DEPARTMENT OF THE ARMY
HEADQUARTERS, US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
810 SCHREIDER STREET
FORT DETRICK, MARYLAND 21702-5000

REPLY TO
ATTENTION OF

MCMR-RP 22 April 2015

MEMORANDUM FOR COMMANDING GENERAL

SUBJECT: Report of 26 March 2015 Site Visit and Assessment of Protocol Compliance for, "Gulf War Illness – Evaluation of An Innovative Detoxification Program," Principal Investigator: David O. Carpenter, M.D., University at Albany, State University of New York (SUNY), Rensselaer, NY, Research Site: Severna Park Health and Wellness Center, Annapolis, MD, Proposal Log Number GW093066, Award Number W81XWH-10-1-1004, HRPO Log Number A-16131

1. References:

a. 32 Code of Federal Regulations (CFR) 219, DOD Protection of Human Subjects (The Common Rule).

b. 21 CFR 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application).

c. Department of Defense Instruction 3216.02, Protection of Human Subjects in DOD-Supported Research, November 8, 2011.

d. Army Regulation (AR) 70-25, Use of Volunteers as Subjects of Research, 25 January 1990.

e. AR 40-7, Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances, 19 October 2009.

f. International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice.

2. Summary. As requested by U.S. Army Medical Research Acquisition Activity (USAMRAA) on 24 February 2015, the USAMRMC Office of Research Protections, Human Research Protection Office (HRPO) conducted a site visit to the above-referenced research site on 26 March 2015 to assess ongoing study activities for compliance with human subjects protection regulations and requirements. The HRPO site visit team audited the study Master File/Regulator Binder and all consented subjects' study records, inspected investigational product accountability, and conducted

interviews with research team members and three study subjects. The team identified a number of findings and concerns, e.g., failure to record and track study adverse events and protocol deviations, use of unapproved study documents, missing documentation in the master file and subject records, and documentation practices that are inconsistent with Good Clinical Practice Guidelines. Although the site visit team identified a number of issues, these findings can be addressed and corrected by the researchers. There are no findings that would support stopping the study at this time. Recommendations for protocol revisions and implementation of additional study documentation practices to mitigate the findings follow in section 6 of this report.

3. Purpose. The ORP HRPO conducted this on-site assessment to evaluate the human subjects protection regulatory compliance for the Congressionally Directed Medical Research Programs (CDMRP)-funded research protocol, "Gulf War Illness-Evaluation of An Innovative Detoxification Program." The responsible US Army Medical Research Acquisition Activity Grants Officer notified the University at Albany, SUNY Office of Sponsored Programs of the site visit on 24 February 2015 (enclosure 1).

Two non-compliance issues arose during the ORP HRPO oversight of this research that precipitated the assessment visit: expiration of the Federalwide Assurance for the Study Physician's office where subject eligibility screening and medical consultation take place; and the prior use of recruitment materials that had not received review and approval by the responsible IRB(s).

The objectives of the on-site assessment were:

a. To evaluate subject screening and enrollment procedures, documentation and process of informed consent, investigational product administration, and data collection activities in accordance with the IRB-approved study protocol.

b. To assess and examine the data reporting and subject safety systems in place. To identify issues with identification and documentation of: protocol deviations; reporting and follow-up of adverse events, including serious adverse events; and any issues with required regulatory reporting to responsible Institutional Review Boards and to the US Food and Drug Administration.

c. To provide on-site education and feedback on appropriate regulatory documentation requirements and best practices, Good Clinical Practice guidelines, and considerations for general and source study documentation practices.

