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Report No. SPO-2011-005 March 31, 2011

Inspector General
United States Department of Defense

Special Plans and Operations

Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq

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Inspector General

United States Department of Defense

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INSPECTOR GENERAL
DEPARTMENT OF DEFENSE
400 ARMY NAVY DRIVE
ARLINGTON, VIRGINIA 22202-4704

March 31, 2011

MEMORANDUM FOR DISTRIBUTION

SUBJECT: Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Report No. SPO-2011-005)

We are providing this report for review and comment. This report discusses our findings concerning the integrity of a traumatic brain injury research project that was conducted in Iraq from December 2008 – March 2009.

In preparing our report, we considered comments from the following Department of Defense Components: Under Secretary of Defense for Acquisition, Technology and Logistics; Commander, U.S. Army Medical Command; and the Chief, Bureau of Medicine and Surgery. We have redirected several recommendations and added recommendations; therefore, we request additional comments on Recommendations A.1.1 – A.6.1; B.1.2; B.2.2; and B.3.2 by May 6, 2011.

DoD Directive 7650.3 requires that all recommendations be resolved promptly. If possible, send your comments in electronic format (Adobe Acrobat file only) to SPO@dodig.mil. Copies of your comments must have the actual signature of the authorizing official for your organization. We are unable to accept the /Signed/ symbol in place of the actual signature. If you arrange to send classified comments electronically, you must send them over the SECRET Internet Protocol Router Network (SIPRNET).

We appreciate the courtesies extended to the staff during the conduct of this assessment. Please direct questions to [redacted] at (703) 604-[redacted] (DSN 664-[redacted], [redacted]@dodig.mil.

Kenneth P. Moorefield
Deputy Inspector General
Special Plans and Operations

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Report No. SPO-2011-005 (Project No. D2009-D00SPO-0242.00) March 31, 2011

Results in Brief: Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq

What We Did

This assessment was initiated in response to allegations brought to the attention of the Department of Defense, Office of Inspector General, concerning the integrity of a traumatic brain injury research project in Iraq. The overall objective of the assessment was to review these allegations and determine whether:

- DoD guidance regarding the performance of research on human subjects (in this case deployed, injured U.S. Military personnel in Iraq) was violated in a DoD-approved clinical research trial evaluating a treatment for mild traumatic brain injury.
- Research misconduct occurred during this specific DoD-approved clinical research trial.

We visited organizations, conducted interviews, and reviewed records and standards pertinent to the conduct and oversight of the research protocol, "The Use of Anti-Oxidants to Reduce Sequela of Mild Traumatic Brain Injury (mTBI) After Blast Exposure," conducted at Camp Al Taqaddum, Iraq, between December 2008 and March 2009. We considered both U.S. Navy and U.S. Army regulations, because the Principal Investigator for this research was a U.S. Navy physician, and since the U.S. Army Surgeon General approved the DoD Assurance of Compliance for the Multi-National Corps – Iraq, setting standards for the conduct of human-subject medical research in Iraq.

What We Found

We identified the following principal concerns:

- The management and conduct of the clinical trial were inconsistent with military standards for human subject medical research
- Possible sub-standard patient care
- Weaknesses in the process used to review and approve medical research in Iraq

What We Recommend

The Under Secretary of Defense for Acquisition, Technology and Logistics:

- Update relevant medical research policies to ensure that procedures are in place to adequately protect the rights of deployed personnel from coercion and undue influence to participate in research studies.
- Coordinate with the Military services to ensure DoD and Service level medical research policies are pertinent to research conducted in a joint-service environment. Specifically ensure there are clear lines of accountability and responsibility for the investigation of alleged research misconduct which may involve more than one Military service.

The Assistant Secretary of Defense for Health Affairs:

- Conduct health assessments to determine if there were any adverse effects on the health of the U.S. Service members who participated in the mTBI clinical trial.
- Coordinate a review of the Joint Theater Trauma System (JTTS) Clinical Practice Guideline (CPG) "Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting."

The U.S. Army Medical Command:

- Investigate potential medical research misconduct by a U.S. Navy physician and take appropriate action as required.
- Update relevant policies and procedures to ensure a standardized approach to the conduct of medical research that provides an appropriate standard of protection for the rights and welfare of research participants.

What We Recommend (cont.)

The U.S. Army Medical Command (cont.):

- Ensure that procedures are in place to adequately address the use of nutritional supplements as investigational drugs.
- Ensure individuals involved in medical research receive training in the use of investigational drugs and applicable FDA regulations.
- Conduct a review of the Institutional Review Board's deliberations which resulted in the approval of the research protocol.
- Conduct a review of the Deployed Combat Casualty Research Team's report which evaluated the research at Camp Al Taqaddum.

The U.S. Navy Bureau of Medicine and Surgery:

- Identify the research participants and conduct a Quality of Care Review to determine whether these Military service personnel received appropriate medical care.
- Update relevant policies and procedures to ensure a standardized approach to the conduct of medical research that provides an appropriate standard of protection for the rights and welfare of research participants. Ensure that procedures are in place to adequately address the use of nutritional supplements as investigational drugs.
- Ensure all individuals involved in clinical research receive training in the use of investigational drugs and Food and Drug Administration regulations.

Management Comments and Our Response

Under Secretary of Defense for Acquisition, Technology and Logistics (USD [AT&L]):

The Assistant Secretary of Defense for Research and Engineering, responding on behalf of USD(AT&L), generally concurred with our recommendations and has taken action to update draft DoD Instruction 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research" accordingly.

U.S. Army Medical Command (USAMEDCOM):

The Commanding General, USAMEDCOM generally concurred with our recommendations. We commend the Commanding General and his staff for proactively implementing corrective actions for many of the recommendations, and agreeing to take additional actions within the next several months. Furthermore, we appreciate their willingness to complete an investigation into all allegations of potential research misconduct.

U.S. Navy Bureau of Medicine and Surgery (BUMED):

BUMED concurred with several recommendations and plans to take corrective action.

~~(FOUO)~~However, subsequent to their Quality of Care Review, [redacted]

~~(FOUO)~~The Chief, BUMED did not concur with our initial recommendation to conduct an investigation into allegations of potential research misconduct. Specifically, he did not believe that the Navy had any authority over this clinical trial since it was conducted under the direction and approval of the U.S. Army. Consequently, we revised the recommendation and requested that the U.S. Army complete any necessary investigation.

Additional Recommendations: We added several recommendations due to management comments. We request that the Assistant Secretary of Defense for Health Affairs and the Commanding General, U.S. Army Medical Command provide additional comments to the final report by May 6, 2011. Please see the recommendations table on the next page.

Report No. SPO-2011-005 (Project No. D2009-D00SPO-0242.00) March 31, 2011

Recommendations Table

Management	Recommendations Requiring Comment	No Additional Comments Required
Under Secretary of Defense for Acquisition, Technology, and Logistics		C.5.1; C.5.2 C.6.1; C.6.2
Assistant Secretary of Defense for Health Affairs	B.1.2; B.2.2; B.3.2	
U.S. Army Surgeon General/ U.S. Army Medical Command	A.1.1; A.2.1; A.3.1; A.4.1; A.5.1; A.6.1	C.1.1; C.1.2; C.1.3; C.1.4; C.1.5 C.2.1; C.2.2; C.2.3; C.2.4; C.2.5 C.3.1; C.3.2; C.3.3 C.4.1; C.4.2; C.4.3 C.5.3; C.5.4
U.S. Navy Surgeon General/ U.S. Navy Bureau of Medicine and Surgery		B.1.1; B.2.1; B.3.1 C.2.6; C.2.7

Please provide comments by May 6, 2011.

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Table of Contents

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Background and Objective

Background

This assessment was initiated in June 2009, in response to a complaint brought to the Department of Defense (DoD), Office of Inspector General (OIG), alleging that a military physician was conducting sub-standard human subject research on deployed, injured U.S. Service members in Iraq. This research protocol[1], "The Use of Anti-Oxidants to Reduce Sequela of Mild Traumatic Brain Injury[2] (mTBI) After Blast Exposure" (hereafter referred to as the "Clinical Trial[3]"), was conducted by a U.S. Navy physician (hereafter referred to as the "Investigator" or "Researcher") at Camp Al Taqaddum (hereafter referred to as "Camp TQ"), Iraq, between December 2008 and March 2009.

The research protocol proposed that early treatment with the antioxidant n-Acetylcysteine (NAC)[4] could reduce the effects of mTBI after a concussion, specifically, dizziness and hearing loss. According to a U.S. Army official, this study was the first clinical drug trial conducted with U.S. Service members in a combat zone. Potential human subjects for this study were deployed U.S. Service members, recently exposed to a blast incident (e.g., improvised explosive devices) and evacuated to Camp TQ for evaluation and treatment.

Clinical Drug Trial at Camp TQ

Between December 2008 and March 2009, the Investigator conducted a clinical drug trial at Camp TQ, using approximately 80 U.S. Service members as human subjects. The research protocol was reviewed and authorized by the following U.S. Army medical research oversight authorities. (For a summary of the process and an approximate timeline, please see Appendix D.)

> ***Research Institutional Official.*** The Multi-National Corps – Iraq (MNC–I)[5] Surgeon was the Research Institutional Official responsible for the review and approval of research protocols conducted in Iraq. His office had been designated by the

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[1] A research protocol is a formal document detailing the study methodology and the scientific basis for the research to be conducted, and is used for review and approval of the research by oversight boards.

[2] Mild traumatic brain injury (also called concussion) in military operational settings is defined as an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact or motor vehicle accident which causes an alteration in mental status. Related symptoms may include: headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering and/or difficulty concentrating.

[3] A clinical trial is human subject research, conducted to assess the safety and effectiveness of a new medication, or a new dose or new indication for an existing medication.

[4] n-Acetylcysteine is an antioxidant derived from a naturally occurring amino acid.

[5] MNC–I and Multi-National Force – Iraq (MNF–I) were merged into U.S. Forces – Iraq (USF-I) on Jan. 1, 2010.

U.S. Army's Assistant Surgeon General for Force Projection to retain the DoD Assurance of Compliance[6] (hereafter referred to as "DoD Assurance") for medical research in Iraq. Accordingly, U.S. Army regulations and procedures were applicable in reviewing the research protocol.

Deployed Combat Casualty Research Team (referred to here as the "Deployed Research Team" or "DRT"). When this research protocol was requested, the DRT was physically located in Iraq, serving as research subject matter experts (SMEs) in support of the MNC–I Surgeon's role as responsible authority for the conduct of clinical research in Iraq. Members of the DRT had the conduct and facilitation of clinical research as their primary roles and clinical care as an additional duty.

Human Protections Administrator (HPA). The MNC–I HPA was responsible for evaluating research protocols for compliance with regulations governing human subject research. The Deputy Director of the DRT served as the HPA as an additional duty. Once the scientific peer review was completed, the Deputy Director of the DRT submitted the protocol to an Institutional Review Board for final evaluation.

Institutional Review Board (IRB). The United States Army Human Research Protections Office, U.S. Army Office of the Surgeon General, is responsible for oversight of all human subject research conducted or supported by the Army or under an Army Assurance. The MNC-I Assurance (DoD A20146) and the MNC-I Human Research Protections Program identified the Brooke Army Medical Center's (BAMC) Institutional Review Board (IRB) as the IRB of record (hereafter referred to as the "BAMC IRB" or "IRB".) Accordingly, the BAMC IRB is responsible for evaluating the protocol for human subject protection and compliance with the scientific peer reviewer's recommendations.

Scientific Peer Reviewers. The MNC-I's Human Research Protections Program plan requires scientific peer review to ensure that research is scientifically sound in its design and methods, and that the proposed research is worthy of performance. Specifically, the U.S. Army Institute for Surgical Research (USAISR) at Fort Sam Houston, TX, was responsible for the scientific peer review of Iraq research proposals.

Medical Monitor. Medical monitors are assigned to "greater than minimal risk" clinical studies. They are required to be independent of the research protocol to ensure maximum protection for the human subjects participating in the clinical study. They are typically healthcare providers with sufficient educational and professional experience to afford them the requisite skills to perform this oversight role.

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[6] An Assurance of Compliance (referred to as an "Assurance") is an official, legal document representing a commitment made by an institution of the U.S. Government, assuring that all activities related to human research will be guided by ethical principles and will comply with Federal regulations. An Assurance is required before any human subject research can be conducted.

Gray Team Report

In January 2009, the Chairman of the Joint Chiefs of Staff ordered a review of in-theater medical care provided to Service personnel suffering from TBI. This review was conducted by the "Gray Team," a multi-disciplinary DoD team with combat medical experience, as well as expertise in neurological, emergency, and trauma care. During February 2009, the Gray Team conducted brief visits of multiple sites throughout Afghanistan and Iraq. While at Camp TQ, the Gray Team identified concerns with the medical care of mTBI patients and the conduct of clinical research on mTBI patients. Specifically, the team identified concerns related to possible coercion of human research subjects, research protocol deviations, and misrepresentation of research data. The Gray Team leader shared these concerns directly with the U.S. Central Command (CENTCOM) Surgeon.

Deployed Research Team Report

As a result of concerns raised in the Gray Team report, the MNC–I Surgeon requested that the Director and HPA from the DRT travel to Camp TQ to conduct a review of the Clinical Trial. During their February 2009 visit, the DRT identified concerns related to the perceived coercion of subjects, in addition to apparent premature claims of treatment effectiveness. After discussing these concerns with the Investigator, several recommendations were implemented. (For a summary of the report, please see Appendix E.) Subsequently, the DRT report found the research largely compliant with applicable Federal, DoD and Department of the Army human research protection laws and regulations, and it recommended that the study be allowed to continue.

Complaint to DoD OIG

Despite the results of the Army's research review completed by the DRT and implementation of recommendations, a DoD official remained concerned that the Clinical Trial failed to meet appropriate standards of scientific rigor, that the Investigator's conduct was not ethical, and that the rights and welfare of the human research subjects were not appropriately protected. Consequently, this official contacted the DoD OIG in June 2009 and filed a complaint. As a result of that complaint, we initiated this assessment.

Objective

The overall objective of this assessment was to review the integrity of medical research conducted in Iraq to study an experimental treatment for mTBI. Specifically, our goals were to determine whether, in the conduct of this medical research:

- DoD guidance was violated, regarding the performance of research in Iraq on human subjects (U.S. Military personnel).
- Research misconduct occurred during this specific DoD-approved clinical research trial.

To achieve this objective, we reviewed the overall conduct of the Clinical Trial and potential impact on the rights and welfare of the participants. Specifically, we visited DoD organizations, conducted interviews, and reviewed records and standards pertinent to medical research. These standards included relevant U.S. Army and U.S. Navy regulations because, while the principal investigator for this research was a U.S. Navy physician, the U.S. Army

Surgeon General retained the DoD Assurance of Compliance for the Multi-National Corps – Iraq to conduct human subject medical research in Iraq.

Observation A.
Medical Research Misconduct

Observation A. Medical Research Misconduct

The management and conduct of the Clinical Trial were inconsistent with military standards for human subject medical research. Specifically, we identified concerns in the following areas:

- **A.1** A potential financial conflict of interest was not disclosed.
- **A.2** Documentation of funding is unclear.
- **A.3** An Investigational New Drug application was not submitted to the Food and Drug Administration.
- **A.4** There were deviations from the protocol approved for the Clinical Trial.
- **A.5** Patients were exposed to possible coercion or undue influence.
- **A.6** Research data was disseminated prior to the conclusion of the study.

This was caused by possible violations of regulations and guidelines related to standards of conduct and scientific rigor in the performance of human subject research.

As a result, the research integrity of the Clinical Trial was compromised. This jeopardized the rights of the research participants, as well as the standing of DoD research in the scientific community.

A.1 A potential financial conflict of interest was not disclosed

The Investigator was associated with patents involving NAC, the substance under examination in the Clinical Trial; however, this potential financial conflict of interest was not disclosed to the BAMC Institutional Review Board.

A.1 Applicable Criteria

- 18 United States Code (USC) Section 208, "Acts Affecting a Personal Financial Interest," January 3, 2007, provides for criminal penalties for financial conflict of interest violations.
- The Department of Defense's Regulation, DoD 5500.7-R, "Joint Ethics Regulation," August 1, 1993, provides that a DoD military employee has a duty to follow ethics rules and specifically to disclose potential financial conflicts of interest.
- Secretary of the Navy Instruction (SECNAVINST) 3900.39D, "Human Research Protection Program," November 6, 2006, defines conflict of interest in section 6.b as "any situation in which financial or personal interests may compromise or present the appearance of compromising an individual's or group's judgment in supporting research." Additionally, "investigators must disclose all conflicts of interest, including any financial interests," to the IRB.
- The Multi-National Corp – Iraq's "Human Research Protection Program" (MNC–I HRPP), June 24, 2008, Section 3.2, states that an investigator is "obligated to disclose any possible conflict of interest prior to protocol review and approval." Additionally, this document identifies "possible conflicts of interest to include a proprietary interest in the tested product, including, but not limited to, a patent, a trademark, copyright, or licensing agreement."

A.1 Findings

a. The Investigator was listed as an inventor on two U.S. patents which are associated with the use of n-Acetylcysteine (NAC). Specifically:

- "Prevention or Reversal of Sensorineural Hearing Loss Through Biological Mechanisms - Patent no.: US 6,177,434 BI, dated Jan. 23, 2001"
- "Prevention or Reversal of Sensorineural Hearing Loss Through Biological Mechanisms - Patent no.: US 6,649,621 B2, dated Nov. 18, 2003"

b. A review of the research protocol application, that was completed and submitted by the Investigator, did not identify any conflicts of interest.

c. We consulted with a counsel and intellectual property attorney at the Naval Medical Research Command who stated that the two U.S. patents (listed under a.) ... "related to the

methods of use of NAC" as implicated in the research protocol." Additionally, this Navy official explained that the "existence of these patents could have been disclosed" when the Investigator submitted the research protocol to the IRB.

d. The Chairman of the BAMC IRB stated during an interview that the board was not aware that the Investigator held patents that were related to the Clinical Trial. Additionally, he acknowledged that the patents should have been disclosed during the research application process. Furthermore, he explained that the IRB should have asked about any potential conflicts of interest.

A.1 Discussion

The Investigator was listed as an inventor on U.S. patents, which specifically related to NAC, the drug implicated in the Clinical Trial. However, neither the "Human Use Protocol" template received by the BAMC IRB from the Investigator, or subsequent correspondence with the Investigator, contained disclosure of this fact. Under military and federal medical research regulations, disclosure of potential conflicts of interest is clearly defined as the responsibility of the Investigator, but there was no indication that he adhered to this standard. Consequently, the IRB did not consider the impact of the Investigator's NAC patents during their review of the Clinical Trial, constraining their ability to make adequately informed decisions. Furthermore, since the IRB lacked this pertinent information, it was impossible for study participants to have been made aware of it under their right to informed consent.

A.1 Conclusion

The Investigator failed to disclose a potential conflict of interest that should have been considered by the BAMC IRB prior to rendering a decision to approve the Clinical Trial. Consequently, the conduct of the Clinical Trial was inconsistent with regulations governing human subject medical research. As such, the validity of the research became questionable, and the rights of the research participants were jeopardized.

A.1 Recommendations, Management Comments, and Our Response

Recommendation A.1.1 Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation on February 18, 2010.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) did not concur with our recommendation that the Navy conduct the investigation. He explained that although the investigator was a Navy physician, he (the investigator) conducted his research efforts under the Army's human research assurance issued to CENTCOM and the U.S. Army Brooke Army Medical Center (BAMC) Institutional Review Board. Consequently, BUMED believed that the Navy had no authority regarding this specific Clinical Trial nor would it have had any cognizance of its conduct or progress. Therefore, the Chief, BUMED recommended that these allegations be assigned to the appropriate Army medical command that had the responsibility for approval and oversight of the research.

Our Response

We concur with BUMED's recommendation. The Clinical Trial was conducted under the authority of MNC-I, a joint-service command in Iraq, which held the Army's assurance giving them the responsibility for the oversight of research in Iraq. Consequently, on March 7, 2011, we requested that the Army complete the investigation into the allegations of potential medical research misconduct (see Appendix H).

Revised and Redirected Recommendations

Recommendation A.1.1 is revised as follows:

We recommend that the U.S. Army Medical Command:

A.1.1 Conduct an investigation into allegations of potential medical research misconduct by a U.S. Navy physician. Specifically, investigate the allegations that the researcher failed to disclose potential financial conflicts of interest while conducting research in Iraq.

A.2 Source of funding used to support Clinical Trial is unclear

The Office of Naval Research (ONR) was listed as the funding source to support the Clinical Trial; however, ONR could not find any evidence that they provided the funding.

