day, or two cups two times a day. You will be reminded of the daily dose at your scheduled contacts.

DVA NJHCS IRB
SEPT 12 2016
APPROVED

4. Your dose of CGJ (or placebo) will increase every two weeks to the highest dose you tolerate without side effects up to 16 oz. of CGJ (or equivalent placebo). You will remain on the highest dose you tolerate until the end of the study (week 24).

5. At weeks 2, 4, 6, 8, 12, 16, 20 and 24 you will come back to the clinic. You will need to bring back the empty bottles, any unused juice, and the completed log sheet and food frequency questionnaire. You will also complete some questionnaires at this visit which should take approximately 30 minutes of your time.

6. You will receive a weekly phone call when not scheduled to make a visit to remind you of scheduled visits, to ask about side effects, and to address any questions or concerns you may have.

7. At each visit you will complete some questionnaires to determine your general wellbeing during the intervals between your last and current clinical visit.

8. At the week 12 visit, you will be asked to fill out some questionnaires on paper or online, complete neuropsychological testing and have 9ml of blood drawn (approximately 2 tbsp.) just like you did when you first started the study. This visit should last approximately 2 hours of your time.

9. At the end of week 24 you will be asked to fill out some questionnaires on paper or online, complete neuropsychological testing and have 9ml of blood drawn (approximately 2 tbsp.) just like you did when you first started the study. This visit should last approximately 2 hours of your time.

10. Because this is an experimental use of the juice, we do not know all of its bad effects. You should contact Dr. Drew Helmer at 908-202-4382, your study doctor, if you have any bad effects.

11. We cannot guarantee that you will continue receiving this juice after the study is over.

12. You must be honest with the study doctor about your health history or it may not be safe for you to be in the study.

13. All blood samples will be coded with an identification number and stored in a locked freezer at the WRIISC until shipped to ISMMS for analysis. Blood samples will be analyzed to check for any flavonoid content in the blood. These samples will be discarded by ISMMS staff 1 year after analysis is completed.

14. Your study records that are kept at the VA, including the links, will be destroyed six years after the study is completed, as required by the VA's policy for destruction of study records.

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POSSIBLE RISKS OR DISCOMFORTS

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Blood Draw
There is some minor risk of fainting from having your blood drawn. Minor residual soreness and/or bruising at the site of blood draw may occur in addition to the minor chance of infection. However, this risk is minimized by use of sterile techniques and having a trained registered nurse perform the blood draws.

Questionnaires/Neuropsychological testing
Emotional stress while completing the questionnaires or during the neuropsychological testing. A psychologist will be available at all times.

Study Dietary Supplementation
Study staff do not know if the flavonoid enriched product (CGJ) will make your health better or improve your Gulf War Illness. The research team does not know of all the risks to you from taking part in the study. You should talk to your research team about any side effects you have while taking part in the study.

The study staff does not know of all the risks of FEP (CGJ) to the embryo or fetus if you are or become pregnant.

Study Information
There is a risk that study information (data) could be connected to your name. This is called “loss of confidentiality”. We minimize these risks by utilizing a study ID which is a code (not associated with your personal information) and apply that code to all study related material. The link between your study ID code and your personal information is kept in a password protected file that is stored on a protected VA server with access granted only to the Principal Investigator (PI) and research study staff.
The study staff will tell you about any new risks or new side effects that could happen to you from taking part in the study.

If you would like to stop taking part in the study, it is important to tell the study staff. Not telling the study staff about your decision could be harmful and reduce the value of the research study. The study staff will take you off the study in a safe manner and will discuss other care options with you.

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Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

POTENTIAL BENEFITS

None. Taking part may help others by learning more about the feasibility of using FRP (CGJ) in the treatment of Gulf War Illness.