4. Team Membership. This Assessment Visit was conducted by representatives from the Headquarters, US Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections, Human Research Protection Office (ORP HRPO). The Assessment Team members included:

a. (b) (6) M.S., C.I.P., Director, ORP Institutional Review Board (IRB) Office. (Team Lead)

b. (b) (6), Ph.D., C.I.P., Deputy Director, ORP HRPO.

c. (b) (6) M.S., C.I.P., Human Subjects Protection Scientist (HSPS), ORP HRPO.

d. (b) (6) R.N., M.S.N., C.I.P., P.M.P., HSPS, General Dynamics Information Technology Corporation

Additionally, two representatives from the ~~Congressionally Directed Medical Research Programs (~~CDMRP~~)~~, Gulf War Research Program observed the site visit activities: (b) (6) Ph.D., Program Manager; and (b) (6) M.B.A., Science Officer.

5. Scope. The ORP HRPO Assessment Team conducted the following activities in the course of this site visit assessment:

a. Study document reviews. The Assessment Team inspected and completed audit checklists for:

(1) The Principal Investigator (PI) master study file.

(2) All subject files for individuals who signed an informed consent form.

(3) Electronic screening/enrollment logs and specimen logs.

(4) Study records for investigational product accountability.

b. Interviews and discussions. The Assessment Team interviewed and held discussions with:

(1) Study Team. PI, Dr. David Carpenter; Associate Investigator, Dr. Kathleen Kerr; Study Coordinator, (b) (6) Study Physician, (b) (6); and (b) (6), (b) (6)

(2) Research subjects. Interviews with three study subjects.

c. Review of recruitment and informed consent processes and documentation.

d. Inspection of product accountability and specimen management procedures.

e. Facility and systems reviews, including discussion of protocol procedures/controls for the following systems: interactions with the Study Physician and medical clinic; sauna facility procedures; and procedures for emergency response.

6. Findings.

a. Strengths

(1) Investigators showed a clear commitment to respect the voluntary participation and significant time commitment of each subject in the study. The implementation of the tiered process of recruitment and informed consent thoroughly described in the protocol and informed consent form and described in subject interviews demonstrate investigator commitment to ethical principles of respect for subjects, voluntary participation in research, and conditions free from subject coercion or undue influence to participate in the study.

(2) The assessment team was impressed by the organization of the subject and regulatory files and the attention to detail observed in the records for each telephone contact made with potential subjects by (b) (6)

b. General Observations.

(1) The Assessment Team did not identify any serious adverse events or unanticipated problems in the research records reviewed during the visit that met Institutional Review Board or FDA prompt reporting requirements.

(2) Specific areas of concern noted by the Team include:

(a) Lack of adherence to the IRB approved protocol for subject screening procedures.

(b) Insufficient/missing documentation in subject records, master file, and treatment adherence records.

(c) Use of unapproved and non-current versions of study documents.

(d) Failure to record and track study adverse events and protocol deviations

c. Findings and ~~Required~~ Recommended Corrective Actions. The following are the substantive findings from the Assessment and their respective ~~required~~ recommended corrective actions. Specific subject study file findings are attached (enclosure 2).

(1) Subject self wash-out of medication in preparation for study participation. Per discussion with (b) (6) and review of screening logs, (b) (6) informs potential subject that in order to participate in the study, they may need to go to their treating physician to discontinue certain medications and then call back within 2 weeks. (Telephone screening form A on file does not specify this). Two subjects interviewed reported they did not want to go to their VA treating physician and instead completed a wash-out of medications on their own. One subject interviewed reported a self- wash-out of hydrocodone on his own, then a wash-out of sleep meds during screening with (b) (6), which delayed his participation in the intervention. Another subject interviewed reported a self-washout of 'psychotropic' medication and tramadol. Study records document another subject 'weaned' himself off gabapentin, fluoxetine and hydrocodone before clinical screening visit with (b) (6)

Recommendation: Persons who complete telephone screening are not consented for participation yet, and could be found ineligible. The FDA requires informed consent prior to medication wash-out procedures if the washout is required for subjects to be eligible for the study. Revise the study protocol to describe obtaining informed consent of subjects for this purpose and submit the revisions to the Institutional Review Board. Discontinuance of medication in preparation for research participation should be documented in the subject records and conducted under medical supervision with informed consent. Provide all approved documents to HRPO.