A.2 Findings

a. The research protocol application, that was completed and submitted by the Investigator, cited that "Funds will be required to conduct the study (buy the medicine) but these funds already exist as this study is pre-funded by the Office of Naval Research (ONR)."

b. An ONR official acknowledged that he could not find any evidence that ONR provided the funding for the Clinical Trial.

c. Navy officials from the Naval Medical Center in San Diego, CA and the Naval Medical Research Command (NMRC) in Silver Spring, MD stated that they could not locate funding documents related to the Iraq research. Additionally, a senior official from NMRC clarified that they had "suspended project funded during the time that (the Investigator) was deployed."

A.2 Discussion

The Investigator submitted a research protocol application to the IRB. In this application he

identified that funds needed to support the Clinical Trial were provided by ONR. However, in discussion with an ONR Navy official, they acknowledged that they could not find any evidence that ONR provided funding to support the Clinical Trial at Camp TQ, Iraq. Additionally, both Naval Medical Center San Diego and the Naval Medical Research Command could not find any funding documents related to the Iraq research.

A.2 Conclusion

The funding documentation for the Clinical Trial is unclear and requires investigation.

A.2 Recommendations, Management Comments, and Our Response

Recommendation A.2.1 Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation on February 18, 2010.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) concurred with our recommendation and initiated an investigation into allegations surrounding the source of funding for this Clinical Trial. The investigation was completed on February 4, 2011. BUMED determined that "as strictly defined under federal regulations, research misconduct per se was not discovered." However, they did acknowledge that a "lack of oversight, regulatory violations, and non-compliance with research financial management standards" were issues affecting the Research Protocol and other research system-wide.

~~(FOUO)~~ Consequently, BUMED indicated that they would take several actions to address these investigative findings. Specifically, BUMED will:

- ~~(FOUO)~~ Direct further investigation utilizing subject matter experts to more thoroughly detail compliance/non-compliance with research administration and management processes to include financial management standards. This investigation shall commence no later than March 31, 2011.
- ~~(FOUO)~~ Issue regulations for financial management of research funds by June 30, 2011. In addition, BUMED will establish a comprehensive Navy Medicine policy and regulation on research administration and management to include financial management standards and oversight. Expected completion date is October 31, 2011.
- ~~(FOUO)~~ Design, direct and implement comprehensive education and training conferences in research administration and management for research related personnel of all disciplines. This training will be completed within 60 days from the establishment of the Navy Medicine policy and regulation on research administration and management.

~~(FOUO)~~ In addition, the Chief, BUMED recommended that the U.S. Army Medical Command also conduct an investigation into the funding source for this research project given that only the "Army would have access to specific information regarding use of time, effort or resources in the CENTCOM area of responsibility."

Our Response

The Chief, BUMED's comments are responsive and the actions meet the intent of the recommendation as stated in the draft report. Once completed, BUMED should forward the findings and results of their additional investigation into allegations surrounding compliance/ non-compliance with research administration and management processes to the DoD OIG.

~~(FOUO)~~ Furthermore, we concur with BUMED's comments that additional investigation may be needed to fully investigate all concerns related to the funding of this Clinical Trial. The Clinical Trial was conducted under the authority of MNC-I which held the Army assurance giving them the responsibility for the oversight of research in Iraq. Consequently, our position is that the Army work collaboratively with BUMED to ensure that all concerns are properly investigated.

Added Recommendations

As a result of BUMED's comments and our response we have added recommendation A.2.2 as follows:

We recommend that the U.S. Army Medical Command:

A.2.2 Coordinate with BUMED to ensure that all matters concerning the source of funding for the Clinical Trial are properly investigated.

A.3 An Investigational New Drug application was not submitted to the Food and Drug Administration

The Clinical Trial examined the effectiveness of an experimental drug on human subjects, thereby requiring an Investigational New Drug (IND) application. However, an IND was not submitted.

A.3 Applicable Criteria

- 21 Code of Federal Regulations (CFR), Part 312, "Investigational New Drug Application," April 1, 2008, states that an IND is required for the clinical investigation of a drug product supporting a new indication[7] for use, or involving a patient population or other factors that may increase the risks associated with use of the drug.
- Both Army and Navy regulations require an IND when a drug is to be used for an unapproved indication in a clinical trial:

[7] The medical term "indication" refers to a condition for which a particular course of action is advised.

- Army Regulation (AR) 40-7, "Use of Investigational Drugs and Devices in Humans and the Use of Schedule 1 Controlled Drug Substances," January 4, 1991, defines a drug as investigational "when the composition is such that its proposed use is not recognized for the use under the conditions prescribed, or its proposed use is not recommended or suggested in its approved labeling."
- Additionally, AR 40-7, section 4-12 stipulates that a physician in an Army treatment facility is conducting a clinical investigation requiring an IND when using an approved drug for an unapproved indication "in situations where data on drug effects from one or more patients are being systematically recorded by a physician for the purpose of substantiating or refuting a claim of therapeutic efficacy in an unlabeled indication for an approved drug."
- Furthermore, AR 40-7 further stipulates that an IND is required unless ALL of the following apply: The investigation will not be reported as a well controlled study in support of a new indication for use... nor any other significant change in labeling[8]; the investigation does not support a significant change in advertising for a lawfully marketed prescription drug product; the route of administration, dosage level, patient population or other factors do not significantly increase risks associated with the product; the investigation complies with Army requirements for human use review and informed consent; AND the drug is not being promoted as safe or effective for the purposes under investigation.
- U.S. Navy Bureau of Medicine and Surgery Instruction (BUMEDINST) 3900.6B, "Protection of Human Subjects," October 4, 2001, Enclosure 2 defines "unlabeled use" in research as "any deviation from the indications, dose, route of administration, dosage form or treatment population of a drug approved or licensed by FDA." It further clarifies that "treatment of an individual patient" is considered the practice of medicine, and "a scientific study using human research participants" is considered research, is regulated by the FDA and usually requires an IND.

A.3 Findings

a. The Food and Drug Administration (FDA) is responsible to protect the public's health by assuring the "safety, efficacy and security of human drugs." Specifically, the FDA's Center for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs to ensure that they are safe and effective for human use. Accordingly, the clinical divisions within the CDER offer consultation on IND matters for researchers and research agencies.

b. Per the FDA, an "Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population." Furthermore, the FDA stipulates that clinical drug trials require that an IND is reviewed by the FDA and the local institutional review board prior to initiation of the research.

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[8] FDA pharmaceutical labeling regulations and supplement labeling guidelines protect consumers by establishing criteria for the communication of product claims and other important product information.

c. The hypothesis that was listed by the Investigator on the research protocol application proposed that "the administration of NAC (n-Acetylcysteine) for seven days along with observation will result in improved hearing and balance function in individuals who demonstrate these disorders after blast exposure when compared to observation alone at the seven day time point."

d. While there are forms of NAC that are approved as drugs (e.g. Mucomyst Solution for Tylenol overdose) under FDA regulations, the substance under examination in this Clinical Trial is an antioxidant tablet sold in retail stores as an unregulated nutritional supplement[9].

e. The Scientific Peer Reviewer and the BAMC IRB questioned the Investigator to ascertain whether an IND application was needed to support the Investigator's use of NAC as part of the Clinical Trial. In response, the Investigator stated that "the FDA has repeatedly said that an IND is not needed for the dose of medication we are using." The IRB accepted the Investigator's response and approved the research protocol as submitted by the Investigator.

f. In response to our query, the U.S. Army Medical Materiel Development Activity (USAMMDA) requested that the FDA review the research protocol application to determine if an IND was required to administer NAC tablets as intended in the protocol. Accordingly, the FDA determined that an "IND was necessary for FDA review". Additionally, they (the FDA) explained that "any substance intended for use in diagnosis, cure, mitigation, treatment or prevention of disease…is a drug". Furthermore, they added that "if the substance (drug) is not a lawfully marketed drug product, it cannot be administered to humans without being the subject of an IND."

g. The Investigator initiated the Clinical Trial in December 2008 and administered NAC to research subjects without the necessary IND application.

A.3 Discussion

The Clinical Trial proposed to examine the effectiveness of an experimental drug, specifically NAC, to support a new, unapproved indication for its use, in treating U.S. service members with concussion injuries in combat-deployed environments. Under federal and military medical research regulations, submission of an IND application was required before the Investigator was permitted to begin recruiting human subjects and conduct any research. In response to our query, a Food and Drug Administration (FDA) letter confirmed that an IND was, indeed, required for this Clinical Trial.

The question whether an IND was needed for the Clinical Trial was first raised during the scientific peer review and later by the BAMC IRB. In both instances, the Investigator's responses dismissed the concern and insisted this standard was not applicable to the Clinical Trial. Consequently, the Clinical Trial was authorized by the IRB, and the research was

[9] "Nutritional supplements" are not regulated by the FDA, because they are intended to supplement the diet with nutrients the body utilizes in normal, healthy functioning.

conducted on U.S. Service members without the required FDA oversight to ensure research quality, treatment effectiveness, and participant safety.

A.3 Conclusion

The Investigator did not submit an IND application in support of his Clinical Trial. Additionally, the BAMC IRB accepted the Investigator's responses that an IND was not necessary. Consequently, the conduct of the Clinical Trial without an IND was inconsistent with regulations governing human subject medical research. As such, the validity of the research became questionable, and the rights of the research participants were jeopardized.

A.3 Recommendations, Management Comments, and Our Response

Recommendation A.3.1 Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation on February 18, 2010.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) did not concur with our recommendation that the Navy conduct the investigation. As previously discussed under the Management Comments in Observation A.1, the Chief, BUMED recommended that any allegations pertaining to research misconduct should be assigned to the appropriate Army medical command that had the responsibility for approval and oversight of the research.

Our Response

We concur with BUMED's recommendation and on March 7, 2011, requested that the Army complete the investigation into the allegations of potential medical research misconduct (see Appendix H).

Revised and Redirected Recommendations

Recommendation A.3.1 is revised as follows:

We recommend that the U.S. Army Medical Command:

A.3.1 Conduct an investigation into allegations of potential medical research misconduct by a U.S. Navy physician. Specifically, investigate the allegations that the researcher failed to submit an Investigational New Drug (IND) application prior to initiating his research in Iraq.

A.4 There were deviations from the research protocol approved for this Clinical Trial

The Investigator administered to study participants unapproved, undocumented treatments that deviated from the approved research protocol.

A.4 Applicable Criteria

- MNC-I's Human Research Protection Program, June 24, 2008, states that the Principal Investigator is responsible to report "any proposed changes to the research activity." Additionally, this policy stipulates that "changes shall not be initiated without prior IRB review and approval."
- Brooke Army Medical Center (BAMC) IRB Standard Operating Procedures (SOPs), July 7, 2008, identify the procedures used to submit amendments to approved protocols. Specifically, page 47 states that "an amendment is defined as any change in the approved study protocol" and that "all amendments must be submitted to the IRB prior to instituting the change."

A.4 Findings

a. The MNC–I approved Clinical Trial specified the experimental treatment[10] as "NAC along with observation" for seven days. The control group was to receive only "placebo medicine and observation."

b. The research protocol application, prepared and submitted by the Investigator, acknowledges that the Investigator will report any "protocol deviations" to the Chairman of the BAMC IRB.

c. The Deployed Research Review Team (DRT) acknowledged in their report to the MNC-I Surgeon that the investigator was using other treatment to include "active rehabilitation and exercise" during the conduct of the Clinical Trial. Additionally, the DRT referenced a presentation that the Investigator conducted at Camp TQ, whereby he (the Investigator) cited in a briefing that he was using "active rehabilitation" in the care of mTBI patients. Specifically, one slide stated "Recent modification in procedures (addition of active rehabilitation) has increased seven day cure rate to 85%."

d. Our review of the IRB minutes and other documentation related to the research protocol

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[10] A treatment is any "specific procedure used for the cure or the amelioration of a disease or pathological condition." The "experimental treatment" that is referred to in this report indicates the treatment that was approved by the Institutional Review Board, specifically, administering NAC and then observing whether the research participants noted any effect from taking the NAC.

did not reveal that the Investigator had submitted any proposed changes to the description of the study. Specifically, we did not find evidence that he added "active rehabilitation" and/or "exercise" as a form of treatment that he proposed to study.

A.4 Discussion

The Investigator proposed in his research protocol to study whether the administration of NAC, along with observation, would improve symptoms related to mTBI. The BAMC IRB recommended approval for this study based on the research protocol that the Investigator submitted which indicated "NAC" and "observation" as the methods of treatment.

According to the DRT, the Investigator referred to additional treatments, specifically, "active rehabilitation" and "exercise", when he made a presentation to visiting officials at Camp TQ. Our review of the approved research protocol and IRB minutes, revealed that there was no mention of "active rehabilitation and exercise" under the design section (section 5.4) of the protocol. Military medical research regulations require deviations to an approved protocol to be submitted to an IRB prior to implementation in a research study. However, there was no indication that the Investigator adhered to this standard.

A.4 Conclusion

The Investigator utilized unapproved treatments that were not part of the approved research protocol. Deviations from the approved protocol are inconsistent with DoD medical research regulations. As such, the validity of the research became questionable, and the rights of the research participants were jeopardized.

A.4 Recommendations, Management Comments, and Our Response

Recommendation A.4.1 Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation on February 18, 2010.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) did not concur with our recommendation that the Navy conduct the investigation. As previously discussed under Management Comments in Observation A.1, the Chief, BUMED recommended that any allegations pertaining to research misconduct should be assigned to the appropriate Army medical command that had the responsibility for approval and oversight of the research.

Our Response

We concur with BUMED's recommendation and on March 7, 2011, requested that the Army complete the investigation into the allegations of potential medical research misconduct (see Appendix H).

Revised and Redirected Recommendations

Recommendation A.4.1 is revised as follows:

We recommend that the U.S. Army Medical Command:

A.4.1 Conduct an investigation into allegations of potential medical research misconduct by a U.S. Navy physician. Specifically, investigate the allegations that the researcher deviated from the approved research protocol while he was conducting research in Iraq.

A.5 Patients were exposed to possible coercion and undue influence

Mandatory transport of Service members with blast injuries to Camp TQ contributed to a perception of coercion and undue influence to participate in the Clinical Trial.

A.5 Applicable Criteria

- 32 CFR, Part 219, "Protection of Human Subjects," July 1, 2008, includes guidance for protecting subjects from unnecessary risk, stipulating that additional safeguards should be included "when some or all of the subjects are likely to be vulnerable to coercion or undue influence."
- AR 70-25, "Use of Volunteers as Subjects of Research," January 25, 1990, cautions that human subject research should minimize risk to the subjects. It also acknowledges that some participants may be vulnerable to coercion and undue influence and requires "proper additional safeguards" to protect their rights and welfare.

A.5 Findings

a. The Investigator conducted the Clinical Trial at Camp TQ from December 2008 to March 2009. Specifically, he used NAC as a form of treatment to reduce the effects of mTBI after blast exposure.

b. Multi National Forces-West (MNF-West) Fragmentary Order (FRAGO) 445-08, February 01, 2009, required evacuation of Service members with blast injuries to Camp TQ for a medical evaluation.

c. The Gray Team expressed concerns during their visit to Camp TQ in February 2009, that

the Investigator was sharing "pilot data" from his study. Particularly concerning to this team was the concern that the research was conducted as a "placebo-controlled, double blind study"[11] and results were discussed prior to the conclusion of the research. Additionally, they expressed their concern that the FRAGO requiring the transport of Service members who were exposed to a blast injury could be interpreted as a form of coercion or undue influence for wounded Service members to participate in the Clinical Trial.

d. During our interview, a U.S. Navy official from Camp TQ's Surgical Company stated that Camp TQ's surgeons were concerned that they were underutilized. Specifically, the surgeons expressed the concern that patient volume was very light and that medevac helicopters were bypassing Camp TQ to bring patients directly to the nearest Army Combat Support Hospital. Additionally, the U.S. Navy official explained that the Investigator felt that he was at Camp TQ for the purpose of completing research and that the low patient volume was making it difficult for him to conduct his research. Furthermore, he acknowledged that the Investigator expressed support to have mTBI patients transported to Camp TQ in support of what he (the Investigator) called the "Center of Excellence for TBI."

e. As a result of the Gray Team's concerns of possible coercion of research participants, the Deployed Research Team (DRT) was sent to conduct a review of the Clinical Trial that was conducted at Camp TQ. The DRT agreed that the FRAGO led to perceived coercion of Marine mTBI patients to participate in the research, and stated in their report that "the strategy may appeal to a military member's sense of honor, duty and loyalty in such a way that they may feel obligated to enroll." The DRT's report concluded, however, that the "Investigator acted to mitigate this perception by separating the processes used for medical evaluation and solicitation of research subjects."

f. Additionally, the DRT in their report to the MNC-I Surgeon acknowledged that the Investigator had been interviewed by U.S. Marine Corps reporters in December 2008 and January 2009. Information in various articles and press releases referred to the Investigator's research and made reference to Camp TQ as the "hub of TBI treatment" and "TBI Center of Excellence". Specifically;

- Press Release 081222-M-81871-001, "AT-Taqaddum, Iraq"

"The Theater TBI Center of Excellence, a result of (the Investigator's) two-year initiative, is the first of its kind here in Anbar. It was established initially in September and finalized as the province's hub of TBI treatment in December."

- Press Release 081228-MLG-81871-TBI, "Navy captain's crusade against TBI takes root in Anbar TQ treatment center first of its kind"

"So we recognized the fact that although we're set up to do 'blood and guts' surgery,

[11] A placebo-controlled, double blind study is a research study where one group of research subjects is given a medication, and the second group, called the control group, is given a placebo, and neither the researcher, nor the research subjects know who was given the medication or the placebo.

(Taqaddum Surgical) can take on a secondary mission." ... "Taqaddum Surgical's secondary mission: the Theater TBI Center of Excellence. The center... is the first of its kind here in Anbar. It was established initially in September and finalized as the province's hub of TBI treatment in December."

"Since the center has opened, 42 patients have received treatment. Thirty-five have returned to finish their deployments, 100 percent recovered."

"Whereas late patients only recovered to approximately 85 percent normalcy, patients seen immediately tend to recover to 100 percent normalcy."

- Press Release 090110-MLG-81871-HASC, "House Armed Services Committee reps tour Taqaddum Surgical"

"(Our methods) are almost considered to be policy, and these are the people who help influence policy," said (the Investigator), San Diego. (The Investigator) said he hopes to have persuaded the members to use their leverage to make Camp Taqaddum's mTBI treatment method policy for all services."

g. Furthermore, the DRT also acknowledged in their report that the Investigator had "caused significant confusion" by referring to "cure rates" and "early treatment" during the Investigator's presentation to Staff Members for the House Armed Services Committee. Specifically the Investigator cited the following on briefing slides;

- "Research indicates that early treatment can significantly reduce long and short term sequel (of mTBI)"
- "Achieved an overall 66% seven day cure rate (for reference the cure rate at 3 months without early treatment is less than 20%), and,
- "Recent modification in procedures (addition of active rehabilitation) has increased seven day cure rate to 85%"

h. During our interview, the leader of the DRT explained that the Investigator's reference to a TBI "cure" possibly influenced the decision for MNF-West to issue the FRAGO requiring transport of TBI patients to Camp TQ.

A.5. Discussion

The Gray Team identified concerns that mTBI patients at Camp TQ were coerced to participate in the Clinical Trial, in part because of undue influence from MNF-West FRAGO number 445-08, dated February 01, 2009, which required evacuation of Service members with blast injuries to Camp TQ for a medical evaluation.

As a result of the Gray Team's report, the DRT was sent to conduct a review of the Clinical Trial that was conducted at Camp TQ. The DRT agreed that the FRAGO led to perceived coercion of Marine mTBI patients to participate in the research, and stated in their report that

"the strategy may appeal to a military member's sense of honor, duty and loyalty in such a way that they may feel obligated to enroll." However, the DRT felt that the Investigator acted to "mitigate this perception by separating the processes used for medical evaluation and solicitation of research subjects."

The DRT also observed that the Investigator had generated a high level of visibility for the research being conducted at Camp TQ, due to U.S. Marine Corps press releases and presentations to government officials citing "100% recovery" rates and referring to Camp TQ as the "Theater TBI Center of Excellence."

Furthermore, when we raised questions regarding the potential of coercion, a Navy official explained that the surgeons at Camp TQ were concerned that their skills were underutilized due to the low patient volume and the Investigator was concerned that his ability to do research was hindered by the low patient volume. Additionally, the Navy official acknowledged that the Investigator felt that the identification of Camp TQ as a "Center of Excellence for TBI" would support getting more patients at Camp TQ, which would help allay the surgeon's concerns that they were underutilized.