CONFIDENTIALITY

1. Your records may be reviewed by quality assurance and federal regulatory authorities as well as the Institutional Review Board.
2. All information acquired from and about you in the study will be kept by WRIISC staff. Only investigators and study team members will have access to the information. Your name and other personal information will be on the questionnaires, letters, and informed consent document, all this information will be kept in a locked cabinet.
3. You will be assigned a subject number. The questionnaire data will be inputted in a database and that will only contain your subject number.
4. The data and the link will permanently reside on a secure server in the VA NJ Information Resource Management (IRM) server room with restricted access to the PI and study team members.
5. All coded data and blood samples will be sent to the Icahn School of Medicine at Mount Sinai (ISMMS) for analysis. Blood samples will be shipped via traceable courier. Only PI and study personnel at each of the sites will have access.
6. A research monitor nominated and approved by the VA- New Jersey Healthcare System Institutional Review Board may be present during conduct of research activities to ensure the safety of participants and report concerns about the conduct to the appropriate research monitoring entities.
7. Your study records including the links will be destroyed six years after study completion as required by the VA's policy for destruction of study records.

Information about you will be combined with information from other people taking part in the study. We will write about the combined data we have gathered. Any talks or papers about this study will not identify you.

The information collected for this study will be kept confidential. We will include information about your study participation in your medical record. There are times when we might have to show your records to other people. For example, someone from the

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Office of Human Research Protections or other federal, state, or international regulatory agencies
VA Office of Research Compliance
VANJHCS IRB and Research and Development Committees
Food & Drug Administration (FDA)
Collaborating Institutions (Icahn School of Medicine at Mount Sinai (ISMMS))
Department of Defense (DoD) – the sponsor of this study
Veterans Biomedical Research Institute (VBRI)
Dr. Carol Gibson-Gill – Research monitor, may look at or copy portions of records that identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

COSTS TO PARTICIPANTS AND PAYMENT

Costs to Participants

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

Tax law may require the reporting of the amount of payment you received for participating in research to the Internal Revenue Service (IRS) or other agencies, as applicable. Generally, this reporting would take place if you received payments that equal $600 or more from the Veterans Biomedical Research Institute (VBRI) in a calendar year.

Payment Offered for Participation:

You will be compensated a total of $360 in appreciation for your time and travel:
a. Baseline visit (about 2 hours total) = $60.
b. Weeks 2, 4, 6, 8 = $25 each.
c. Week 12= $70
d. Weeks 16, 20 = $25 each.
e. Week 24 = $80.

You will fill out a voucher and a check will be mailed to you within 4-6 weeks.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury was due to your not following the study procedures.

If you think you have been injured by the research, you should contact Dr. Drew Helmer at 908-202-4382 and the emergency room at 973-395-7236 after hours.

Emergency and ongoing medical treatment will be provided as needed.

The VA NJ H Health Care System will provide you medical care if you are injured from taking part in this study. This does not apply if your injury was caused from not following study procedures. This is called non-compliance with study procedures. Except in limited circumstances, the necessary care will be provided in VA medical facilities. If you are injured from taking part in this study you may be able to take legal action under federal law to receive monetary compensation for your damages. This study has not set money aside to compensate you for injuries caused by taking part in this study.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

PARTICIPATION IS VOLUNTARY

It is up to you to decide whether or not to take part in this study. If you decide to take part you may still withdraw at any time. If you do not wish to be in this study or you decide leave the study early, you will not lose any VA benefits to which you are entitled. If you don't take part, you can still receive all usual care that is available to you at the VA. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

Should you decide to withdraw from the study all study data and blood samples already collected before your withdrawal may still be used in study analysis.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION

The principal investigator may terminate your participation in the study for any of the following reasons:

- If it is determined that your participation is unsafe for you
- If you meet study exclusion criteria

PERSONS TO CONTACT ABOUT THIS STUDY

If you have any questions, complaints or concerns about the study you should contact the Principle Investigator Dr. Drew Helmer at 908-202-4382

If you have any questions, complaints or concerns about your rights as a study participant, you should contact the **Patient Representative at 973-676-1000 extension 3399**.

If you want to make sure this is a valid VA study, you may contact the VANJHCS Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VANJHCS IRB at 973-676-1000 ext.1- 2778 if you have questions, complaints or concerns about the study or if you would like to obtain information.