(2) Self-administration of study supplements without adherence monitoring. During interviews of study staff and subjects, it was reported that some of the study supplements (vitamin regimen, oils, cal-mag drink) were self-administered by subjects at home. This is NOT considered a protocol deviation as supervised administration of all study products is not required per protocol (except for niacin administration that is controlled by the sauna supervisor). However, best practice documentation of treatment adherence and accounting of self-administration requires improvement for this population who may have memory or concentration difficulties as a result of Gulf War Illness.

Recommendation: See ~~required~~ recommended action in below section c.

(3) 'Key' subject facilitation of study supplement administration. Through study staff interviews, the Team identified an unusual practice in which multi-dose bottles of study supplements were given to a 'key' subject to distribute to other subjects living together to 'encourage them to stick to the regimen.' This study is designed to test whether the treatment is safe and effective; documentation of treatment adherence is critical to study integrity. This practice does not lend itself to individual documentation of treatment adherence.

Recommendation: Revise the protocol to **implement** use of a subject diary card for each subject to record every study supplement taken outside of the sauna center. Modify the protocol to include sauna supervisor documented review of subject diary entries along with subjects daily report information. Provide all IRB-approved documents to HRPO. Recommend discontinuing the practice of study supplement administration via a 'key' subject.

(4) Adverse events and protocol deviations. As discussed with the study team on 26 March 2015, in this study with intense subject interactions over a significant period of time, one would expect a number of protocol deviations and adverse events to occur, be recorded, and monitored over the study period. The study team did not record AEs on the AE/SAE log per protocol page 42~~51~~, although there were several events recorded in subject records. There was no documentation of correspondence with the Principal Investigator regarding follow-up/disposition of these events. [Note: Protocol p. 42 states, "the Study Coordinator will maintain the Master Log (GW Study Participant and Event log) that will list~~s~~, by unique subject number.~~-~~. .~~-~~ any treatment errors, any adverse events, any missed study appointments or testing points. Protocol p, 63 states, All adverse events or Serious Adverse Events will be communicated to the Study Physician and Study Coordinator in real time and followed in the appropriate manner.] ~~There was no documentation of correspondence with the Principal Investigator regarding disposition of these events.~~ Note for consideration: per US FDA 21 CFR 312.64, an investigator must promptly report to the sponsor (In this case, Dr. Carpenter) any serious adverse event whether or not considered drug related, including those listed in the protocol or investigator's brochure.

(a) Documented hypotensive episode that resolved. Event itself and sauna supervisor actions taken are well-recorded, but no evidence of review/communication to Principal Investigator or recording in AE/SAE log. Dr. Romero reported she was consulted on this event and recommended and adjustment to the subject's blood pressure medication.

(b) In Daily Report Day 2, subject reported inflammation of hands/feet, increased heart rate, fatigue which quickly resolved overnight. Subject also experienced pain related to previous shoulder injury (per Daily Report Day 3) Upon interview, subject confirmed reporting this to Sauna Supervisor and he told the Team he understood these medical symptoms were expected. No record of study team review/disposition or documentation on AE log,

(c) Subject records indicate subject was administered potassium at levels three times higher than the protocol's specified dose, but the dose given was not recorded. The audit team found no record of deviation reporting or

corrective actions. The audit team reviewed the Daily Log and determined the subject did not report any resulting subject AEs from this event.

Recommendation: Recommend recording and assessing all study events that meet the criteria for an adverse event on the adverse event log and deviations on the deviation log. US FDA 21 CFR 312.32(a) defines adverse event as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Please see this section of the regulations for the definitions of when an adverse event is considered 'serious' or 'unexpected.' Recommend submitting the adverse event log and deviation log to the Institutional Review Board as a modification to the continuing review report approved 20 March 2015.