A.5 Conclusion

The Investigator's claims regarding the effectiveness of his treatment (e.g. NAC) and the benefit of "early treatment" of concussive injuries were premature. Specifically, the Clinical Trial was conducted as a placebo-controlled, double blind study which required that neither the researcher nor subjects knew who received the experimental drug or treatment and who received the placebo. Additionally, the interpretation of these research results was expected to occur after conclusion of the Clinical Trial. However, the Investigator made claims in December 2008 and January 2009 (prior to the conclusion of the research) that he noted Service members were "100% recovered". Additionally, he made unsubstantiated references to Camp TQ as a "Theater TBI Center of Excellence". Consequently this information was inconsistent with the tenants of valid research and constituted potentially improper actions by the Investigator as well as undue influence which may have contributed to the issuance of the FRAGO mandating transport of mTBI patients.

The mandatory transport of Service members with blast injuries to Camp TQ exposed potential research participants to coercion and undue influence, as well as to increased risk due to unnecessary travel. Furthermore, these consequences are inconsistent with regulations governing the conduct of medical research. As such, the rights of the research participants were jeopardized.

A.5 Recommendations, Management Comments, and Our Response

Recommendation A.5.1 Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation on February 18, 2010.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) did not concur with our recommendation that the Navy conduct the investigation. As previously discussed under

Observation A.1, the Chief, BUMED recommended that any allegations pertaining to research misconduct should be assigned to the appropriate Army medical command that had the responsibility for the approval and oversight of the research.

Our Response

We concur with BUMED's recommendation and on March 7, 2011, requested that the Army complete the investigation into the allegations of potential medical research misconduct (see Appendix H).

Revised and Redirected Recommendations

Recommendation A.5.1 is revised as follows:

We recommend that the U.S. Army Medical Command:

A.5.1 Conduct an investigation into allegations of potential medical research misconduct by a U.S. Navy physician. Specifically, investigate the allegations that the researcher may have unduly influenced a Service member's participation in the Clinical Trial.

A.6 Research data were disseminated prior to the conclusion of the study

Prior to conclusion of the Clinical Trial, the Investigator released press notifications, and made presentations referring to research results.

A.6 Applicable Criteria

- DoD Directive 5230.09, "Clearance of DoD Information for Public Release", August 22, 2008, includes guidance that "Any official DoD information intended for public release that pertains to military matters ... or subjects of significant concern to the Department of Defense shall be reviewed for clearance prior to release."
- The MNC-I "Human Research Protection Program", June 24, 2008, provides specific policies and procedures for the regulatory review and approval of human subject research conducted under the authority of the MNC-I Surgeon. Specifically these guidelines require that the Public Affairs Officer must review and approve research-related presentations and publications, and that cleared presentations and publications must contain DoD/Department of the Army (DA) disclaimers in accordance with federal policy.

A.6 Findings

a. The Investigator conducted the Clinical Trial at Camp TQ from December 2008 to March 2009. Specifically, he used NAC as a form of treatment to reduce the effects of mTBI.

b. The Gray Team expressed concerns during their visit to Camp TQ in February 2009, that the Investigator was sharing "pilot data" from his study. Particularly concerning to this team was the concern that the research was conducted as a "placebo-controlled, double blinded study" and results were discussed prior to the conclusion of the research.

c. The Deployed Research Team (DRT) acknowledged in their report to the MNC-I Surgeon in February 2009 that the Investigator had made a presentation to staff officers for the House Armed Services Committee on January 10, 2009. Specifically, the Investigator made reference to results of his research at the "mTBI Center at Al Taqaddum Surgical":

- "Achieved an overall 66% seven day cure rate (for reference the cure rate at 3 months without early treatment is less than 20%)" and "Recent modification in procedures (addition of active rehabilitation) has increased seven day cure rate to 85%.

d. Additionally, the DRT identified a press release where there was mention of research results (Press Release 081228-MLG-81871-TBI, "Navy captain's crusade against TBI takes root in Anbar TQ treatment center first of its kind"):

- "Since the center has opened, 42 patients have received treatment. Thirty-five have returned to finish their deployments, 100 percent recovered."

- "Whereas late patients only recovered to approximately 85 percent normalcy, patients seen immediately tend to recover to 100 percent normalcy."

e. The statement of assurance signed by the Investigator states "I am aware that any presentation or publications resulting from this research must be cleared by the appropriate Public Affairs Office, undergo OPSEC review and be reviewed for release of actionable medical information."

f. Our review of available documents did not reveal that any of the articles, nor presentations made by the Investigator were cleared by appropriate authorities prior to their release. Additionally, they did not have the required DoD/DA disclaimer annotated on the documents.

A.6 Discussion

The DRT report cited specific references made by the Investigator demonstrating mTBI "cure rates" and "recovery rates," which were disseminated via U.S. Marine Corp press releases and a PowerPoint presentation to Staff Officers from the House Armed Services Committee. Because this release of information occurred while the Clinical Trial was ongoing, the DRT found it premature and misleading and recommended to the Investigator that he refrain from using such terminology. Additionally, the DRT recommended to the MNC-I Surgeon that these specific press releases be recalled.

Furthermore, the Clinical Trial called for a placebo-controlled, double blind experimental design, which required that neither the researcher nor any subjects knew who received the experimental drug or treatment and who received the placebo. Therefore, the basis on which the Investigator generalized premature results of the NAC research is unclear. The authority under which this scientific information was released also is not clear.

A.6 Conclusion

The Investigator's release of scientific information pertaining to the effectiveness of NAC in treating mTBI was misleading since the research was ongoing and the results were unavailable. Additionally, this premature release of information was inconsistent with military regulations governing research. As such, the validity of the research became questionable and the research participants' rights as human subjects were jeopardized.

A.6 Recommendations, Management Comments, and Our Response

Recommendation A.6.1 Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation on February 18, 2010.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) did not concur with our recommendation that the Navy conduct the investigation. As previously discussed under Observation A.1, the Chief, BUMED recommended that any allegations pertaining to research misconduct should be assigned to the appropriate U.S. Army medical command that had the responsibility for approval and oversight of the research.

~~(FOUO)~~ Notwithstanding any of the Army's investigative efforts, BUMED acknowledged that there is a need to ascertain whether the Investigator continued any mTBI project-related activities after returning from deployment. BUMED contends that such continuations would fall under the authority, responsibility and liability of the Investigator's parent command and DoD Component, namely Navy. Specifically, BUMED indicated that they would determine whether the Investigator notified and received approvals from the Naval Medical Center, San Diego Institutional Review Board and other authorities for such continued activities after his return from deployment. Furthermore, BUMED stated that they will determine whether relevant presentation materials, manuscripts for publication, or other similar materials received requisite reviews and approvals from the Navy chain of command and from Navy Medicine Public Affairs Officials per regulations.

Our Response

~~(FOUO)~~ We concur with BUMED's recommendation and on March 7, 2011 requested that the Army complete the investigation into the allegations of potential medical research misconduct. Additionally, we agree with BUMED's stated concern whether the Investigator continued any mTBI project-related activities upon his return from deployment, and if these activities were conducted with the approval of the appropriate Naval authority. We concur with BUMED's actions to conduct a review into these matters.

Revised and Redirected Recommendations

Recommendation A.6.1 is revised as follows:

We recommend that the U.S. Army Medical Command:

A.6.1 Conduct an investigation into allegations of potential medical research misconduct by a U.S. Navy physician. Specifically, investigate the allegations that the researcher may have disseminated research data prior to the conclusion of the study.

Additional Management Comments to Observation A and Our Response

Additional Management Comments

~~(FOUO)~~ The Chief, BUMED believed that we used the term "research misconduct" incorrectly in Observation A.1 through A.5. Specifically, he explained that the matters we discussed did not meet federal-wide (OSTP 2000 Federal Policy on Research Misconduct and 42 CFR 50 and 93) and agency-specific (DoDI 3210.7) definitions of research misconduct which include falsification, fabrication and plagiarism.

Our Response

We acknowledge BUMED's comments; however, our position is that we have used the term "research misconduct" appropriately. Our findings characterize deviations in the research protocol as well as irregularities in the conduct of the investigator which require investigation to determine if, in fact, research misconduct or other violations occurred.

Observation B.
Possible Sub-Standard Patient Care

Observation B. Possible Sub-Standard Patient Care

Wounded U.S. military Service members who participated in the Clinical Trial received treatment that was inconsistent with military standards for patient care. Specifically, we found that:

B.1 Neurological assessments did not adhere to clinical practice guidelines for mTBI.

B.2 The experimental drug was not approved by the Food and Drug Administration for clinical study.

B.3 Medications contraindicated[12] in the treatment of early mTBI were administered.

This was caused by possible violations of regulations and guidelines related to patient care.

As a result, deployed U.S. Service members being evaluated and treated for mTBI may have received sub-standard patient care.

[12] The medical term "contraindication" refers to a condition which makes a particular treatment or procedure inadvisable. For example, aspirin is contraindicated in babies because of the danger that aspirin will cause Reye Syndrome.

B.1 Neurological assessments did not adhere to clinical practice guidelines for mTBI

The neurological assessments for mTBI conducted on research participants did not include the Military Acute Concussion Evaluation (MACE) recommended by clinical practice guidelines and required by MNC–I orders.

B.1 Applicable Criteria

- The Multi National Corps – Iraq (MNC-I) Operational Orders (Tab G to Appendix 2 to Annex Q) "Mild Traumatic Brain Injury (Concussion)" and MNC-I Standard Operation Procedures Manual (Tab P, Appendix 4, Section Q) "Mild Traumatic Brain Injury," November 30, 2007, required all medical personnel to be aware of and use the Joint Theater Trauma System (JTTS) Clinical Practice Guideline (CPG) "Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting," November 2008. The MNC-I Operational Orders, SOP and the JTTS CPG specify that the Military Acute Concussion Evaluation (MACE) tool is to be used during a patient's neurological assessment.

B.1 Findings

a. The Gray Team expressed concern during their visit to Camp TQ in February 2009, that there was a lack of standard metrics to assess traumatic brain injury in patients at Camp TQ. Specifically, the Gray Team identified that the Investigator stated he was following theater mTBI treatment guidelines, including using the MACE tool. However, upon the Gray Team's questioning, the Senior Corpsman at Camp TQ stated he never had heard of the MACE, nor had they seen it used.

b. The JTTS CPG on the "Management of Mild Traumatic Brain Injury (mTBI)/ Concussion in the Deployed Setting" established the MACE as a standardized tool for evaluating the symptoms and cognitive defects that may occur as a result of a concussion injury.

c. During their visit to Camp TQ in February 2009, the Deployed Research Team (DRT) stated that the mTBI patients at Camp TQ "may or may not receive a MACE examination." Furthermore, the team acknowledged that the Investigator stated that "rather than do a MACE examination he (the Investigator) goes to the next step in the evaluation and performs additional testing to include a neurological examination, the TRAIL Making Test, Controlled Oral Word Association Test..." and other tests.

d. During our interviews with the members of the DRT, they acknowledged that there were no mTBI patients present at Camp TQ on the day of their visit in February 2009.

B.1 Discussion

The MACE is a required assessment tool for military physicians to use in evaluating mTBI in deployed settings. However, the DRT confirmed in their report that the Investigator did not employ the MACE in the neurological assessments he conducted on participants in the Clinical Trial. By military order, use of the guideline for the evaluation of mTBI and the MACE tool is clearly defined as the responsibility of medical personnel, but there was no indication that the Investigator adhered to this standard.

B.1 Conclusion

The Investigator's neurological assessment of the U.S. Service members who participated in the study did not include an examination using the MACE tool. Consequently, without a standardized baseline assessment tool, there was an increased risk that the Investigator and/or other medical staff overlooked subtle changes in the patients' neurological status that may have indicated a decline in their medical condition. Furthermore, this lack of adherence to established guidelines raises concerns regarding the adequacy of safeguards for the health and safety of the wounded U.S. Service members who participated in the study.

B.1 Recommendations, Management Comments and Our Response

Recommendation B.1.1 Allegations of sub-standard patient care performed by a U.S. Navy physician were referred to the U.S. Navy on February 18, 2010 for further investigation and a Quality of Care Review.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) concurred with our recommendation and completed a Quality of Care Review on November 30, 2010.

[redacted]

~~(FOUO)~~ [redacted]

~~(FOUO)~~ [redacted]

Our Response

The Chief, BUMED's comments are responsive and their actions meet the intent of the recommendation as stated in the draft report.

b(5)

~~(FOUO)~~ [redacted]

We acknowledge that such guidelines provide a path to take in the diagnosis and management for the clinician that is unfamiliar with the particular clinical presentation or scenario, and provides the scientific and research rationale behind it. Our experience shows us that most guidelines are consensus documents; meaning they represent the experts in the field getting together and hammering out a guideline that usually is adequate. We believe that the caveat about the clinical practice guideline not meaning to replace good clinical judgment should be interpreted as not allowing the guideline to limit or restrain the diagnostic or management steps that a clinician should take. Specifically, our position is the use of the MACE as a measurement criteria that is repeated over time is a minimum standard – it does not constrain the clinician from taking other measurement or surveillance steps, but it does compel the clinician to at least use the MACE assessment tool.

Notwithstanding our comments, we believe it would be beneficial to ask the Assistant Secretary of Defense (ASD) for Health Affairs (HA) to work with the Services and the Combatant Commanders to ensure that operational orders and procedures used to evaluate and manage mTBI patients are clear and are not in conflict with each other.

Revised and Added Recommendations

As a result of BUMED's comments and our response, Recommendation B.1.2 is added as follows:

We recommend that the Assistant Secretary of Defense for Health Affairs:

B.1.2 Coordinate a review of the Joint Theater Trauma System (JTTS) Clinical Practice Guideline (CPG) "Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting". Additionally, coordinate with the Services and the Combatant Commanders to ensure that current operational orders and procedures are clear and meet the standard of care for the care of mTBI patients.

b(5)

B.2 The experimental drug was not approved by the Food and Drug Administration for clinical study

Wounded U.S. Service members participating in the Clinical Trial received an investigational new drug for the treatment of mTBI, which had not been reviewed and approved for clinical study by the Food and Drug Administration (FDA).

B.2 Applicable Criteria

- Both Army and Navy regulations require that an application for an Investigational New Drug (IND) is submitted to the FDA when a drug is to be used for an unapproved indication in a clinical trial:
  - AR 40-7, "Use of Investigational Drugs and Devices in Humans and the Use of Schedule 1 Controlled Drug Substances," January 4, 1991, defines a drug as investigational "when the composition is such that its proposed use is not recognized for the use under the conditions prescribed, or its proposed use is not recommended or suggested in its approved labeling."
  - Additionally, AR 40-7, section 4-12 stipulates that a physician in an Army treatment facility is conducting a clinical investigation requiring an IND when using an approved drug for an unapproved indication "in situations where data on drug effects from one or more patients are being systematically recorded by a physician for the purpose of substantiating or refuting a claim of therapeutic efficacy in an unlabeled indication for an approved drug."
  - AR 40-7 further stipulates that an IND is required unless ALL of the following apply: The investigation will not be reported as a well controlled study in support of a new indication for use... nor any other significant change in labeling; the investigation does not support a significant change in advertising for a lawfully marketed prescription drug product; the route of administration, dosage level, patient population or other factors do not significantly increase risks associated with the product; the investigation complies with Army requirements for human use review and informed consent; AND the drug is not being promoted as safe or effective for the purposes under investigation.
  - U.S. Navy Bureau of Medicine and Surgery Instruction (BUMEDINST) 3900.6B, "Protection of Human Subjects," October 4, 2001, Enclosure 2, defines "unlabeled use" in research as "any deviation from the indications, dose, route of administration, dosage form or treatment population of a drug approved or licensed by FDA." It further clarifies that "treatment of an individual patient" is considered the practice of medicine, and "a scientific study using human research participants" is considered research, is regulated by the FDA and usually requires an IND.

B.2 Findings

a. The Food and Drug Administration (FDA) is responsible to protect the public's health by assuring the "safety, efficacy and security of human drugs." Specifically, the FDA's Center for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs to ensure that they are safe and effective for human use. Accordingly, the clinical divisions within the CDER offer consultation on IND matters for researchers and research agencies.

b. Per the FDA, an "Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population." Furthermore, the FDA stipulates that clinical drug trials require that an IND is reviewed by the FDA and the local institutional review board prior to initiation of the research.

c. The research protocol application that was completed by the Investigator, cited in his hypothesis that "the administration of NAC (n-Acetylcysteine) for seven days along with observation will result in improved hearing and balance function in individuals who demonstrate these disorders after blast exposure when compared to observation alone at the seven day time point." The research protocol further stated that the NAC proposed for use in this study was in tablet form.

d. While there are forms of NAC that are approved as drugs (e.g. Mucomyst Solution for Tylenol overdose) under FDA regulations, the substance under examination in this Clinical Trial is an antioxidant tablet sold in retail stores as an unregulated nutritional supplement.

e. Discussion with an FDA representative from the Division of Neurology Products, at the Center for Drug Evaluation and Research identified that the tablet form of NAC is not FDA approved. Additionally, he explained that any research protocol that proposes to study a product to treat a disease (for example to treat mTBI) could require an IND application. Furthermore, he specified that an IND is needed if the NAC is used to treat mTBI.

f. The research protocol application did not indicate that an IND application to use NAC was submitted to the BAMC IRB. Additionally, as discussed under Observation A.3, upon the questioning by the IRB, the Investigator claimed that "the FDA has repeatedly said that an IND is not needed for the dose of medication we are using."

g. In response to our query, the FDA's Center of Drug Evaluation and Research reviewed the research protocol application and provided a written determination that an "IND was necessary for FDA review". Additionally, they explained that "any substance intended for use in diagnosis, cure, mitigation, treatment or prevention of disease…is a drug." Furthermore, they added that "if the substance (drug) is not a lawfully marketed drug product, it cannot be administered to humans without being the subject of an IND."

h. The BAMC IRB recommended approval for the Clinical Trial and the Investigator conducted research at Camp TQ from December 2008 to March 2009 using NAC (without an IND) to treat mTBI symptoms.

B.2 Discussion

NAC in tablet form is used as a nutritional supplement and is not subjected to the regulations of the FDA. However, the NAC tablets administered in the Clinical Trial were used with the intent to treat a condition, specifically mTBI, therefore, according to federal and military medical research regulations, an IND application was required before the Investigator was permitted to begin the Clinical Trial. When questioned by the BAMC IRB, the Investigator explained that the FDA stated that an IND was not needed to use the NAC tablets. The IRB accepted the Investigator's response and recommended approval for the study without an IND in December 2008. Consequently, the Investigator proceeded to conduct research at Camp TQ, beginning in December 2008, using a substance that was not FDA approved or under an IND. Therefore, the human subjects in this study received an experimental drug without FDA oversight of research quality, treatment effectiveness, and participant safety and were exposed to increased risk to their health and safety.

B.2 Conclusion

The treatments administered to U.S. Service members through this Clinical Trial did not undergo the FDA scrutiny required of clinical trials conducted appropriately with an IND. This was inconsistent with military and federal guidelines for medical research and protection of human research subjects. As a result, the health and well being of these wounded Service members may have been jeopardized.

B.2 Recommendations, Management Comments and Our Response

Recommendation B.2.1 Allegations of sub-standard patient care performed by a U.S. Navy physician were referred to the U.S. Navy on February 18, 2010 for further investigation and a Quality of Care Review.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) concurred with our recommendation and conducted a Quality of Care Review. [redacted]

~~(FOUO)~~ [redacted]

Our Response

~~(FOUO)~~ The Chief, BUMED's actions meet the intent of our recommendation. [redacted]

The research was conducted under the authority of MNC-I, a joint-service command, which

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held the DoD Assurance giving them the responsibility for the oversight of research in Iraq. Additionally, the research was conducted on 80 Service members who represented a cross section of military services (U.S. Marine Corps – 57; U.S. Army National Guard – 13; U.S. Army – 5; and U.S. Navy – 5.)

Consequently, our position is that any additional effort to assess the health of the research subjects should be a joint DoD responsibility. Therefore, on February 17, 2011, we requested that the Assistant Secretary of Defense for Health Affairs (ASD[HA]) conduct the necessary health assessments of the 80 military personnel who participated in the mTBI clinical trial (see Appendix H).

Revised and Added Recommendations

As a result of BUMED's comments and our review, Recommendation B.2.2 is added as follows:

We recommend that the Assistant Secretary of Defense for Health Affairs:

B.2.2 Conduct health assessments to determine if there were any adverse effects on the health of the U.S. Service members who received n-Acetylcysteine (NAC) and participated in the mTBI clinical trial.

B.3 Medications contraindicated in the treatment of early mTBI were administered

Blast injured Service members received seizure and migraine medications for headaches, which were contraindicated for headaches resulting from concussion.