FUTURE USE OF DATA AND RE-CONTACT

Your data may be reused at a later date. This data will be stored in a research repository created by the War Related Illness and Injury Study Center. All the data will be coded and will reside on a secure server administered by the VA NJ Health Care System Information Resource Management (IRM).

Please read each sentence below and think about your choice. After reading each sentence, check the box "Yes or No" and place your initials on the line. If you have questions, please talk to your doctor or principal investigator. Remember, no matter what you decide to do about the storage and future use of your data, your decision will not affect your medical care or your participation in the study, you may still take part in the study.

I am giving my permission for VHA to:

Store my health information in a research data repository

☐**YES** ☐**NO** _____**Initials**

I give my permission for the principal investigator or study doctor to share my data outside the VA.

☐**YES** ☐**NO** _____**Initials**

Explain to whom and how the data will be transferred using the table below:

Name of receiving Center/Investigator	City, State	What private information is involved	How will the information get there?
Icahn School of Medicine at Mount Sinai (ISMMS)/ Lap Ho, PhD / Dr. Giulio Pasinetti	New York, NY	Coded research data and blood samples	Traceable courier

I give my permission for the principal investigator or study doctor to contact me to ask me to take part in more research.

☐**YES** ☐**NO** _____**Initials**

Future research of data maintained within a research repository will only occur after further Institutional Review Board and/or other applicable approvals to ensure the protection of your individual privacy.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr. Drew Helmer or study staff has explained the research study to you. You have been told of the:

- risks or discomforts and
- possible benefits of the study

You have been told of:

- other choices of treatment available to you.

You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

I agree to participate in this research study as has been explained in this document.		
Participant's Name	**Participant's Signature**	**Date**
Name of person obtaining consent	Signature of person obtaining consent	Date

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Gursahai, Susan

From: Klein, Natalie M CIV USARMY MEDCOM USAMRMC (US) <natalie.m.klein.civ@mail.mil>
Sent: Friday, April 01, 2016 3:16 PM
To: Pasinetti, Giulio
Cc: Grants; King, Michael; Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Dubner, Lauren; Winter, Thomas S CIV USARMY MEDCOM USAMRAA (US); Chaney, Brett L CTR USARMY MEDCOM CDMRP (US); Ho, Lap; Gursahai, Susan; 'Helmer, Drew A.'; 'Fobler, Malusha M.'; Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Rotimi, Jamie E CTR USARMY MEDCOM USAMRMC (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Daphtary, Maithili M CTR USARMY MEDCOM USAMRMC (US); Klein, Natalie M CIV USARMY MEDCOM USAMRMC (US)
Subject: Gulf War Approval-A-18461.a HRPO Approval Memorandum (Proposal Log Number GW130070, Award Number W81XWH-14-1-0599) (UNCLASSIFIED)

Classification: UNCLASSIFIED
Caveats: NONE

SUBJECT: Initial Approval for the Protocol, “Development of Dietary Polyphenol Preparations for Treating Veterans With Gulf War Illness,” Submitted by Giulio M. Pasinetti, MD, PhD, Mount Sinai School of Medicine, New York, New York, Proposal Log Number GW130070, Award Number W81XWH-14-1-0599, HRPO Log Number A-18461.a

1. The subject protocol was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (IRB) on 16 January 2016. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the and protocol and determined compliance with applicable DOD, US Army, and USAMRMC human subjects protection requirements.

2. This no greater than minimal risk study is approved for the accrual of 60 specimens collected at the VA New Jersey Health Care System, East Orange.

3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to Usarmy.detrick.medcom-usamrmc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 2 February 2017. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.;

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this approval is Maithili Daphtary, PhD, Human Subjects Protection Scientist, at 301-619-1029/maithili.m.daphtary.ctr@mail.mil.

8. The HRPO point of contact for post-approval oversight is Jamie Rotimi, MS(c), Human Subjects Protection Scientist, at 301-619-1126/Jamie.e.rotimi.ctr@mail.mil.

NATALIE M. KLEIN, PhD, CIP
Human Subjects Protection Scientist
Human Research Protection Office
Office of Research Protections
US Army Medical Research and Materiel Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

Classification: UNCLASSIFIED
Caveats: NONE