(5) Use of Unapproved Study Forms. (~~1~~a) The team identified a "Success" form in subject files for subjects to record improvements of symptoms or other 'wins' experienced through study participation. The Institutional Review Board did not approve this form for use. This form does not provide an opportunity for subjects to identify any problems or concerns. Consider providing subjects a more balanced assessment form; (~~2~~b) The team identified two versions of the Daily Report Form (Form F) in the subject records, one was not approved by the Institutional Review Board; (~~3~~c) The Team could not verify the Telephone Screen A version in subject files was approved by HRPO.

Recommendation: Submit these study documents for review by the Institutional Review Board and report their use as a deviation from IRB-approved study procedures. Consider adding a version/date in footer for document control purposes.

(6) Documentation of Missing Data on Study Instruments – The team noted incomplete study instruments, missing data points (e.g., Daily Report Forms missing from subject file). ~~For example, medical exam 2 (8 August 14) is blank in the file for subject 4095.~~ For example, Subject 4095 ~~also~~ had missing data on his/her niacin doses on Day 9 and 12. ~~There is no record of the Day 30 visit completion for subject 4118~~. There was no record in the file for Day 5 Daily Report for subject 4056 (this may have been stored separately from subject files).

(7) Incorrect Version of ICF: The simple majority of subjects signed consent form version 25 May 2012. One subject signed version 16 October 2012. All subjects should have signed version 4 February 2014. Specific subject informed consent form findings are attached (enclosure 3)

Recommendation: This finding should be reported to the Institutional Review Board with a request for determination on whether all subjects should be re-consented with the current informed consent form, dated 5 February 2014. Provide the report and IRB review outcome to HRPO. Additionally, all study team members should complete GCP refresher training modules through CITI or other course and provide training certificates to HRPO.

(8) Irregular Informed Consent Form Documentation: (b) (6) signature as consenter was inconsistently completed as witness, consenter, or left blank. Of the 17 persons who agreed to participate in the study and signed the consent form, 11 persons left the 'future use of samples' options blank and two persons initialed both 'yes' and 'no' options. Specific subject informed consent form findings are attached (enclosure 3)

Recommendation: Same as above required action in Section f.

(9) Master File/Regulatory Binder. Files did not include all approved versions of the protocol, informed consent form and recruitment materials for the study as required under Good Clinical Practice: Consolidated Guidance (ICH-E6) Section 8.2. Files did not include all amendment approval letters as issued by the Institutional Review Board.

Recommendation: Place all IRB-approved versions of study documents and all IRB approval letters in the study regulatory file.

(10) Study Documentation Practices. Use of white-out and pencil were used across several subject records. Any change or correction to subject source records should be dated and initialed and should not obscure the original entry. Use of correction fluid (White out) over subject numbers is unacceptable per Good Clinical Practice: Consolidated Guidance (ICH-E6) Section 4.9.3. (Subject 4118 2nd medical report had two subject numbers present). All instrument blanks were not completed in subject records. For example, structured medical exam forms not signed/dated by coordinator, medical exam form 14 Mar 14 not signed on page 2 (Subject 4095).

Recommendation: Proper documentation of errors was discussed at on-site out briefing, including any missed procedures should be documented per protocol page 42 and staff entries should be signed or initialed and dated.

(11) Therapeutic Misconception. In interviews with three subjects, it was clear the subjects understood the actual detoxification procedures, risks of participation, and the voluntariness of participation. However, it appeared the subjects believed they were participating in a detoxification program (like others who are going through the program outside of the research protocol). It was not clear they understood this is a research protocol with the purpose to determine ~~whether the program was safe and effective~~the effectiveness and safety of an investigational treatment.

Recommendation for consideration: During ongoing subject visits, investigators should emphasize that subjects are participating in research and ensure ongoing consent throughout participation.

(12) Principal Investigator as Sponsor-Investigator. Given our experience with Sponsor-Investigator studies, the Team noted the following observations:

(a) The sponsor is required under 21 CFR 312.33 to submit annual reports to FDA on the progress of the clinical investigation. **Recommendation**: Please confirm this report has been completed to date.