B.3 Applicable Criteria

- MNC–I Operational Orders (Tab G to Appendix 2 to Annex Q) "Mild Traumatic Brain Injury (Concussion)" state that narcotics should be avoided in the treatment of post-concussive symptoms.
- The Joint Theater Trauma System (JTTS) Clinical Practice Guideline (CPG) "Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting," November 2008, specifies that only acetaminophen (e.g., Tylenol®) should be used to treat a headache as a result of a concussion. Furthermore, the CPG states that narcotics are not indicated for the management of post-traumatic headaches. Additionally, the "Concussion Patient Information Sheet" included within the CPG clarifies that the

treatment of choice for headaches related to a concussion is acetaminophen. Furthermore, these instructions clarify that narcotics may cause significant sedation and interfere with a Service member's ability to perform.

B.3 Findings

a. A member of the Gray Team who visited Camp TQ in February 2009 explained during our interview that they observed several Service members who appeared "dazed" and "zombie-like, possibly due to medications." Additionally, the team acknowledged in their report that they had concerns that "he (the Investigator) has given these medications (Topiramate and Sumatriptan), by his report, to every single protocol patient" as "they all have headaches."

b. The MNC-I Surgeon sent the Deployed Research Team (DRT) to Camp TQ in February 2009 to conduct a review of the Clinical Trial based on concerns raised by the Gray Team. The DRT stated in their report that the Investigator was using "Sumatriptan and Topiramate in the treatment of mTBI." The DRT further explained that when questioned, the Investigator acknowledged that he only used these medications as "treatment for patients who have headaches and are not given to all patients but rather based on this symptom."

c. Sumatriptan is a medication used to treat migraine headaches. Side effects include drowsiness, dizziness and vomiting, among others.

d. Topiramate is an anti-seizure medication and can also be used to prevent migraine headaches. Side effects include difficulty concentrating, confusion, memory problems and drowsiness, among others.

e. The "Concussion Patient Information Sheet" that is included in the JTTS CPG for mTBI/Concussion lists the following symptoms (among others), which are associated with concussion: difficulty concentrating, confusion, difficulty remembering, insomnia/drowsiness/sleep disturbances, nausea/vomiting, and dizziness. The information sheet provides a warning that if these symptoms persist or do not improve within 24 hours, the patient should seek additional medical treatment.

f. During our interview, the senior member of the DRT explained that at the time of the DRT's visit to Camp TQ, there were no research participants available. Consequently, the team did not conduct any patient interviews or health record reviews, nor were there any research participants available to observe for any "dazed" behavior. Additionally, he explained that medications the Investigator used to treat the Service member's headaches were appropriate for headaches. Furthermore, he stated that he felt that the Investigator was "aggressive with his treatment of headaches" using Sumatriptan and Topiramate. However, he further clarified that he was not asked to do a quality of care review to determine whether the care provided was appropriate.

g. The senior member of the DRT was a physician with a clinical background in perinatology (a medical specialty related to the diagnosis and treatment of disorders affecting the mother and fetus or newborn during late pregnancy or childbirth.) He stated that in researching Sumatriptan and Topiramate he found that these medications were indicated to treat headaches; therefore, he felt this was acceptable treatment. Additionally, during the

discussion of his clinical background, he clarified that the treatment of TBI was not in his purview.

h. We interviewed one of the members of the Gray Team (a U.S. Army neurologist) who expressed concern whether the appropriate standard of care was delivered to those U.S. Service members suffering from mTBI who were participating in the Clinical Trial. Additionally, he clarified that "atypical headache medications" were "preferentially used" by the Investigator.

i. "Atypical" in the medical sense, refers to a deviation from normal. Therefore, the U.S. Army neurologist, who stated that the Investigator used "atypical headache medications", was referring to medications that were not normally used to treat headaches associated with a head injury (e.g. mTBI).

j. According to a Navy official assigned to Camp TQ, the Investigator "aggressively" treated research subjects for headaches.

B.3 Discussion

The clinical practice guidelines for the treatment of mTBI in theater specify that only acetaminophen (e.g., Tylenol®) should be used to treat headaches resulting from concussion. Additionally, these guidelines specifically stated that narcotics should be avoided.

The Investigator used medications such as Topiramate (an anti-convulsant medication used to treat seizures) and Sumatriptan (a migraine treatment) to treat headaches for patients with mTBI. These medications were not listed in the MNC-I approved research protocol, nor are they indicated for the treatment of headaches resulting from concussion or a head injury. Additionally, the side effects of these medications are similar to the symptoms of a concussion. Consequently, a Service member may be confused as to whether their continued symptoms are related to the concussion (and require medical attention) or to the side effects of medications they received due to headaches related to the concussion.

B.3 Conclusion

Although some anti-seizure and migraine medications are approved by the FDA to treat certain headaches, they are contraindicated for the early treatment of headaches resulting from concussion, because their side effects (memory problems, drowsiness, and confusion) can mask symptoms of a life-threatening intracranial hemorrhage or more severe concussion.

The DRT did not recognize that Topiramate and Sumatriptan were inappropriate medications for the treatment of headaches in the U.S. Service members participating in the Clinical Trial. Consequently, research participants were exposed to increased risk to their health and safety.

U.S. Service members that participated in the Clinical Trial received medications that were contraindicated for their condition, specifically, mTBI. This was inconsistent with military guidelines for patient care. As a result, the health and welfare of the participants may have been jeopardized. Therefore, a Quality of Care Review and health assessment are needed to determine whether human subjects were harmed as a result of participation in this research.

B.3 Recommendations, Management Comments and Our Response

Recommendation B.3.1 Allegations of sub-standard patient care performed by a U.S. Navy physician were referred to the U.S. Navy on February 18, 2010 for further investigation and a Quality of Care Review.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) concurred with our recommendation and conducted a Quality of Care Review. [redacted]

Our Response

~~(FOUO)~~ The Chief, BUMED's actions meet the intent of our recommendation. [redacted]

Our position is that any additional effort to assess the health of the research subjects should be a joint DoD responsibility. Therefore, on February 17, 2011, we requested that the Assistant Secretary for Health Affairs (ASD(HA)) conduct the necessary health assessments of the 80 military personnel who participated in the mTBI clinical trial (see Appendix H).

Revised and Added Recommendations

As a result of BUMED's comments and our response Recommendation B.3.2 is added as follows:

We recommend that the Assistant Secretary of Defense for Health Affairs:

B.3.2 Conduct health assessments to determine if there were any adverse effects on the health of the U.S. Service members who may have received medications that were contraindicated while they were participating in the Clinical Trial and undergoing treatment for a mTBI injury.

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Observation C.
Weaknesses in the Process used to Review and Approve Medical Research in Iraq

Observation C. Weaknesses in the Process used to Review and Approve Medical Research in Iraq

Weaknesses were noted in the process used to review and approve the research protocol for the proposed Clinical Trial in Camp TQ, Iraq. Specifically, we identified opportunities for improvement in the following areas:

- **C.1** Identifying and addressing potential conflicts of interest
- **C.2** Compliance with FDA regulations and guidelines
- **C.3** Communication during the scientific peer review
- **C.4** Selection and assignment of the Medical Monitor
- **C.5** Identification and protection of vulnerable populations
- **C.6** Investigation of medical research misconduct in joint-service environments

These weaknesses were caused by a lack of specificity and consistency in existing processes and tools, as well as by a lack of rigor which medical research authorities exercised during their review and approval of the research protocol.

As a result, the research integrity of the Clinical Trial was compromised and the rights of the human research subjects were jeopardized.

C.1 Identifying and addressing conflicts of interest

Although two potential conflicts of interest existed, processes used during the review and approval of medical research were not effective in identifying and addressing them.

C.1 Applicable Criteria

- 18 USC Section 208, "Acts Affecting a Personal Financial Interest," January 3, 2007, provides for criminal penalties for financial conflict of interest violations.
- The Department of Defense's Regulation, DoD 5500.7-R, "Joint Ethics Regulation," August 1, 1993, provides that a DoD military employee has a duty to follow ethics rules and specifically to disclose potential financial conflicts of interest.
- SECNAVINST) 3900.39D, "Human Research Protection Program," November 6, 2006, defines conflict of interest in section 6.b as "any situation in which financial or personal interests may compromise, or present the appearance of compromising, an individual's or a group's judgment in supporting research." Additionally, it mandates that "investigators must disclose all conflicts of interest, including any financial interests, to the IRB."
- The Multi-National Corp – Iraq's "Human Research Protection Program" (MNC–I HRPP), June 24, 2008, Section 3.2, states that "possible conflicts of interest include a proprietary interest in the tested product, including, but not limited to, a patent, a trademark, copyright, or licensing agreement."

C.1 Findings

a. The Investigator did not disclose his interest in U.S. patents related to NAC, which was the drug used in the Clinical Trial (see Observation A.1 "A potential financial conflict of interest was not disclosed".)

b. The BAMC IRB provided a templated form ("Human Use Protocol") for researchers to use when completing their application to submit a research proposal. This form included a section for each required research protocol element (e.g. Research Plan, Objectives, Hypothesis, and Design etc.) Researchers were required to use this templated form to ensure that all required components of their research protocol application were complete prior to the review by the IRB.

c. The Human Protection Administrator (HPA) of the Deployed Research Team (DRT) assisted the Investigator during his submission of the research protocol. The HPA reviewed the protocol as written and facilitated correspondence between the Investigator (who was in Iraq) and the BAMC IRB (which was in Texas) to address specific questions posed by the scientific reviewers and the IRB.

d. The MNC-I Surgeon requested that the DRT investigate concerns raised by the Gray

Team, in February 2009, regarding the conduct of the Clinical Trial at Camp TQ. Two members of the DRT, the Medical Director and the Deputy Director of the team, visited Camp TQ in February 2009. The Deputy Director of the team was designated as responsible for the Operation Iraqi Freedom Theater Human Research Protection Program and also served as the HPA where she specifically was responsible to assist the Investigator during the submission of his research protocol.

e. Our review of Army regulations revealed that the Army regulations lacked specific guidance regarding the policy and procedure for Investigators to identify and reveal potential conflicts of interest to institutional review boards. Additionally, these regulations do not address the purpose of and process used by deployed research review teams who help to provide a level of oversight for research conducted in-theater.

C.1 Discussion

The Investigator did not disclose his interest in U.S. patents related to NAC although both research regulations and the Joint Ethics Regulation established a duty to do so. The "Human Use Protocol" template used to submit the research protocol to the BAMC IRB did not specifically ask the investigator to disclose potential conflicts of interest. This contributed to a passive approach by which the IRB relied on the Investigator to fulfill his responsibility for disclosure.

The MNC–I Human Research Protection Program provides limited guidance on conflicts of interest. However, higher-level Army Regulations (AR 70-25 and 40-38) are 20 years old and lack specific guidance regarding the disclosure of potential conflicts of interest. Similarly, the BAMC IRB's Standard Operating Procedures (SOPs) do not specify a proactive process for identifying or prompting an investigator's disclosure of potential conflicts of interest.

Additionally, the Human Protection Administrator (HPA), who was involved in the application, review and approval of the Clinical Trial, also served as a reviewer on the Deployed Research Team, which was responsible to investigate potential violations related to the same research protocol.

C.1 Conclusion

Two potential conflicts of interest existed, which were not identified, nor addressed by research authorities. First was the Investigator's non-disclosure of a potential financial conflict of interest. Although, it is the researcher's responsibility to disclose financial conflicts of interest, the lack of a standardized approach by the BAMC IRB to request information on proprietary interests contributed to the board's lack of awareness of any potential conflicts of interest.

Secondly, research authorities did not recognize that a conflict of interest existed when one of the members of the DRT who investigated potential research misconduct was also involved in the review and approval process used during consideration of the research protocol.

As a result of the failure of research authorities to recognize and address conflicts of interest, in addition to the Investigator's non-disclosure of potential conflicts of interest, the validity of

the research became questionable, and the rights of the participants were jeopardized.

C.1 Recommendations, Management Comments and Our Response

Recommendation C.1.1: We recommend that the U.S. Army Medical Command review and update AR 70-25 and AR 40-38 to clarify requirements for disclosing potential conflicts of interest during the conduct of clinical research.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He stated that the Army would combine AR 70-25 and AR 40-38 into an updated consolidated Army human research protections regulation that clarifies the requirements for disclosing and managing potential and actual conflicts of interests that occur prior to and during the conduct of research involving human subjects. He expected this regulation to be approved by April 30, 2012. Additionally, the Commanding General explained that, in the interim, he would be sending a targeted message detailing these requirements to all Army Activities that support research involving human subjects by the date of our final report. Furthermore, he intended to follow-up with an official message to all Army Activities by March 15, 2011.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.1.2: We recommend that the U.S. Army Medical Command ensure the BAMC IRB's Standard Operating Procedures are updated to clarify requirements for disclosing potential conflicts of interest. Additionally,

Recommendation C.1.3: Implement the use of a "disclosure form" to be submitted along with research protocols for IRB consideration, in order to ensure potential conflicts of interest are identified by the Investigator and considered by the IRB.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendations. He stated that the Director, Army Human Research Protections Office will ensure that the BAMC IRB Standard Operating Procedures are updated to clarify requirements for disclosing potential conflicts of interest. Additionally, he explained that these procedures will include the use of a comprehensive "disclosure form" to ensure potential conflicts of interest are identified by the investigator and considered by the IRB. The SOPs will be updated, reviewed and approved by the date of our final report.

Furthermore, he explained that the Army has implemented a new process and procedures for medical research conducted in theater. Specifically, as of August 2010, the U.S. Central Command (USCENTCOM) now holds the Army approved DoD Assurance which covers research conducted in the Joint Operation Areas (JOA) of Iraq, Kuwait and Afghanistan. Furthermore, the U.S. Army Medical Research and Materiel Command (HQ USAMRMC) IRB now serves as the IRB of record for research conducted in these areas. Consequently, the

Commanding General, U.S. Army Medical Command explained that the current research policies and procedures, as developed by USCENTCOM and USAMRMC, meet the intent of the DoD OIG recommendations as stated in this report.

Our Response
The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.1.4: We recommend that the U.S. Army Medical Command ensure that there are policies and procedures in place for individuals or teams that are responsible to conduct research study reviews and investigations in a deployed setting. Specifically, ensure that individuals involved in the review of clinical research must be independent and not previously involved in the research protocol review and approval process.

U.S. Army Medical Command Comments
The Commanding General, U.S. Army Medical Command concurred with our recommendation. He explained that in March 2009, an independent MNF-I Human Protections Administrator (HPA) position was established to ensure that there was an objective review of research conducted in Iraq. Additionally, the Commanding General stated that USCENTCOM's Human Research Protection Plan and standard operating procedures clearly describes the HPA's responsibilities and that the HPA is independent of the now "Joint" (formerly "Deployed") Combat Casualty Research Team.

Our Response
The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.1.5: Pending the outcome of the U.S. Navy investigation, we recommend that the U.S. Army Medical Command conduct a review of the process used during the Deployed Research Team's visit to Camp TQ to identify any necessary changes needed to ensure that future reviews are complete and accurate.

U.S. Army Medical Command Comments
The Commanding General, U.S. Army Medical Command concurred with our recommendation. He identified that the Director, Army Human Research Protections Office, would conduct a review of the Deployed Combat Casualty Research Team's visit to Camp TQ to identify if changes were needed to ensure that future reviews were complete and accurate. This report is expected to be completed by May 15, 2011. Additionally, the Commanding General stated that once the investigation was completed, they would further evaluate if any additional changes were necessary to ensure that in-theater research reviews were complete and accurate.

Our Response
The Commanding General's comments are responsive. No further action is required.

C.2 Compliance with Food and Drug Administration regulations and guidelines

The BAMC IRB was not effective in acknowledging or complying with Food and Drug Administration (FDA) regulations for the conduct of clinical trials using Investigational New Drugs (IND).

C.2 Applicable Criteria

- 21 USC 321, Sec. 201, "Federal Food, Drug and Cosmetic Act," January 3, 2007, defines and differentiates drugs and new drugs.
- 21 CFR Part 312, "Investigational New Drug Application," April 1, 2008, states that an IND is required for the clinical investigation of a drug product that supports a new indication for use, or that involves a patient population or other factors that may increase risks associated with use of the drug.
- AR 40-7, "Use of Investigational Drugs and Devices in Humans and the Use of Schedule 1 Controlled Drug Substances," January 4, 1991, defines a drug as investigational "when the composition is such that its proposed use is not recognized for the use under the conditions prescribed, or its proposed use is not recommended or suggested in its approved labeling."
- Additionally, AR 40-7, section 4-12 stipulates that a physician in an Army treatment facility is conducting a clinical investigation requiring an IND when using an approved drug for an unapproved indication "in situations where data on drug effects from one or more patients are being systematically recorded by a physician for the purpose of substantiating or refuting a claim of therapeutic efficacy in an unlabeled indication for an approved drug." This regulation further stipulates that an IND is required unless ALL of the following apply: The investigation will not be reported as a well controlled study in support of a new indication for use... nor any other significant change in labeling; the investigation does not support a significant change in advertising for a lawfully marketed prescription drug product; the route of administration, dosage level, patient population or other factors do not significantly increase risks associated with the product; the investigation complies with Army requirements for human use review and informed consent; AND the drug is not being promoted as safe or effective for the purposes under investigation.
- BUMEDINST 3900.6B, "Protection of Human Subjects," October 4, 2001, Enclosure 2 defines "unlabeled use" in research as "any deviation from the indications, dose, route of administration, and dosage form or treatment population of a drug approved or licensed by FDA." It further clarifies that "treatment of an individual patient" is considered the practice of medicine, and "a scientific study using human research participants" is considered research, is regulated by the FDA and usually requires an IND.

C.2 Findings

a. The FDA is responsible to protect the public's health by assuring the "safety, efficacy and security of human drugs." Specifically, the FDA's Center for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs to ensure that they are safe and effective for human use. Accordingly, the clinical divisions within the CDER offer consultation on IND matters for researchers and research agencies.

b. Per the FDA, an "Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population." Furthermore, the FDA stipulates that clinical drug trials require that an IND is reviewed by the FDA and the local institutional review board prior to initiation of the research.

c. The Investigator hypothesized that "the administration of NAC (n-Acetylcysteine) for seven days along with observation will result in improved hearing and balance function in individuals who demonstrate these disorders after blast exposure when compared to observation alone at the seven day time point."

d. The form of NAC that was used in the Clinical Study was a tablet.

e. NAC in tablet form is available as a nutritional supplement sold in retail stores. This nutritional supplement is not regulated by the FDA as a drug.

f. The only forms of NAC that are FDA approved are solutions. Specific solutions approved are: 1) Inhaled solution for mucolytic therapy (dissolves thick mucus making it easier to cough up secretions in certain respiratory conditions such as bronchitis and pneumonia), and 2) Injectable solution used to treat acetaminophen (e.g., Tylenol®) overdose.

g. The tablet form of NAC is not approved by the FDA to treat mTBI.

h. Federal guidelines describe "drugs" as substances that are intended to diagnose, cure, mitigate, treat, or prevent disease.

i. In response to our query, the FDA reviewed the research protocol application and determined that an "IND was necessary for FDA review". Additionally, they explained that "any substance intended for use in diagnosis, cure, mitigation, treatment or prevention of disease…is a drug". Furthermore, they added that "if the substance (drug) is not a lawfully marketed drug product, it cannot be administered to humans without being the subject of an IND."

j. During our interview, the Chairman of the BAMC IRB acknowledged that one of the peer reviewers who conducted the scientific review of the research protocol, as well as the IRB itself, posed questions to the Investigator whether an IND was needed to use NAC in the Clinical Trial. In response, the Investigator stated than the "FDA has repeatedly said that an IND is not needed for the dose of medication we are using." (See Observation A.3, "An

Investigational New Drug Application was not submitted to the Food and Drug Administration".)

k. Our review of the research protocol template used by the Investigator to present his research proposal did not have a specific section related to experimental drugs or INDs. Additionally, the form used by the scientific reviewers did not have a section specific to experimental drugs or INDs.

l. The Chairman of the IRB did not remember if there was additional discussion during the board meetings specific to the need for an IND, nor could he remember if the IRB members considered the scientific reviewer's IND questions and the Investigator's responses to those questions prior to voting to recommend approval for this research protocol.

m. The Chairman of the IRB stated that he had extensive experience using NAC in the solution form as an FDA approved medication for Tylenol® overdose, and believed that the dosage as proposed by the Investigator fell within the adult dosage range for the drug. When asked about the Investigator's intent to use NAC pills (tablets) vice the FDA approved solution, he said that the Investigator explained that pills were an approved method.

n. We reviewed the IRB's minutes specific to this Clinical Study and found evidence of documentation of decisions made (e.g. Protocol recommended for approval), however did not find a description of discussions that occurred which led to those decisions. Specifically, there was limited evidence of deliberations/discussions regarding the use of NAC and possible need for an IND.

o. The BAMC IRB's Standard Operating Procedures (SOP) manual identified that a representative of the Pharmacy Department should be included as a member of the institutional review board. However, this SOP did not identify specific responsibilities for the pharmacy representative, nor did the SOP include any details for consideration of drug trials or IND requests.

p. The Chairman of the BAMC IRB acknowledged that they have a Pharmacist who is a member of the IRB, however, this Pharmacist was not present during the board's deliberations regarding the administration of NAC and the possible need for the Investigator to pursue an IND.

q. The Chairman of the IRB stated that he believed the members of the IRB "performed due diligence," however, may not have "pursued all avenues" available to the board in rendering a recommendation to approve the protocol as submitted without an IND.

r. The U.S. Army Medical Materiel Development Activity (USAMMDA) Division of Regulated Activities and Compliance (DRAC) serves as the U.S. Army subject matter expert regarding FDA regulations and IND determinations. An Army official from USAMMDA verified that neither the Investigator, nor the BAMC IRB, consulted with the DRAC regarding whether the NAC tablets, as intended for use in the Clinical Trial, needed an IND.

s. The BAMC IRB recommended approval of the research protocol in December 2008. Consequently, the Investigator initiated the Clinical Trial in December 2008 and administered NAC to research subjects without the necessary IND application.

C.2 Discussion

The research protocol that was submitted to the IRB for review and approval hypothesized that the Investigator intended to use NAC to improve hearing and balance function for those U.S. Service members who were exposed to blast injuries. While there are forms of NAC that are approved as drugs under Food and Drug Act (FDA) regulations (e.g. Mucomyst Solution for Tylenol® overdose), the substance under examination in this Clinical Trial is an antioxidant tablet sold in retail stores as an unregulated nutritional supplement.

One of the scientific reviewers and the BAMC IRB questioned whether an IND was required to use NAC as intended in the Clinical Trial. In response, the Investigator stated that the FDA indicated that an IND was not needed. Consequently, without further consideration, the IRB approved the research protocol and the Investigator administered NAC to U.S. Service members without an IND.

Although one member of the IRB was a pharmacist, that member was not consulted regarding the use of NAC and the possible need for an IND. Additionally, there was no evidence that the U.S. Army Medical Materiel Development Activity (USAMMDA) Division of Regulated Activities and Compliance (DRAC) was consulted regarding the intended use of NAC in the Clinical Trial. Furthermore, the BAMC IRB's SOP did not specify procedures for subject matter experts to be engaged when considering research protocols involving the use of a medication that may require an IND or that otherwise might fall beyond the scope of expertise of the IRB members present at the time of review of the research protocol.

Federal and Army regulations provide specific guidance on the factors that trigger the need for an IND application in proposed research, as well as the factors that permit exemption from this requirement. In addition, Federal guidelines define and differentiate drugs, new drugs, nutritional supplements, and the lawful labeling and marketing of each. NAC, as it was intended for use in this Clinical Trial, is considered a drug because it was used to treat a condition, specifically, hearing and balance impairments related to blast exposures. Given that the tablet form of NAC is not FDA approved to treat mTBI, this research was for a clinical drug trial that studied the effectiveness of an experimental drug on human subjects. Submission of the proposal to the FDA via an IND application was required. Additionally, the conduct of the Clinical Trial with an IND would provide an additional layer of scrutiny for the quality of research and safety of participants.

C.2 Conclusion

The FDA confirmed that the Clinical Trial required an IND. However, this requirement was not appropriately recognized and addressed by the BAMC IRB during the review and approval of the research protocol. Consequently, this study proceeded without required FDA scrutiny. As a result, the validity of the research became questionable, and the rights of the participants were jeopardized.

C.2 Recommendations, Management Comments and Our Response

Recommendation C.2.1: We recommend that the U.S. Army Medical Command conduct a review into the process used by the BAMC IRB which led to the decision to recommend approval for this research protocol without submission of an Investigational New Drug application.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He identified that the Director, Army Human Research Protections Office (AHRPO), will conduct a review into the process used by the BAMC IRB which led to the decision to recommend approval for this research protocol. Additionally, AHRPO will review the current BAMC IRB processes and SOPs to ensure that the system deficiencies that led to the failure to identify the requirement for an IND application in this case have been addressed. AHRPO's reports are to be completed by the date of the final report.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.2.2: We recommend that the U.S. Army Medical Command review and update AR 40-7 to clarify requirements regarding use of investigational drugs in medical research, to include intended use of nutritional supplements as experimental drugs. Additionally, identify the U.S. Army Medical Materiel Development Activity Division of Regulated Activities and Compliance as a consulting agency for researchers and institutional review boards regarding interpretation of FDA regulations and Investigational New Drug determinations.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He stated that the U.S. Army Medical Materiel Development Activity Division of Regulated Activities and Compliance (USAMMDA DRAC) will update AR 40-7 with respect to clarifying, based on FDA regulations and the latest guidance from the FDA, requirements for submission of IND applications for studies utilizing nutritional supplements as experimental drugs. Additionally, this update will include identifying USAMMDA DRAC as the consulting agency for interpretation of FDA regulations and IND determinations. This update is to be completed by April 30, 2012.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.2.3: We recommend that the U.S. Army Medical Command update the BAMC IRB's policies and procedures to ensure compliance with Investigational New Drug considerations and procedures. Additionally, ensure that these policies and procedures prompt consultation with a subject matter expert for FDA-related matters, particularly for Investigational New Drugs, as well as for any other matters outside the

scope of members of the IRB. Additionally;

Recommendation C.2.4: Develop a specific checklist for researchers to use at the time of protocol submission which identifies the criteria used in making an Investigational New Drug determination. Additionally, this form could be used by scientific reviewers and institutional review boards to ensure that requirements for Investigational New Drug considerations are met.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendations. He identified that the Director, Army Human Research Protections Office, would ensure that BAMC's IRB SOPs are updated to require the comprehensive review of clinical research involving the use of medical products and/or devices to ensure compliance with FDA regulations regarding INDs and Investigational Device Exemptions (IDEs). Additionally, he explained that these SOPs will identify procedures for consulting the USAMMDA DRAC for interpretation of FDA regulations and provision of IND/IDE determinations. He further explained, the SOPs will include checklists for researchers to use at the time of protocol submission which identify the criteria used in making an IND or IDE determination. These SOPs will be updated, reviewed and approved by the date of our final report.

Furthermore, the HQ USAMRMC IRB protocol application template currently in use for all new research in Theater includes two sections to solicit information from the researcher regarding planned use of any investigational or approved drugs, dietary supplements, biologics, or devices in the proposed research. This information is used by the IRB in making regulatory determinations and/or requesting subject matter expert consultation to ensure that all requirements for IND considerations are met.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.2.5: We recommend that the U.S. Army Medical Command ensure that all individuals involved in the submission, review, and approval of clinical research protocols receive training in the use of investigational drugs, Food and Drug Administration regulations and the Investigational New Drug process.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He identified that AR 70-25 and AR 40-7 will be updated to include a requirement for individuals involved in the submission, review, and approval of clinical research protocols to receive training in FDA regulations applicable to the conduct of studies involving the administration of medical products and the use of medical devices. These regulations will be updated by April 30, 2012.

Our Response

The Commanding General's comments are responsive. No further action is required.

Recommendation C.2.6: We recommend that the U.S. Navy Bureau of Medicine and Surgery review and update BUMEDINST 3900.6B to clarify procedures regarding the use of investigational drugs in medical research, to include intended use of nutritional supplements and other over-the-counter products as experimental drugs.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) concurred with our recommendation. He stated that the BUMED Special Assistant for Ethics and Professional Integrity/Executive Research Integrity Officer will be responsible for the revision of BUMEDINST 3900.6B in coordination with the BUMED Office of Special Assistant for Medical Research/Director, Navy Medicine Research and Development Center. Estimated completion date is December 31, 2011.

Our Response

The Chief of BUMED's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.2.7: We recommend that the U.S. Navy Bureau of Medicine and Surgery ensure that all individuals involved in the submission, review, and approval of clinical research protocols receive training in the use of investigational drugs, Food and Drug Administration regulations and the Investigational New Drug process.

U.S. Navy Bureau of Medicine and Surgery Comments

~~(FOUO)~~ The Chief, Bureau of Medicine and Surgery (BUMED) concurred with our recommendation. He stated that the Director, Navy Medicine Research and Development Center ((NMRDC) and relevant NMRDC subject matter experts will have the responsibility to identify relevant professional education programs for incorporation into local command education and training curricula by July 31, 2011. This training will be based on the revision of BUMEDINST 3900.6B, previously discussed under recommendation C.2.6.

Our Response

The Chief of BUMED's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

C.3 Communication during Scientific Peer Review

Existing procedures used during the review of the Research Protocol failed to resolve scientific peer reviewer concerns.

C.3 Applicable Criteria

- AR 70-25 "Use of Volunteers as Subjects of Research," January 25, 1990, Section 3-2, defines a scientific review as a type of peer review "to assure that the protocol design

yields scientifically useful data which meets the objective(s) of the study."

- The MNC – I's Human Research Protection Program (HRPP), June 24, 2008, states that scientific review and assessment determines whether a research protocol contains scientific merit. The HRPP further identifies roles, responsibilities and procedures for scientific review, stipulating that the Human Protections Administrator (HPA) is responsible for facilitating communication between the investigator and peer reviewers. Additionally, the HPA serves as the "central point of contact for coordinating communications and effecting individuals to complete their requirements." Furthermore, the HRPP states that the U.S. Army Institute for Surgical Research (USAISR) is responsible for the scientific review of Iraq research proposals, and the USAISR Senior Scientist's signature on the protocol "indicates a scientific review of the protocol has been conducted and that the protocol is approved for submission to the BAMC IRB."

C.3 Findings

a. The research protocol application, that was completed by the Investigator, specified in the hypothesis that "the administration of NAC (n-Acetylcysteine) for seven days along with observation will result in improved hearing and balance function in individuals who demonstrate these disorders after blast exposure when compared to observation alone at the seven day time point."

b. Two medical professionals conducted the Clinical Trial's scientific peer review using a checklist provided by the IRB. The checklist did not have a specific section related to the use of investigational drugs. Consequently, only one of the reviewers identified concerns regarding the Investigator's planned use of NAC to treat mTBI and wrote that "an IND application for the use of [the] compound [NAC] may be required from the FDA."

c. Staff from the U.S. Army's Institute of Surgical Research (USAISR), Regulatory Compliance and Quality Management Division collected all information from the scientific peer reviewers and forwarded any questions and or concerns to the Human Protections Administrator (HPA) in Iraq who served as a facilitator for communication between the Investigator (in Iraq) and the research authorities (in CONUS), including the scientific peer reviewers and the BAMC IRB. Consequently, the concerns expressed by the peer reviewer were relayed by USAISR to the HPA in Iraq, who then forwarded the email listing the concerns to the Investigator.

d. The Investigator provided the answers (noted below) in an email to the HPA in response to the peer reviewer's question. The HPA then forwarded the Investigator's emailed responses to USAISR for their consideration:

- "The reason we picked NAC is the 40 year safety history of the medicine as Mucomyst® and our MCRD [Marine Corps Recruit Depot] study with Marines and NAC with no side effects higher than placebo or background."
- "This medicine has no increased risk over not taking the medicine and the patients will be on light duty while taking the medicine so minor things like stomach upset will be acceptable."

- "The FDA has repeatedly said that an IND is not needed for the dose of medicine we are using."

e. One of the peer reviewers stated that she raised the concern whether an IND was needed for the NAC during her scientific review of the protocol. She provided comments about her concerns on the checklist that was provided by the IRB. She acknowledged that she did not receive any additional follow-up questions, or feedback regarding her concerns about the IND. Furthermore, the peer reviewer explained that in comparison between this review and scientific reviews that she conducted for other agencies, she felt that she was more involved with the other reviews. She expressed her concern that a less interactive review process might not take into account the reviewer's concerns and whether the responses adequately addressed those concerns.

f. During our interview, an U.S. Army Official at USAISR acknowledged that one of the peer reviewers expressed concern whether an IND was needed for the NAC as proposed in the research protocol. He further explained that in his role as "Senior Scientist" for the Clinical Trial, he felt that the Investigator's responses to this concern were vague. Additional emails were exchanged with the Investigator (using the HPA as the person who relayed the emails) to ask for further clarification. The senior scientist, however, believed that there was no resolution of the expressed concern with the IND consideration and forwarded this information to the IRB for their consideration.

g. During our interview, the Chairman of the BAMC IRB explained that he was aware that a peer reviewer who reviewed the research protocol prior to its approval expressed concerns about NAC, as well as the IRB itself questioned whether an IND was needed to use NAC in the Clinical Trial. He did not remember if there was discussion at the board level specific to the need for an IND, nor could he remember if the board members considered the scientific reviewer's IND questions and the Investigator's responses to those questions prior to voting to recommend approval for this research protocol.

h. Our review of the IRB's minutes did not reveal any detailed discussions about the need for an IND, nor was there any evidence in the minutes that the peer reviewer's concerns, nor the Investigator's responses were considered by the IRB.

i. The IRB Chairman stated that he believed the IRB "performed due diligence" during their review of the research protocol, however, may not have "pursued all avenues" available to the board in rendering a recommendation to approve the protocol as submitted without an IND

j. The USAISR official clarified that he was not requested to provide any further consultation with the IRB other than forward the scientific peer review checklists, questions asked by the peer reviewer and responses provided by the Investigator.

C.3 Discussion

Research protocols undergo a scientific peer review prior to consideration by an institutional review board. The purpose of the scientific review is to ensure that the research protocol contains scientific merit and that the protocol design ensures useful data which meets the objective(s) of the proposed research.

Two medical professionals conducted the Clinical Trial's scientific peer review using a checklist provided by the IRB. A senior scientist from the U.S. Army Institute of Surgical Research (USAISR) was responsible to ensure that the scientific peer review was completed and forwarded this information to the BAMC IRB for their consideration.

During the scientific peer review process, the MNC-I Human Protections Administrator (HPA) acted as a facilitator for communication among the parties: the scientific peer reviewers, USAISR's Senior Scientist, the Investigator, and the IRB. Specifically, the USAISR forwarded questions from the scientific reviewers to the HPA, who then forwarded the questions onto the Investigator. Responses were forwarded from the Investigator to the HPA, who then relayed the response to USAISR, who eventually forwarded them to the BAMC IRB for their consideration. We did not find any evidence that the Investigator's responses regarding a possible need for an IND were provided to the scientific peer reviewer who originally posed the question.

Consequently, the scientific reviewers had no opportunity to respond or ask further questions, and there is no evidence that the HPA, the reviewers, nor the Senior Scientist at USAISR assessed the adequacy of the Investigator's responses to concerns raised.

Additionally, our interview with one of the scientific peer reviewers revealed that other agencies and individual institutional review boards have different expectations for the extent of interaction between scientific peer reviewers and the Investigator. Specifically, she explained that several boards that she was involved with encouraged direct communication between the reviewers and the researcher, as well as the institutional review board itself. In this case, neither USAISR nor the BAMC IRB had procedures requiring a dialogue between the scientific peer reviewers and the Investigator, or between the scientific peer reviewers and the IRB.

Furthermore, our review of the Scientific Review Checklist used by the peer reviewers revealed that the checklist included the minimal requirements for conducting a scientific review. However, it did not specifically address the use of investigational drugs. As a result, only one of the two reviewers identified a concern related to the need for an IND.

C.3 Conclusion

The Investigator dismissed concerns regarding the need for an IND, and the procedures used during the scientific review failed to resolve the scientific peer reviewer's concerns and identify that an IND was required. The lack of two-way communication between the Investigator and the scientific peer reviewers and the lack of specific IND questions on the Scientific Review Checklist contributed to the BAMC IRB approving the Clinical Trial without consideration of an IND. As a result the validity of the research was questionable, and the rights of the participants were jeopardized.

C.3 Recommendations, Management Comments and Our Response

Recommendation C.3.1: We recommend that the U.S. Army Medical Command conduct a review into the process used by the HPA and USAISR during the scientific review of the research protocol and identify improvements needed to ensure that future

scientific reviews are thorough, accurate and address all concerns necessary for a valid and scientifically sound research proposal.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. On June 19, 2010, the USCENTCOM and U.S. Army Institute of Surgical Research (USAISR) established a revised process for scientific review and approval of USCENTCOM research protocols. The current SOP for scientific review includes robust procedures to ensure that future scientific reviews are thorough, accurate and address all concerns necessary for a valid and scientifically sound research proposal.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.3.2: We recommend that the U.S. Army Medical Command review and update AR 40-7 to include a more detailed description of the process and procedure for communication used during a scientific peer review, to ensure that actions taken are adequate to address any of the reviewers' stated concerns or questions. Consider the encouragement of an open exchange of information among the scientific peer reviewers, the investigator, and the institutional review board to resolve any concerns or differences of opinion.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendations. He explained that although the current AR 40-7 addresses the requirement for scientific review, AR 70-25, "Use of Volunteers as Subjects of Research" dated January 25, 1990 is more specific in its discussion of scientific review requirements. Consequently AR 70-25 is the regulation which requires an update according to our recommendation.

Furthermore, the Commanding General identified that AR 70-25 and AR 40-7 will be consolidated into one updated Army regulation governing the conduct of research involving human subjects. Expected completion and approval for the revised regulation is expected to be April 30, 2012. This updated regulation will include a more detailed description of the minimum requirements for the scientific review process and it will address procedures for communication used during a scientific peer review. Additionally, this updated regulation will encourage an open exchange of information among the scientific peer reviewers, the investigator, and the IRB to resolve any concerns or differences of opinion.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.3.3: We recommend that the U.S. Army Medical Command update the BAMC IRB's Standard Operating Procedure Manual to include a detailed scientific

peer review checklist which includes a section dedicated to medications and considerations for Investigational New Drug determinations.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He explained that it is the Institution engaged in research (specifically, MNC-I) and its IRB (Brooke Army Medical Center(BAMC)) who is responsible to identify the FDA regulatory requirements for the conduct of human subject research. Accordingly, the Army Medical Command will ensure that checklists outlining regulatory considerations for INDs and IDEs will be included in the BAMC IRB SOP, as well as the revised AR 70-25.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

C.4 Selection and assignment of the Medical Monitor

Existing processes and tools used during the review and approval of the Clinical Trial failed to effectively leverage the Medical Monitor role in protecting research participants.

C.4 Applicable Criteria

- DoD Directive (DoDD) 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," April 24, 2007, stipulates that the "rights and welfare of human subjects in research supported or conducted by the DoD Components shall be protected." Additionally, this directive stipulates that "for research involving more than minimal risk to subjects, an independent medical monitor shall be appointed by name ... and shall be capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety." Furthermore, this directive states that medical monitors... "shall possess sufficient educational and professional experience to serve as the subject/patient advocate."
- AR 70-25 "Use of Volunteers as Subjects of Research," January 25, 1990, defines a medical monitor as a "physician qualified by the training and/or experience required to provide care to research subjects for conditions that may arise during the conduct of the research, and who monitors human subjects during the conduct of research." Additionally, this regulation requires that a medical monitor is appointed by name if the (institutional review board) determines the risk as more than minimal.
- The BAMC Institutional Review Board's Standard Operating Procedure (SOP) Manual, July 7, 2008, specifies that "the Institutional Review Board will appoint a Medical Monitor for all research protocols involving greater than minimal risk. The Medical Monitor will receive a memorandum of appointment after the protocol is approved. The memorandum will review the responsibilities of the Medical Monitor."

C.4 Findings

a. The BAMC IRB's minutes dated 5 November 2008 identified the Clinical Trial as "greater than minimal risk" due to the fact that there was a "placebo arm in the study that will be conducted in a combat zone."

b. The IRB's policy is that a medical monitor is assigned to research protocols involving greater than minimal risk and that there is a memorandum listing the name of the appointed individual and their responsibilities.

c. According to the Chairman of the IRB, he (the chairman) was initially assigned to serve in the role as medical monitor, however, this assignment was later changed to a physician deployed to Camp TQ, the same location where the Investigator was conducting research.

d. During our interview, the assigned medical monitor for this research protocol stated that he had no concerns regarding the conduct of the study. However, when questioned, he acknowledged that he lacked experience with mTBI and was unfamiliar with the clinical practice guidelines and tools for the assessment of mTBI in deployed settings. Additionally, he stated that he did not remember receiving an appointment letter as the medical monitor.

e. Our review of the IRB's did not reveal that a medical monitor was identified by name, nor could we find evidence of an appointment letter.