(b) It is noted the protocol does not describe the Sponsor-Investigator plan for site monitoring, data management, safety reporting beyond the statement on page 43 describing 'the PI will provide a summary of the DSM report to the IRB and DoD on an annual basis as part of the progress report.' **Recommendation**: The PI should seek Institutional Review Board guidance on whether protocol revision is required to comply with Dr. Carpenter's Sponsor-Investigator responsibilities. Recommend study team develop a schedule of routine reporting of any study adverse events and protocol deviations for review and disposition.

(13) 2015 Continuing Review Report. The subject consented/screened/enrolled numbers reported to HRPO appear to be inconsistent with those reported to the Institutional Review Board continuing review report.

Recommendation: Submit a modification to the IRB continuing review report approved 20 March 2015 to clarify the following subject numbers: 1 screen failure; subjects who have completed all study participation; and number of subjects active in the study.

8. Plan for follow-up. The Principal Investigator should provide an itemized written response to the issues identified in this report within 30 days of receipt. Any of the findings noted within this report that are applicable to other subjects should be addressed in the response. If the Principal Investigator determines that any of the findings will not be reported to the Institutional Review Board, please provide a justification for this determination in the report response. At this time there are no plans for a subsequent HRPO monitoring visit.

9. Points of Contact (POC). Direct questions regarding this report to (b) (6) at (b) (6) Provide your written response to this report within 30 days of receipt to (b) (6) via email at (b) (6)

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Enclosure 1: HRPO Site Visit Notification (File separately attached as Award No. W81XWH-10-1-1004 Site Visit Notification.pdf)

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Enclosure 2: Subject File Findings

Subject	File	Comments
~~4095~~	~~Medical Exam 2~~	~~8 August 2014 is blank~~
4098~~8~~5	Product Administration	Niacin doses were missing on Day 9 and 12
~~4118~~	~~Daily Report~~	~~Day 30 subject visit completion missing from file~~
4056	Daily Report	Day 5 appears to be missing (may be stored separately from subject file)

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Enclosure 3: Informed Consent Form Documentation Findings. Twenty five subjects signed consent forms. Seven subjects withdrew after consent and did not participate in study procedures. The following documentation issues were found:

	Subject	Version Signed	Comments
1	4041	25 May 2012	Future Use: Blank
2	4095	4 Feb 2014	Future Use: Both options initialed
3	4013	25 May 2012	Future Use: Blank, subject signed, not printed
4	4119	25 May 2012	Future Use: Blank
5	4118	25 May 2012	Future Use: Blank
6	4077	16 Sep 2012	Future Use: Blank
7	4056	25 May 2012	Future Use: Blank
8	4105	25 May 2012	Future Use: Blank
9	5038	4 Feb 2014	Future Use: Blank
10	5104	4 Feb 2014	Future Use: Blank
11	5011	4 Feb 14	Future Use: Blank
12	5089	4 Feb 2014	Future Use: Blank
13	5072	4 Feb 2014	Future Use: both options initialed, signed in pencil
14	4017	25 May 2012	Future Use: ok
15	4005	Outdated (v. not recorded)	Future Use: ok
16	5061	4 Feb 2014	Future Use: blank
17	5091	4 Feb 2014	Future Use:
18	4109	4 Feb 2014	Future Use: subject indicated NO, cannot use samples. Signature page is ICF v. 25 May 12
19	4110	25 May 2012	Future Use: ok, no consentor sig.
20	4056	16 Sep 2012	Future Use: blank
21	4020	Outdated (v. not recorded)	Future Use: ok
22	Dropped (No subj #)	Outdated (v. not recorded	Future Use: blank
23	Dropped (No subj #)	Outdated (v. not recorded	Future Use: blank
24	Dropped (No subj #)	Outdated (v. not recorded	Future Use: blank
25	Dropped (No subj #)	Outdated (v. not recorded	Future Use: blank