C.4 Discussion

According to the transcribed notes of the BAMC IRB's meetings, the board identified the Clinical Trial as "greater than minimal risk," which required a medical monitor to oversee the protections afforded to the research participants, ensuring that the study was conducted properly and risks to participants were minimized. Ultimately, a staff physician assigned to Camp TQ was identified as the medical monitor. This information was not annotated in the IRB's minutes or other correspondence, as required by SOPs. Additionally, during an interview, the Medical Monitor had no recollection of receiving an appointment letter outlining the role's objectives and responsibilities, nor could one be produced.

Furthermore, by self-report, the Medical Monitor did not have the experience in caring for mTBI patients, nor was he familiar with the Joint Theater Trauma System Clinical Practice Guidelines which were used to treat mTBI patients. As a result, the Medical Monitor did not recognize the concerns related to the Investigator not using the MACE tool when conducting neurological assessments as required in the guidelines (See Observation B1, "Neurological assessments did not adhere to clinical practice guidelines for mTBI".) Additionally, possibly due to his inexperience in treating mTBI patients, the monitor did not recognize that certain medications (specifically Topiramate and Sumatriptan) that were given by the Investigator, were contraindicated in the treatment of headaches as a result of a head injury (e.g. blast related) (See Observation B3, "Medications contraindicated in the treatment of early mTBI were administered").

C.4 Conclusion

The designated in-theater medical monitor for the research protocol lacked experience in

treating mTBI patients. Consequently, as the medical monitor, he did not have the experience necessary to "provide care to research subjects for conditions that may arise during the conduct of the research" as required by U.S. Army regulations. The BAMC IRB's standard operating procedures (SOPs) lacked specificity regarding selection qualifications and communication of objectives and responsibilities regarding medical monitors for research studies. Finally, the IRB did not adhere to its own SOP in writing a memorandum of appointment specifying the monitor's roles and responsibilities. As a result, the medical monitor identified may not have been the best qualified individual with the appropriate knowledge and experience to ensure that the rights and welfare of research participants were protected.

C.4 Recommendations, Management Comments and Our Response

Recommendation C.4.1: We recommend that the U.S. Army Medical Command conduct a review into the process used by the BAMC IRB to select an appropriate individual to serve as medical monitor for the Research Protocol. Additionally, identify improvements needed for research studies to involve medical monitors to ensure that there are maximum protections of the rights and welfare of research participants.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He explained that the Director, AHRPO, will conduct a review of the process used by the BAMC IRB to select an appropriate individual to serve as medical monitor for the Research Protocol. Additionally, AHRPO will identify improvements needed for research studies to involve medical monitors to ensure that there are maximum protections of the rights and welfare or research participants. This review will be completed by May 15, 2011.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.4.2: We recommend that the U.S. Army Medical Command review and update AR 70-25 to ensure there is appropriate detail regarding roles and responsibilities, as well as qualifications of a medical monitor. Specifically this guidance should require that medical monitor roles and responsibilities be provided in writing in the form of an appointment letter with clearly stated reporting requirements.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He explained that the Army will combine AR 70-25 and AR 40-7 into an updated, consolidated Army human research protections regulation that will included appropriate detail regarding medical monitor roles, responsibilities, and qualifications. Additionally, the requirement for written designation of the medical monitor will be established and included in the revised regulation. This regulation is expected to be published by April 30, 2012.

Our Response
The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.4.3 We recommend that the U.S. Army Medical Command ensure that the BAMC IRB's Standard Operating Procedures include procedures and/or checklists to ensure all research protocol requirements are met prior to giving approval to initiate the research. Specifically, ensure that criteria are developed to document that a medical monitor was assigned (if required) and appointed in writing including details on their role and responsibilities.

U.S. Army Medical Command Comments
The Commanding General, U.S. Army Medical Command concurred with our recommendation. He identified that the Director, AHRPO, will ensure that BAMC IRB SOPs are updated to include procedures and checklists to ensure all research protocol requirements that are specific to the requirement for a medical monitor are met prior to giving approval to initiate the research. These SOPs will be updated, reviewed and approved by the date of our final report.

Our Response
The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

C.5 Identification and protection of vulnerable populations

Existing regulations and procedures used by the Investigator and research authorities failed to identify and appropriately protect deployed U.S. Service members as a vulnerable human subject group

C.5 Applicable Criteria
- 32 CFR Part 219.111, "Protection of Human Subjects," July 1, 2008 provides criteria for Institutional Review Board (IRB) approval of research, which includes a statement that "risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk." Further, 32 CFR 219 requires "additional safeguards" to be included in research protocols when subjects are "likely to be vulnerable to coercion or undue influence" because such safeguards are intended to "protect the rights and welfare of these subjects."
- U.S. Army Regulation 70-25 "Use of Volunteers as Subjects of Research," January 25, 1990, explains that research using human subjects is to be conducted "in such a manner that risks to the subjects are minimized and reasonable to anticipated benefits." Additionally this regulation identifies some research participants, such as "persons with acute or severe physical or mental illness, or those who are economically or educationally

challenged" as potentially vulnerable to coercion or undue influence, and requires that "proper additional safeguards will be included in the study to protect the rights and welfares of these subjects."

- SECNAVINST 3900.39D, "Human Research Protection Program," November 6, 2006, stipulates that "the rights, welfare... and safety of human subjects shall be held paramount at all times," and further emphasizes that "additional safeguards shall be provided for subjects who may be considered vulnerable to coercion or undue influence." Additionally, this instruction specifies that "Groups warranting additional protection include deployed active duty personnel."

C.5 Findings

a. The Clinical Trial was conducted on U.S. Service members brought to Camp TQ, Iraq within 24 hours of blast exposure.

b. During a visit to Camp TQ, the Gray Team raised concerns about the conduct of mTBI clinical research on deployed Service members. These concerns prompted the MNC-I Surgeon to order an investigation into the conduct of the Clinical Trial at Camp TQ. Specifically, the MNC-I Surgeon ordered the Deployed Research Team (DRT) to conduct a review of the following: 1) Did the research conform to the written protocol? 2) Was the mTBI treatment at Camp TQ acceptable medical treatment? And 3) Was there any evidence of coercion for deployed Service members to participate in the research (see Appendix E for a summary of the DRT's report.)

c. During our interview, a U.S. Army official from the Office of Research Protections at the U.S. Army Medical Research and Materiel Command (USAMRMC) explained that research conducted in-theater at the time of the Clinical Trial was approved using a DoD Assurance delegated to the MNC-I Surgeon by the U.S. Army's Assistant Surgeon General for Force Projection. She stated that the Brooke Army Medical Center's Institutional Review Board (IRB) was named as the IRB of record in this DoD Assurance. She further clarified that this IRB had other responsibilities besides Southwest Asia research projects, and was not properly resourced for this effort. Consequently, USAMRMC was pursuing the development of an Assurance with the U.S. Central Command (CENTCOM). Ultimately, the plans indicated that the IRB of record for the CENTCOM Assurance would shift to the Human Subject Research Review Board at USAMRMC where there was additional clinical experience and multi-service input available for research approval recommendations.

d. Additionally, the USAMRMC official verified that this Clinical Trial was the first interventional (placebo-controlled) study conducted in-theater. She further explained that if the IRB had determined that an IND was needed to conduct the research in Camp TQ, that it would not have been recommended for approval due to the inability to adequately control the extensive paperwork and oversight needed to sustain the IND. The FDA conducted a review of the research proposal and determined that an IND application was required to use NAC in the Clinical Trial. The BAMC IRB did not recognize this requirement and recommended approval for the study. (See Observations A.3, B.2 and C.2).

e. During our interview, a senior official from the U.S. Army Institute of Surgical Research, cited his concerns that military medical research, especially casualty care research, posed demands on IRB/research committees who do not have the expertise, nor are able to devote the time to conduct comprehensive reviews, including the scientific review process.

f. A senior official on the MNC-I Surgeon's staff stated, that at the time the research was conducted at Camp TQ, there was on-going discussion between U.S. Navy and U.S. Marine Corps officials that NAC was considered a "great cure-all" for mTBI and that there was support to develop specialized TBI treatment centers in-theater. He additionally explained that he felt that these discussions led support to the issuance of the FRAGO directing movement of blast victims to Camp TQ. Furthermore, he acknowledged that initiation of the FRAGO could be perceived as coercion/undue influence because of the potential to force patients to become study participants.

g. Additional interviews with research oversight authorities (Deployed Research Team (DRT), MNC-I Surgeon, BAMC IRB Chairman), as well as a U.S. Navy official at Camp TQ, did not identify any concerns regarding the potential vulnerability related to research participation by wounded Service members, deployed in a combat environment.

C.5 Discussion

While U.S. Navy Regulations (SECNAVINST 3900.39D) specifically identify "deployed active duty personnel" as a group that require additional protections to ensure their rights are safeguarded, DoD and U.S. Army regulations do not specify "deployed personnel" as a specific category that may be more vulnerable than others. Interviews with research authorities, MNC-I officials, as well as with Camp TQ medical leadership, did not identify any concerns regarding potential vulnerability related to research participation by wounded Service members, deployed in a combat environment. Consequently, there was no evidence of additional controls or measures to safeguard the protections offered to this population of potential research participants.

As previously discussed under Observation A.5, the Gray Team expressed concern that research participants were unduly influenced to participate in the Clinical Trial due to the FRAGO which required the evacuation of Service members with blast injuries to Camp TQ for evaluation. The Deployed Research Team (DRT) agreed with this perception, however concluded that the Investigator did an adequate job mitigating this undue influence. This conclusion may have resulted from the DRT's insensitivity to the increased vulnerability of U.S. Service members deployed in a combat environment.

Additionally, as discussed in Observations A.3, B.2 and C.2, the research participants were given a drug (e.g. NAC) that was not under an IND and therefore was not subjected to increased scrutiny by the FDA. Consequently, the research participants were potentially exposed to unnecessary risks. Discussions with U.S. Army research officials revealed that it was unlikely that this research would have been approved if the requirement for an IND was recognized by the IRB due to the increased complexities of managing research with an IND, especially in a combat environment.

C.5 Conclusion

Deployed U.S. military personnel were not properly identified as a population vulnerable to coercion, and the guidance in place at the time of the study lacked consistency regarding vulnerable groups and additional protections needed to ensure the safety of research participants. Additionally, research authorities responsible for the review and approval of the Clinical Trial were not sensitive to the potential vulnerability of the military members. Consequently, research was conducted that did not adequately protect the rights and welfare of deployed U.S. military personnel.

C.5 Recommendations, Management Comments and Our Response

Recommendation C.5.1: We recommend that the Under Secretary of Defense for Acquisition, Technology and Logistics review and update DoDD 3216.02 to ensure there is appropriate reference to identifying deployed personnel as a group or potential research subjects that could be vulnerable to coercion or undue influence. Additionally, this directive should include a description of additional protections needed to ensure that the rights of research subjects that are deployed are safeguarded.

Under Secretary of Defense for Acquisition, Technology and Logistics Comments

The Assistant Secretary of Defense for Research and Engineering (ASD(R&E)), on behalf of the Under Secretary of Defense for Acquisition, Technology and Logistics (USD(AT&L)) partially concurred with our recommendation. Although, ASD(R&E) agreed that DoDD 3216.02 required an update, he stated that there is no evidence that deployed service members are more vulnerable to coercion than non-deployed service members or other DoD personnel. Therefore, he did not believe that deployed personnel needed to be singled out as a specific population more vulnerable to coercion or undue influence.

Furthermore, ASD(R&E) explained that DoD Directive (DoDD) 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research" was currently undergoing a review and would be updated as DoD Instruction (DoDI) 3216.02. Completion is expected by May 31, 2011. ASD(R&E) believed that this draft instruction better explains the requirements of protection all Military Service members from coercion or undue influence.

Our Response

Our review of the draft DoDI 3216.02, provided by ASD(R&E), shows sufficient detail in the requirements for populations needing additional protections from coercion or undue influence, including DoD personnel as a particular subset of the population. Specifically, the instruction requires the IRB to discuss the need to appoint an ombudsman[13] to monitor the recruitment process to ensure the subject's enrollment is both voluntary and informed. Our position is that this instruction as drafted would meet the intent of our recommendation to ensure that the rights of all research subjects are safeguarded. ASD(R&E)'s comments are responsive and

[13] An ombudsman is a person who acts as an impartial and objective advocate for human subjects participating in research.

the actions meet the intent of the recommendation. No further action is required.

Recommendation C.5.2: We recommend that the Under Secretary of Defense for Acquisition, Technology and Logistics ensure that in-theater research oversight authorities receive training regarding additional safeguards that should be considered to protect the rights of research participants who are deployed to a combat zone.

Under Secretary of Defense for Acquisition, Technology and Logistics Comments

ASD(R&E), on the behalf of USD(AT&L) concurred with our recommendation. He explained that the draft DoDI 3216.02 requires the DoD Components to ensure all DoD personnel receive initial and continuing education commensurate with their duties and responsibilities, specific to research. Additionally, the DoD Components have informally coordinated on a draft framework that lists minimum education topics for different roles that personnel have in protecting human subjects and for different types of research. Furthermore, ASD(R&E) explained that they would work with the DoD Components as they update and implement their policy(s) for protecting human subjects to ensure personnel involved in the oversight of in-theater research have appropriate training.

Our Response

ASD(R&E)'s comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.5.3: We recommend that the U.S. Army Medical Command conduct a review into the process used by the BAMC IRB to recommend approval for the Clinical Trial. Additionally, review the report provided by the Deployed Research Team to ensure it was accurate with appropriate recommendations and actions taken.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He identified that the Director, AHRPO, will conduct a review into the process used by the BAMC IRB to recommend approval of the trial. Additionally, the Director will review the process used during the Deployed Research Team's (DRT'S) visit to Camp TQ to ensure their report was accurate with appropriate recommendations and actions taken. This report will be completed by April 15, 2011.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

Recommendation C.5.4: We recommend that the U.S. Army Medical Command review and update AR 70-25 to ensure there is appropriate reference to identifying deployed personnel as a group of potential research subjects that could be vulnerable to coercion or undue influence. Additionally, this directive should include a description of additional protections needed to ensure that the rights of research subjects that are deployed are safeguarded.

U.S. Army Medical Command Comments

The Commanding General, U.S. Army Medical Command concurred with our recommendation. He explained that "All" Soldiers represent a unique category of vulnerability to coercion or undue influence, however, it was the Army's position that deployed Soldiers will not be considered a subset of this population. Notwithstanding this point, he identified that AR 70-25 and AR 40-7 will be updated and consolidated into a single regulation addressing Army human research protections. Specifically, he explained that the Army will ensure that the regulation considers vulnerabilities of military personnel to undue influence and coercion, and that military-specific protections are included in the regulation. Furthermore, the Army will ensure that the identification of vulnerable groups and protections for military personnel will be consistent with the revision of DoDD 3216.02 (being updated as DoDI 3216.02). The revised Army regulation was expected to be approved by April 30, 2012.

Our Response

The Commanding General's comments are responsive and the actions meet the intent of the recommendations. No further action is required.

C.6 Investigation of medical research misconduct in joint-service environments

A lack of clear guidance for investigating potential research misconduct in a joint-service environment interfered with timely investigation of this matter.

C.6 Applicable Criteria

- U.S. Navy BUMEDINST 6500.3, "Research Integrity, Responsible Conduct of Research Education, and Research Misconduct," June 25, 2009, defines research misconduct as the "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting results." Enclosure 5 of this instruction further stipulates that "research misconduct processes will be performed by the command in which the individual who is alleged to have committed the research misconduct is currently assigned."

C.6 Findings

a. The Investigator was a U.S. Navy physician, who at the time of the study was deployed to Camp TQ, Iraq, under the command and control of 1st Medical Battalion, Camp Pendleton CA.

b. The Clinical Trial was conducted under the authority of the MNC-I "Assurance for the Protection of Human Research Subjects" (DoD A20146) which specified the U.S. Army Brooke Army Medical Center (BAMC) as the institutional review board (IRB) of record. The

BAMC IRB reviewed and approved the research protocol using U.S. Army regulations and guidelines in December 2008.

c. The Clinical Trial was conducted by the Investigator at Camp TQ from December 2008 to March 2009.

d. In February 2009, the Gray Team identified concerns regarding the integrity of the mTBI medical research conducted by the Investigator at Camp TQ. The team relayed these concerns to the CENTCOM Surgeon immediately after their Camp TQ visit.

e. The MNC-I Surgeon sent the Deployed Research Team (DRT) to Camp TQ in February 2009 to investigate concerns that were expressed by the Gray Team. The DRT conducted a review and determined that the "actual practice" of the Investigator and his research "both appeared to be in compliance with theater and IRB standards." Consequently, the DRT recommended that the Clinical Trial be allowed to continue at Camp TQ.

f. The Investigator completed his deployment in March 2009 and redeployed to his parent duty station, under the command and control of the U.S. Navy's Naval Medical Center, San Diego.

g. A complaint was made to the DoD IG's office in June 2009 regarding the Clinical Trial and the conduct of the Investigator while deployed to Camp TQ. Consequently, the DoD OIG initiated an assessment into allegations of research misconduct in June 2009.

h. A U.S. Air Force clinical researcher was retained by the DoD OIG to serve as a subject matter expert and initiated research into the allegations of research misconduct beginning in July 2009. Fieldwork was conducted to gather information on appropriate federal and military regulations specific to this research and to frame any potential allegations of misconduct by the researcher. In the absence of any applicable joint service regulations, additional research was needed to clarify U.S. Army and Navy research regulations to determine the appropriate criteria to apply to this assessment which dealt with a U.S. Navy physician who conducted U.S. Army approved clinical research.

i. One of the allegations was related to the use of an investigational drug, therefore, contact was made with the Drug Enforcement Agency and the Food and Drug Administration to determine proper jurisdiction for the case. After collaboration with Naval Criminal Investigative Services and the Defense Criminal Investigative Services in January 2010, a decision was made to refer allegations of researcher misconduct to the U.S. Navy for investigation. The DoD OIG continued to do assessment work based on the process used by the U.S. Army during the review and approval of the research protocol.

j. DoD and U.S. Army regulations do not specify procedures to follow in the case where more than one military service is involved in allegations of medical research misconduct. U.S. Navy regulations specify that the command that an individual is assigned to is responsible to conduct an investigation into suspected misconduct.

C.6 Discussion

The Clinical Study was approved by the U.S. Army under a DoD Assurance, however the Investigator was a U.S. Navy physician deployed to Iraq. Concerns of potential research misconduct were expressed by the Gray Team in February 2009 and subsequently reviewed by a U.S. Army Deployed Research Team (DRT) since the research was currently ongoing in Iraq. After completion of their assessment, the DRT recommended that the Clinical Study continue. Several months later, concerns regarding the integrity of this research were expressed to a member of the DoD Inspector General staff who initiated an assessment to clarify whether these concerns required investigation. At that time, the Investigator was no longer stationed in Iraq, and was redeployed to a U.S. Navy command. Discussion with DoD and Navy Criminal Investigative Services concluded that potential allegations of misconduct should be referred to the U.S. Navy command at which the Investigator was currently assigned which is in accordance with the Navy's instruction on research misconduct, BUMEDINST 6500.3. Consequently, the DoD IG referred the potential allegations to the Bureau of Medicine and Surgery for investigation and any required action.

C.6 Conclusion

A review of Army and Navy regulations identified that the guidelines defining jurisdiction for the investigation of potential medical research misconduct are unclear when the incident occurs in a joint-service environment. Consequently, the lack of applicable policy and procedures for investigating potential research misconduct in a joint-service environment may have contributed to a delay in the proper disposition of allegations of research misconduct.

C.6 Recommendations, Management Comments and Our Response

Recommendation C.6.1: We recommend that the Under Secretary of Defense for Acquisition, Technology and Logistics coordinate with the Military Services to develop, update and align DoD and Service level policies related to the investigation of medical research misconduct in a joint-service, deployed environment.

Under Secretary of Defense for Acquisition, Technology and Logistics Comments

ASD(R&E), on behalf of USD(AT&L), concurred with our recommendation. Specifically, he stated that DoDD 3216.02 was currently under review and the draft DoDI 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," included a section addressing non-compliance issues related to the instruction. Additionally, he explained that the draft instruction directs the DoD institutions to jointly determine and assign responsibilities for responding to allegations of non-compliance when the allegations involve more than one DoD Component. Estimated completion for this instruction is May 31, 2011.

Furthermore, ASD(R&E) explained that DoDD 3210.7, "Research Integrity and Misconduct" was published to provide guidance on addressing allegations of research misconduct. Specifically, this instruction has coverage of both the potential need to assign joint responsibility, as well as a section on non-compliance by DoD Components concerning intramural research.

Our Response
ASD(R&E)'s comments are responsive and the actions meet the intent of the recommendation. No further action is required.

Recommendation C.6.2: We recommend that the Under Secretary of Defense for Acquisition, Technology and Logistics coordinate with the Military Services to develop, update and align DoD and Service level policies related to the conduct of clinical research to ensure there is better interoperability among the Services in cases where research may be conducted in a joint-service environment.

Under Secretary of Defense for Acquisition, Technology and Logistics Comments

ASD(R&E), on behalf of USD(AT&L), concurred with our recommendation. He explained that the draft DoDI 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," encourages communication, coordination, and reliance to avoid unnecessary duplication of requirements for conducting human subject research. Additionally, he stated that his office will work with the Military Services as they update their policy(s) for protecting human subjects to improve harmonization and reliance when reviewing and approving collaborative research.

Furthermore, ASD(R&E) explained that there are other complementary mechanisms within the DoD to promote interoperability and coordination of joint research programs, such as the Armed Services Biomedical Research Evaluation and Management Committee and the DoD Force Health Protection Council.

Our Response
ASD(R&E)'s comments are responsive and the actions meet the intent of the recommendation. No further action is required.

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Appendix A. Scope and Methodology

We conducted this assessment from June 2009 through March 2011, in accordance with the standards established by the President's Council on Integrity and Efficiency published in the *Quality Standards for Inspections*, January 2005. We planned and performed the assessment to obtain sufficient and appropriate evidence to provide a reasonable basis for our observations and conclusions, based on our assessment objectives. We believe that the evidence obtained provides a reasonable basis for our observations and conclusions based on those assessment objectives.

In accomplishing this assessment, we examined several documents and regulations pertinent to medical research and mTBI to include (but not limited to) the following:

- Code of Federal Regulations (CFR) (21 CFR Parts 219, 321, and 355; 32 CFR Part 219)
- United States Code (USC) (18 USC 208)
- Department of Defense Directives (DoDD) (DoDD 3216.02; DoDD 5230.09; DoDD 5500.7-R)
- Army Regulations (AR) (AR 40-7; AR 70-25)
- Secretary of the Navy (SECNAV) Instruction 3900.39D
- Bureau of Medicine and Surgery (BUMED) Instructions (BUMEDINST 3900.6B; BUMEDINST 6500.3)
- Multi-National Corps-Iraq (MNC-I) Assurance for the Protection of Human Research Subjects (DoD A20146)
- MNC-I Human Research Protection Program Manual
- MNC-I Standard Operating Procedures
- MNC-I Operational Orders
- Joint Theater Trauma System Clinical Practice Guideline on the Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting
- U.S. Army Human Research Protection Office Institutional Policies and Procedures
- U.S. Army Brooke Army Medical Center Institutional Review Board Standard Operating Procedures
- Correspondence from Food and Drug Administration (preIND 108099)

Additionally, we interviewed individuals who were involved in the review and approval of the research protocol. Specifically we interviewed the following (positions and titles listed were current as of the time of the study):

- Chairman, Brooke Army Medical Center Institutional Review Board
- Deputy Director, Clinical Investigation Regulatory Office, U.S. Army Medical Research and Materiel Command
- Senior Scientist, U.S. Army Institute of Surgical Research
- Company Commander, TQ Medical, 1st Medical Battalion – Bravo Company
- Research Director, Deployed Combat Casualty Research Team
- Human Protections Administrator, Deputy Director, Deployed Combat Casualty Research Team

- Multi-National Corps – Iraq Surgeon
- Two Peer Reviewers who completed scientific peer review of research protocol

We also contacted other individuals who were associated with our research of this assessment. Specifically we interviewed or had contact with the following (positions and titles listed were current as of the time of the study):

- Senior Counsel and Intellectual Property Attorney, Naval Medical Research Command
- Project Manager, Medical Development, Naval Medical Research Command
- Comptroller, U.S. Navy Naval Medical Center, San Diego
- U.S. Central Command Surgeon
- Multi-National Corps – Iraq Deputy Surgeon
- Medical Monitor assigned for the Clinical Trial
- Supervisory Regulatory Project Manager, Division of Neurology Products, Food and Drug Administration
- Deputy Director, Clinical Investigations Program, Bureau of Medicine and Surgery
- Deputy Comptroller, Office of Naval Research
- Team Leader, Chairman, Joint Chiefs of Staff (CJCS) Gray Team
- Neurologist Member of CJCS Gray Team

Furthermore, we interviewed and/or contacted key members of the U.S. Army Medical Research and Materiel Command to obtain in depth information on Department of the Army's clinical research policies and procedures to include:

- Director, Office of Research Protections
- Director, Regulated Activities and Compliance
- Chief, Regulatory Affairs Operations, U.S. Army Medical Materiel Development Activity

This assessment was limited to resources that were available in CONUS. The specific clinical trial, "The Use of Anti-Oxidants Used to Treat the Sequela of mTBI After Blast Exposure," was no longer being conducted in Iraq, and all individuals with direct involvement in the review and approval of this clinical trial were no longer deployed to Iraq.

Use of Computer-Processed Data

We did not use computer-processed data to perform this assessment.

Use of Technical Assistance

In order to research applicable legislative, DoD, and military specific criteria, review and assess applicable documents and correspondence, and participate in interviews with key personnel, we obtained the services of a doctorally prepared Air Force nurse researcher. This individual had extensive experience in conducting research and in developing and reviewing research protocols in a combat zone (Iraq); thus, she was qualified to identify areas where the research protocol review and monitoring process may have been inadequate.

Appendix B. Summary of Prior Coverage

No prior coverage has been conducted on traumatic brain injury research integrity in Iraq during the past 5 years.

Appendix C. Acronyms and Abbreviations

AHRPO	Army Human Research Protections Office
AR	Army Regulation
ASD(R&E)	Assistant Secretary of Defense for Research and Engineering
BAMC	Brooke Army Medical Center
BUMED	U.S. Navy Bureau of Medicine and Surgery
BUMEDINST	U.S. Navy Bureau of Medicine and Surgery Instruction
CENTCOM	Central Command
CFR	Code of Federal Regulations
CONUS	Continental United States
CPG	Clinical Practice Guideline
DRT	Deployed Research Team (its official title is "Deployed Combat Casualty Research Team")
DoD	Department of Defense
DoDD	Department of Defense Directive
DoDI	Department of Defense Instruction
DoD OIG	Department of Defense, Office of Inspector General
DON	Department of the Navy
DSN	Defense Switched Network
FDA	U.S. Food and Drug Administration
FRAGO	Fragmentary order
HPA	Human Protections Administrator
HRPO	Human Research Protection Office
HRPP	Human Research Protection Program
HSRRB	Human Subjects Research Review Board
IND	Investigational new drug
IRB	Institutional Review Board
JTTS	Joint Theater Trauma System
MACE	Military Acute Concussion Evaluation
MCRD	Marine Corps Recruit Depot
MD	Maryland
MNC–I	Multi-National Corps – Iraq
MND–W	Multi-National Division – West
MNF–I	Multi-National Forces – Iraq
MNF–W FRAGO	Multi-National Forces – West fragmentary order
mTBI	mild traumatic brain injury

NAC	n-Acetylcysteine
OIG	Office of Inspector General
ONR	Office of Naval Research
ORP	Office of Research Protections
OSD	Office of the Secretary of Defense
SECNAVINST	Secretary of the Navy Instruction
SIPRNET	SECRET Internet Protocol Router Network
SME	subject matter expert
SOP	standard operating procedures
SPO	Special Plans and Operations
TBI	traumatic brain injury
TQ	Camp Al Taqaddum, Iraq
TX	Texas
U.S.	United States
USAMMDA DRAC	U.S. Army Medical Materiel Development Activity, Division of Regulated Activities and Compliance
USC	United States Code
USAISR	U.S. Army Institute for Surgical Research
USAMRMC	U.S. Army Medical Research and Materiel Command
USD	Under Secretary of Defense
USD(AT&L)	Under Secretary of Defense for Acquisition, Technology, and Logistics
USF-I	U.S. Forces – Iraq

Appendix D. Summary of Process and Approximate Timeline

Following is a summary of the process and approximate timeline used during review and approval of the Research Protocol "The Use of Anti-Oxidants to Reduce the Sequela of mTBI After Blast Exposure":

- **September 23, 2008** – The Investigator utilized a template provided by the Brooke Army Medical Center Institutional Review Board (BAMC IRB) to submit his research protocol.
- **Also completed on September 23, 2008** – Military Treatment Facility (MTF) Commander and the Iraq Research Director (Director of the Deployed Combat Casualty Research Team) endorsed the Research Protocol.
    - The MTF Commander's endorsement indicates that the MTF Commander has reviewed the protocol and the investigator's required credentials including any research related training such as the Collaborative Institutional Training Initiative Program and approves the protocol to be forwarded for additional review.
- The Iraq Research Director's endorsement indicates that they have reviewed the protocol and recommend approval for additional review.
- **End of September, 2008** – Two subject matter experts identified by U.S. Army Institute Surgical Research (USAISR) to complete the scientific review of the protocol. USAISR is the designated agency that is responsible for the scientific review.
    - The purpose of a scientific review is to ensure that research is scientifically sound in its design and methods, so that subjects are not put at risk for a study not worthy of performance, and that the study will likely produce valid results.
- **October 3, 2008** – Scientific peer review checklists completed and comments/questions from reviewers collected by USAISR and forwarded to the MNC-I Human Protections Administrator (HPA). The HPA served as a facilitator of information between the scientific reviewers and the researcher.
- **October 8, 2008** – The Investigator provided responses to the scientific reviewer's comments/questions and amended his protocol as necessary. The HPA forwarded the researcher's answers and revised protocol back to the USAISR Senior Scientist.
- **October 15, 2008** – The USAISR Senior Scientist endorsed the protocol indicating that the scientific review was conducted and was approved for forwarding to the BAMC IRB.
- **October 16, 2008** – Multi-National Corps – Iraq (MNC-I) Surgeon acknowledged that the protocol was approved to forward to the BAMC IRB.

- **October 20, 2008** – Amended protocol and scientific review checklists forwarded by USAISR to BAMC IRB for consideration.
- **November 5, 2008** – BAMC IRB meeting discussing Iraq research protocol. IRB identified the study as "greater than minimal risk" and forwarded additional questions to the Investigator to clarify whether the substance used in the study as an intervention was an investigational new drug.
- **November 18, 2008** – Iraq HPA forwarded Investigator's responses to IRB questions.
- **End of November 2008** – BAMC IRB forwarded IRB minutes and Iraq research protocol to the Clinical Investigation Regulatory Office (CIRO) for a second level review as required for all research conducted in theater.
- **December 2, 2008** – CIRO completed their second level review, which was primarily administrative in nature.
- **December 2, 2008** – BAMC IRB approved research protocol and notified the Investigator in writing.
- **Soon after December 2, 2008** – Investigator began research subject accrual in Iraq.

Appendix E. Summary of Deployed Research Team Report

On February 21, 2009, the MNC-I Surgeon ordered that the Deployed Combat Casualty Research Team (referred to as the Deployed Research Team in this report) perform a review of the medical research conducted under the MNC-I approved protocol "The Use of Anti-Oxidants to Reduce Sequela of Mild TBI (mTBI) After Blast Exposure". This research was conducted by a U.S. Navy physician from December 2008 – March 2009, while deployed with the 1st Medical Battalion – Bravo Company in Al Taqaadum, Iraq.

This review was conducted as a result of concerns expressed during Gray Team visit in February 2009. Specifically, the team identified problems related to possible coercion of subjects, research protocol deviations, and misrepresentation of research data.

Questions

The following questions were asked by the MNC-I Surgeon:

- Is the conduct of the research conforming to the written protocol and meeting the standards established by the Human Research Protection Program?
- Is the mTBI treatment being conducted at Camp TQ acceptable medical treatment or unproven research?
- Is there an appropriate separation between the medical treatment provided at TQ and the conduct of the approved research protocol?
- Does the Multi National Forces – West (MNF-W) FRAGO directing evacuation of all Marine mTBI patients to Camp TQ for treatment result in perceived or real coercion of patients to participate in human subjects research?

Findings

The Deployed Research Team completed its review on 23 February 2009, and provided a written response to the MNC-I Surgeon on 27 February 2009. Their conclusions were as follows:

- The research protocol was compliant with applicable federal, DoD and Department of the Army human research protection laws and regulations.
- The mTBI treatment conducted at Camp TQ conformed to the current community standard of care, however, the principal investigator (PI), also known as the "Investigator" in this report, a U.S. Navy Physician, did not follow the clinical practice guidelines established in the "Joint Theater Trauma System Clinical Practice Guidelines for the Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting." Specifically, the PI did not use the Military Acute Concussion Evaluation (MACE) as a standardized tool for the evaluation of symptoms and cognitive deficits that may follow concussion.

- There was an appropriate separation between the medical treatment provided at Camp TQ and the conduct of the approved research protocol.
- The MNF-W FRAGO directing evacuation of all Marine mTBI patients to Camp TQ for treatment could result in perceived coercion of patients to participate in human subject research.

The DRT asserted that the absence of the MACE as an assessment tool did not result in a decrement in the level of care provided to Service members. Additionally, while the FRAGO could be perceived as coercion, the team felt that the Investigator did a reasonable job delineating the separation between the patient's referral for evaluation and the early treatment proposed in the research study, during the initial evaluation and counseling regarding the study. Therefore, they summarized that the perception of coercion was mitigated by the Investigator. As a result of concerns expressed by the DRT and U.S. Marine Corps leadership, the team relayed that the U.S. Marine Corps leadership was reviewing and considering the modification or cancellation of the FRAGO.

Conclusion

The DRT summarized that the "actual practice and research conducted" by the Investigator appeared to be in "compliance with current theater and BAMC Institutional Review Board standards" and recommended that the research protocol be reopened to the accrual of patients.

Additional Concerns

While not included in the questions of the original MNC-I tasking letter, the DRT identified concerns regarding the Investigator's discussion of his observations regarding early treatment of mTBI. The DRT reviewed several press releases, as well as a PowerPoint presentation given by the Investigator, and noted the following expressions:

- Press Release: 081228-MLG-81871-TBI - "...Theater TBI Center of Excellence. The center, a result of (his) two year initiative, is the first of its kind here in Anbar" and "Since the center has opened, 42 patients have received treatment. Thirty-five have returned to finish their deployment."
- PowerPoint Presentation – "Treated over 50 war injured U.S. service members utilizing currently accepted medical interventions...Achieved an overall 66% seven day cure rate (for reference the cure rate at 3 months without early treatment is less than 20%)...Recent modification in procedures (addition of active rehabilitation) has increased seven day cure rate to 85%."
- Press Release: 090110-MLG-81871-HASC – "(Our methods) are almost considered to be policy and these are the people who help influence policy...said he hopes to have persuaded the members to use their leverage to make Camp Taqaddum's mTBI treatment method policy for all services."

The DRT was concerned that the above information shared by the Investigator was premature given that his research protocol was in the early stages, and conducted as a placebo-controlled, double blinded study. Additionally, the DRT felt this information could contribute to confusion regarding the benefits of the Investigator's protocol in the treatment of mTBI.

The team discussed these observations with the Investigator, and he (the Investigator) agreed to modify his future presentations and press releases. The DRT recommended that specific public affairs releases be recalled to avoid confusion.

Appendix F. Standards and Criteria

Standards and Criteria

The following standards and criteria are used in this assessment:

Federal

Code of Federal Regulations (CFR)

Title 21 – "Food and Drugs," April 1, 2008

Part 312 of 21 CFR pertains to the Food and Drug Administration (FDA) and specifies requirements for "Investigational New Drugs"

The following portions of 21 CFR Part 312 are applicable to this assessment:

21 CFR Section 312.2 Applicability

(a) Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act.

21 CFR Section 312.3 Definitions

Clinical Investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Investigational new drug means a new drug or biological drug that is used in a clinical investigation.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

21 CFR Section 312.20 Requirements for an IND

(a) A sponsor shall submit an IND to the FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.

Title 32 – National Defense, July 1, 2008

Part 219 of 32 CFR pertains to the "Protection of Human Subjects." This regulation applies to all "research involving human subjects conducted by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research." Accordingly the Department of Defense formulates its policy and

regulation accordingly.

The following portions of 32 CFR Part 219 are applicable to this assessment:

32 CFR Section 219.101 – [policy application]

(a)(1) Research that is conducted or supported by a federal department or agency... must comply with all sections of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

32 CFR Section 219.103 – Assuring compliance with this policy

(a) Each institution engaged in research, which is covered by this policy and which is conducted or supported by a federal department or agency, shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an Institutional Review Board (IRB) provided for in the assurance. Assurances applicable to federally supported or conducted research shall at a minimum include:

(b)(1) Statement of principles governing the institution in the discharge of the responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution.

(b)(4) Written procedures which the IRB will follow.

32 CFR Section 219.107 – IRB membership

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members ... to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects ... the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

32 CFR Section 219.111 – Criteria for IRB approval of research

(a) The IRB shall determine that, among others, the following requirements are satisfied:

(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to

subjects, and the importance of the knowledge that may reasonably be expected to result.

(a)(7)(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence ... additional safeguards have been included in the study to protect the rights and welfare of these subjects.

32 CFR Section 219.116 – General requirements for informed consent

No investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

(a) Basic elements of informed consent include, among others:

(a)(2) A description of any reasonably foreseeable risks or discomforts to the subjects.

United States Code (USC)

Title 18 – 208 Bribery, Graft and Conflicts of Interest, January 3, 2007

Sec. 208. Acts affecting a personal financial interest

(a) Except as permitted by subsection (b) hereof, whoever, being an officer or employee of the executive branch of the United States Government, or of any independent agency of the United States, a Federal Reserve bank director, officer, or employee, or an officer or employee of the District of Columbia, including a special Government employee, participates personally and substantially as a Government officer or employee, through decision, approval, disapproval, recommendation, the rendering of advice, investigation, or otherwise, in a judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, charge, accusation, arrest, or other particular matter in which, to his knowledge, he, his spouse, minor child, general partner, organization in which he is serving as officer, director, trustee, general partner or employee, or any person or organization with whom he is negotiating or has any arrangement concerning prospective employment, has a financial interest, Shall be subject to the penalties set forth in section 216 of this title.

Title 21 – 321 U.S. Federal Food, Drug and Cosmetic Act," January 3, 2007

Section 201 – Definitions

(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals..."

(p) The term "new drug" means –

(1) Any drug ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling ..."

Title 21 – 355 U.S. Food and Drug Administration

Section 505 – New Drugs

(a) Necessity of effective approval of application. No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

Department of Defense

Department of Defense Directive 5230.09 "Clearance of DoD Information for Public Release," August 22, 2008

Department of Defense Directive 5230.09 is the Department of Defense's guidance regarding the clearance of DoD Information for public release. Specifically:

DoDD 5230.09 Section 4. Policy

4. a. Any official DoD information intended for public release that pertains to military matters, national security issues, or subjects of significant concern to the Department of Defense shall be reviewed for clearance prior to release.

Department of Defense Directive (DoDD) 5500.7-R "Joint Ethics Regulation", August 1, 1993

DoDD 5500.7-R is the Joint Ethics Regulation for all DoD military and civilian employees. Chapter 5 addresses "Conflicts of Interest". Specifically Section 5-410(a) prohibits a member from holding conflicting conflicts of interest.

DoDD 5500.7-R Section 5-410 (a) - Related Rules

There is a prohibition on holding conflicting financial interests. See 5 C.F.R. 2635.403 (reference (d)) in subsection 2-100 of this Regulation, 18 U.S.C. 208 (reference (c)), and 5 C.F.R. 2640 (reference (b)) in subsection 5-200 of this Regulation, above.

Department of Defense Directive (DoDD) 3216.02 "Protection of Human Subjects and Adherance to Ethical Standards in DoD-Supported Research," April 24, 2007

DoDD 3216.02 updates policies for protecting the rights and welfare of humans as subjects of study in Department of Defense (DoD) supported research, development, test and evaluation, and other related activities hereafter referred to as "research." Specifically it states:

DoDD 3216.02 Section 1 – Reissuance and purpose

1.3 Supports implementation of 32 CFR Part 219, referred to as the "Common Rule."

DoDD 3216.02 Section 4 – Policy

4.1 The rights and welfare of human subjects in research supported or conducted by the DoD Components shall be protected.

4.3 Applicability of Federal Policy for Protection of Human Subjects in Research.

4.3.1 The Department of Defense has joined with other Federal Agencies to adopt the "Common Rule" Federal policy for protection of human subjects in research. (32 CFR Part 219 is the requirement for the Department of Defense to implement the Common Rule.)

4.3.3 All human subject research supported or conducted by the Department of the Defense shall be conducted under an assurance of compliance acceptable to the funding Agency. Research performed at DoD facilities and funded by the Department of Defense shall have a DoD assurance of compliance.

4.4.3 For research involving more than minimal risk to subjects, an independent medical monitor shall be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate.

4.4.4 For research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers shall not influence the decisions of their subordinates to participate or not to participate as research subjects.

4.8 Research misconduct – All DoD Components shall establish procedures to monitor and review the ethical conduct of research. The DoD Components that conduct or support research shall ensure that data and data collection are conducted in an ethical manner. In cases in which data are not collected in an appropriate manner, the DoD Component shall determine if the misconduct was intentional or reckless; was an isolated event or part of a pattern; had significant impact on the research record; or had significant impact on other researchers or institutions. The DoD Component shall initiate and carry through on any actions that are necessary to ensure resolution of misconduct findings.

Department of the Army

Army Regulations (AR) 40-7, "Use of Investigational Drugs and Devices in Humans and the Use of Schedule 1 Controlled Drug Substances," January 4, 1991

AR 40-7 discusses Department of the Army-sponsored, non-Department of the Army-sponsored, and investigator-sponsored categories for Investigational New Drug applications and Investigational Device Exemptions. Specifically this regulation contains the following guidance applicable to the completion of this assessment:

AR 40-7 Glossary Section II – Terms

- Investigational drug – A drug may be considered investigational when the composition is such that its proposed use is not recognized for the use under the conditions prescribed, or its proposed use is not recommended or suggested in its approved labeling. Experts qualified by scientific training and experience evaluate the safety and effectiveness of drugs to make this determination.
- Investigator-sponsored Investigational New Drug (IND) – An IND application for which the principal investigator of the drug is also identified as the sponsor of the application

AR 40-7 Chapter 4 – Procedures for Use of Investigational Drugs and Devices in U.S. Army Medical Treatment Facilities, Dental Treatment Facilities, and Research Facilities

4-12 Use of an approved drug for an unapproved indication. In situations where data on drug effects from one or more patients are being systematically recorded by a physician for the purpose of substantiating or refuting a claim of therapeutic efficacy in an unlabelled indication for an approved drug, the physician is conducting a clinical investigation, and must adhere to the requirements of AR 40-38 ... in conducting the investigation.

Such a clinical investigation of a drug product that is lawfully marketed in the United States must be done under an IND, unless ALL of the following apply:

a. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used for any other significant change in labeling for the drug.

b. If the drug that is undergoing investigation, is lawfully marketed as a prescription drug product, and the investigation is not intended to support any other significant change in the advertising for the product.

c. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks associated with the use of the drug product.

d. The investigation is conducted in compliance with the requirements for human use review and informed consent set forth in AR 40-38.

e. The drug is not represented in a promotional context as being safe or effective for the purposes for which it is being investigated.

AR 70-25 "Use of Volunteers as Subjects of Research," January 25, 1990

AR 70-25 implements Department of Defense Directive (DoDD) 3216.01. It reflects the legal requirements pertaining to the use of humans as research subjects funded by Research, Development, Test and Evaluation (RDTE) appropriations. Specifically, the following criteria are applicable to this assessment:

AR 70-25 Section 3-1 – General guidance

(e) The determination of level of risk in a research protocol will be made by a Human

Use Committee (a body set up to provide initial and continuing review of research involving the use of human subjects).

(g) RDTE using human subjects is conducted in such a manner that risks to the subjects are minimized and reasonable to anticipated benefits.

(r) A medical monitor is appointed by name if the HUC or approving official determines that the risk is more than minimal.

AR 70-25 Section 3-2 – Procedural guidance

Organization heads conducting RDTE research involving human subjects will:

(a) (3) Establish a HUC.

(c)(1) A protocol will be prepared for all research requiring approval through the HUC.

(c)(3) The protocol is submitted to a scientific review committee composed of individuals qualified by training and experience, and appointed by the commander of the unit to evaluate the validity of the protocol. The purpose of this peer review is to assure that the protocol design will yield scientifically useful data which meet the objective(s) of the study. The committee's recommendations and actions taken by the investigator in response to the recommendations are submitted with the protocol to the HUC.

AR 70-25 Appendix C – Human Use Committees

C-1 b. Each HUC will have at least five members. Member will have diverse backgrounds to ensure thorough review of research studies involving human volunteers as research subjects. Members should be sufficiently qualified through experience and expertise.

C-1 c. Besides having the professional competency to review research studies, the HUC will be able to determine if the proposed research is acceptable. Acceptability will be in terms of Army Medical Department commitments and regulations, applicable law, and standards of conduct and practice.

C-4 c. Some or all of the subjects may be vulnerable to coercion or undue influence such as persons with acute or severe physical or mental illness, or those who are economically or educationally disadvantaged. If so, proper additional safeguards will be included in the study to protect the rights and welfare of these subjects.

AR 70-25 Glossary Section II – Terms

- Medical Monitor – This person is a military or Department of the Army civilian physician qualified by the training and/or experience required to provide care to research subjects for conditions that may arise during the conduct of research, and who monitors human subjects during the conduct of the research.

Brooke Army Medical Center Institutional Review Board (IRB) Standard Operating Procedures (SOP), July 7, 2008

This SOP includes the policies and procedures which apply to the development, review,

approval, conduct, and reporting of clinical investigation protocols conducted under the BAMC IRB. Relevant policies and procedures, specific to this assessment are included below:

2 – Authority of the IRB

2.c. Description of authorities – The IRB will review and approve all research protocols to be conducted at the institutions for which BAMC is the IRB of record. All submissions will be reviewed for:

2.c.(1)(i) Compliance with Army, DoD and federal research regulations.

2.c(1)(ii) Protection of human subjects.

2.c(1)(iii) Scientific and statistical review.

2.c(1)(iv) Determination of which device studies pose significant or non-significant risk.

3 – IRB organizational relationships

3.e. Second-level review of approved protocols

3.e(1) Clinical Investigation Regulatory Office (CIRO) has oversight responsibility for all research within the MEDCOM. All human use and laboratory science protocols that involve IND or IDE items or extramural funding must be approved by CIRO before subjects are enrolled. All other human use and laboratory science protocols are forwarded to CIRO for review only.

7 – Clinical investigation protocols involving human subjects

b. Preparation for application for clinical investigation project

(i) Greater than Minimal Risk

d. Impact Statement – The impact statement must be signed by the Chief of each service or department which may be affected by the research protocol being proposed. If the protocol involves use of drugs … the impact statement must be signed by the Chief of the Department of Pharmacy.

c. Processing of research protocols involving human subjects

(4)(ii) Full Institutional Review Board – Conduct of the IRB meeting. Members of the IRB shall:

1. Ensure study is found to have scientific merit.

2. Determine the level of risk associated with the protocol: minimal risk or more than minimal risk.

3. Ensure that risks to subjects are minimized by using procedures which are consistent with sound research design.

4. Ensure that risks to subjects are reasonable in relation to anticipated benefits, if any, and to weigh the importance of the knowledge that may reasonable be expected to results.

11. Ensure that appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects, when some or all of the subjects are likely to be vulnerable to coercion or undue influence.

d. Requirements for Reporting

(1) Amendments

(i) An amendment is defined as any change in the approved study protocol

(ii) All amendments must be submitted to the IRB prior to instituting the change.

e. Medical Monitors – The Medical Monitors can be physicians, dentists, psychologists, nurses or other health care providers capable of overseeing the progress of the research protocol, especially issues of individual participant management and safety.

e.(2) The IRB will appoint a Medical Monitor for all research protocols involving greater than minimal risk. The Medical Monitor will receive a memorandum of appointment after the protocol is approved. The memorandum will review the responsibilities of the Medical Monitor.

Department of the Navy

U.S. Navy SECNAVINST 3900.39D – "Human Research Protection Program" (HRPP), November 6, 2006

This instruction establishes policy and assigns responsibility for the protection of human subjects in research conducted by, with, or for the Department of the Navy (DON). Specific sections applicable to this assessment are as follows:

4. a.(1) This instruction applies to all biomedical and social-behavioral research involving human subjects conducted by Navy and Marine Corps activities or personnel, involving naval military personnel and DON employees as research subjects, or supported by naval activities through any agreement (e.g., contract, grant, cooperative agreement, or other arrangement), regardless of the source of funding, funding appropriation, nature of support, performance site, or security classification. It also applies to human subject research using DON property, facilities, or assets.

6.a. – Guiding principles

The DON uses the ethical principles outlined in the Belmont Report, "Ethical Principles and Guidelines for the Protection of Human Subjects and Research," as the foundation for its human research protection program.

6.a.(1) Respect for Persons – The rights, welfare, interests, privacy, confidentiality, and safety of human subjects shall be held paramount at all times and all research projects conducted in a manner that avoids all unnecessary physical and mental discomfort, and economic, social or cultural harm.

6.a.(3) Informed Consent – Voluntary informed consent is fundamental to ethical research with humans. Informed consent is not simply a document. It is a process that begins with subject recruitment. Informed consent includes a thorough discussion with prospective subjects and/or their legally authorized representatives and continues for at least the duration of the research.

6.a.(6) Vulnerability and Additional Protections. Additional safeguards shall be provided for subjects who may be considered vulnerable to coercion or undue influence because of their age, health, employment, financial status, or other circumstances. … Other groups warranting additional protection include…. deployed active duty personnel.

6.b – Conflict of interest

Conflict of interest can be defined as any situation in which financial or personal interests may compromise or present the appearance of compromising an individual's or group's judgment in conducting, reviewing, approving, managing, and supporting research. Investigators….must disclose all conflicts of interest, including any financial interests for themselves.

8.g – Principal Investigators (PIs)

PIs have primary responsibility for compliance with all human subject protection regulations, directives, and instructions.

U.S. Navy BUMEDINST 3900.6B "Protection of Human Subjects," October 4, 2001

This instruction applies to all research involving human research participants and offers policy regarding the protection of volunteer human subjects in research. Applicable sections pertinent to this assessment are as follows:

Enclosure (2) Research involving the unlabeled use of drugs and biologics – Any deviation from the indications, dose, route of administration, dosage form or treatment population of a drug…. Approved or licensed by FDA is considered an unlabeled use. The following comments pertain:

(2) If the purpose is not treatment of an individual patient, but rather a scientific study using human research participants, this is considered research and not the "practice of medicine." Such activities are regulated by the FDA and usually require filing of an Investigational New Drug (IND) and compliance with applicable regulations.

U.S. Navy BUMEDINST 6500.3 "Research Integrity, Responsible Conduct of Research Education, and Research Misconduct," June 25, 2009

This instruction establishes policy for the promotion of research integrity, continuing

education in the responsible conduct of research ,and the handling of allegations of research misconduct. Applicable sections pertinent to this assessment are as follows:

6. Policy
It is the policy of Navy Medicine that all personnel will uphold the highest principles of ethics promoting research integrity and the responsible conduct of research as discussed in enclosure (2):

Enclosure (2) "General Principles of Research Ethics and Integrity."

1. The principles of research ethics have developed from diverse historical sources, but coalesce around four general areas of academic professional commitment:

1.a. Academic and professional excellence including, but not limited to: personal integrity and honesty, maintaining academic/discipline-specific standards and methodologies, continuous scholarly and professional formation, peer review and openness to scholarly critique/quality improvement, substantive and effective mentoring, and sound publication practices and responsible authorship;

1.b. Ethical obligations and compliance responsibilities for research protections including areas such as, but not limited to: human subject protections, animal welfare, environmental protections and safety, sound personnel practices, protections against undue influence, and data integrity;

1.c. The ongoing development of the institution and its services including areas such as, but not limited to: mission relevance and adaptation/expansion, discovery and invention in intellectual property and technology transfer, support for the translation of research efforts for public benefit, effective research collaborations and academic interdisciplinary, and international and cross-cultural enrichment;

1.d. Responsibility for preserving the public trust including areas such as, but not limited to: compliance with sponsor and socio-cultural requirements, financial stewardship, appropriate and transparent management of conflicts of interest and commitment, refusal to engage in research misconduct and a commitment to report all such matters to legitimate authority.

Enclosure (2) "Requirements for Research Misconduct"

1.b. Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

1.h. Research misconduct processes will be performed by the command in which the individual who is alleged to have committed research misconduct is currently assigned or employed.

In-Theater Guidance

Multi-National Corps – Iraq (MNC–I) Assurance, June 30, 2008

The OTSG approved the renewal of the MNC–I "Assurance for the Protection of Human

Research Subjects" (DoD A20146) on 30 June 2008. This assurance refers to all U.S. Military assets which fall under MNC–I for organizational and operational control. For the purpose of this assessment, the effective date of this assurance was current for the conduct of this clinical study. Specifically the assurance states the following that is applicable to this assessment:

Part 1 – DoD-Army institutional information

1.B Name of Institution: Multi-National Corps – Iraq

Part 2 – Ethical principles, compliance, and responsibilities of the institution

A. Ethical Principles of the Institution

A. 1. The institution will ensure that all of its activities associated with research involving human subjects are guided by the ethical principles set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report").

A. 3. This Institution acknowledges and accepts its responsibilities for protecting the rights and welfare of human research subjects.

B. Institutional Compliance with Regulations and Policies

B.1. This Institution will comply with 10 United States Code Section 980; 32 CFR 219, 45 CFR Part 46, 21 CFR Parts 50, 56, 312, and 812, DoD Directive 3216.02.

C. Responsibilities of the Institution

C.1.a. The Institutional Official will maintain a Human Research Protection Program (HRPP) that provides policies and procedures on implementing the federal, state, and local policies referenced in this Assurance. The Institutional Official will monitor and ensure compliance with the HRPP.

C.1.b. The Institutional Official bears full responsibility for the conduct of research covered by this Assurance with respect to compliance with applicable federal, state, and local laws.

C.2.a. The IRB will maintain standard operating policies and procedures, as part of the Institution's HRPP, to comply with the terms of this Assurance.

Part 4 – Designation of Institutional Review Boards (IRB)

IRB not considered part of the Institution, but may review research under this Assurance – Great Plains Regional Medical Command, Brooke Army Medical Center, Institutional Review Board. (Refer to DoD "Institutional Agreement for IRB Review between MNC–I and BAMC.")

Part 6 – Institutional Assurance

6.A. Institutional Official Title: Surgeon, Multi-National Force – Iraq (MNF-I) and Multi-National Corps – Iraq (MNC–I)

MNC – I Human Research Protection Program (HRPP), June 24, 2008

The MNC–I, which is part of Multi-National Force – Iraq is the tactical unit responsible for command and control of operations throughout Iraq. MNC–I is covered by the HRPP. Specifics of this program applicable to this assessment are identified below:

1.1 – Components of the institution covered by the HRPP

- This HRPP will monitor research done by individuals or small groups located in theater.
- Authority for this HRPP rests with the MNC–I Surgeon, who serves as the Institutional Official for the MNC–I Assurance.
- The Deputy Director of the Deployed Combat Casualty Research Team (DC2RT) is assigned as the Human Protections Administrator (HPA) and as such oversees the implementation of this HRPP.

1.2 – Goals and objectives of the HRPP

- The HRPP will ensure that all MNC–I research:
- Recognizes the rights and welfare of human research participants and ensures these are adequately protected.
- Is guided by the ethical principles of respect for persons, beneficence, and justice as set forth in the Belmont Report, and is conducted with the highest level of expertise and integrity.
- Complies with applicable federal, DoD, and DA laws and regulations.

1.5 – Scientific and scholarly validity review and ethics review

- Each human subject research protocol must undergo scientific review and assessment to determine if the protocol contains scientific merit.
- The HPA evaluates a protocol for the following relevant factors:
    a. Is the protocol relevant to military medicine and can it only be conducted in the Theater of Operations?
    b. Is it appropriately designed to yield scientifically useful information?
    c. Is the protocol in the correct format, and have all sections been addressed?
    d. Is the protocol in compliance with the rules and regulations which govern human subject research?

- The HPA forwards the protocol to the Human Use Protocol Coordinator (HUPC), U.S. Army Institute for Surgical Research (USAISR) for scientific review. The HUPC forwards the proposals to the identified reviewers with an accompanying checklist to aid in their review. The HPA facilitates discussion between the scientific reviewers and the principal investigator (PI). All correspondence including scientific reviewer checklists, PI responses to questions and the revised protocol are submitted to the Senior Scientist, USAISR for final review and protocol signature. The signature indicates a scientific review of the protocol has been conducted and that the protocol is approved for submission to the BAMC IRB.

1.6 – Primary officers and organizational components carrying out the HRPP

- The Principal Investigator and other investigators are responsible for reporting promptly to the appropriate IRB, through the HPA, any proposed changes to the research activity. The changes shall not be initiated without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

2.2 – Matching scientific review and IRB resources to volume and types of human research

- All protocols to be conducted in theater will undergo two scientific reviews. These reviews are to determine if the proposed study has scientific merit, proposes to answer a valid scientific question that has not already been sufficiently answered, and is constructed in such a manner as to be able to answer the proposed question.
- The protocol is sent to two subject matter experts (SME) in the field of the proposed research. Upon receiving feedback from the SMEs, the HPA works with the PI to formulate changes and responses to any questions or concerns raised during the review.
- After the scientific review has been addressed, and the MNC–I Research Director and MNC–I Surgeon agree that the research is appropriate to be conducted in theater, the protocol is forwarded to the BAMC IRB for final evaluation. The IRB evaluates the protocol for human subject protection and compliance with the scientific reviewers' recommendations. The IRB holds the final authority to declare a protocol scientifically valid and appropriate to conduct on human subjects with all required and necessary protections in place.

3.2 – Conflict of interest and undue influence

- An investigator is obligated to disclose any possible conflict of interest prior to protocol review and approval. Possible conflicts of interest include … a proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement.

- Regarding undue influence, ethical and regulatory requirements prohibit the coercion of human subjects to take part in human research efforts. In the informed consent process, investigators and research staff will ensure that this matter is strictly enforced.

Chapter 5 – Investigational or unlicensed test articles

In general, no interventional research is done under the MNC–I Assurance using investigational or unlicensed test articles necessarily regulated by the Food and Drug Administration (FDA).

Chapter 9 – Participant recruitment and selection

The HPA will ensure that recruitment of military personnel does not involve any possible coercion or reality of conflict of interest, undue influence, or coercion, no matter how subtle.

Chapter 12 – Dissemination of research findings
Where human research efforts may result either in professional presentations or peer reviewed publications, PAO reviews and approvals must be given before such efforts are presented or published. Publications involving human subject research must contain DoD/DA disclaimers in accordance with federal policy and the policies of publishing houses.

Multi-National Corps – Iraq (MNC–I) Operational Orders (Tab G to Appendix 2 to Annex Q) "Mild Traumatic Brain Injury (Concussion)"

This set of operational orders provides theater-specific guidance for the medical evaluation, management and documentation of mild traumatic brain injury (mTBI)/Concussion.

4. Definition. Mild traumatic brain injury (concussion) in military operational settings is defined as an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicular accident which causes an alteration in mental status. Related symptoms may include: headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering and/or difficulty concentrating.

5. Execution.

a.1(b) MND/F Surgeons, Medical Officers in separate units, and medical unit commanders will ensure all medical providers are familiar with the Concussion Management in a Deployed Setting (enclosure (1) and the Military Acute Concussion Evaluation (MACE) (enclosure 2). For the initial in-theater evaluation and management of possible mTBI (concussion), providers should complete a history and physical exam, with focus on the neurological examination. This encounter should include at a minimum the MACE history (questions I – VIII).

b. Coordinating Instructions.

(3) Providers should follow the guidelines outlined in enclosure (1) (Joint

Theater Trauma System Clinical Practice Guidelines) for the initial management of mTBI.

(7) Providers will monitor for persistent symptoms and neurological findings. Manage post-concussive symptoms as clinically appropriate, avoiding narcotics, non-steroidal inflammatory medications and aspirin until cleared to return to duty.

Multi-National Corps – Iraq (MNC–I) Standard Operating Procedures (Tab P, Appendix 4, Section Q) "Mild Traumatic Brain Injury," November 30, 2007

This document provides leaders and medical personnel with MNC-I theater-specific guidance concerning U.S. Military personnel at risk for having a mild traumatic brain injury and guidance for the medical evaluation and management of these patients.

4. Execution.

A.(1)(B) MND/F Surgeons, Medical Officers in MNC-I separate units, and medical unit commanders will ensure that all medical personnel are aware of and use the JTTS CPG for in-theater evaluation and management of patients with a possible mTBI (concussion). Do a history-documenting any symptoms; perform a physical exam with focus on a complete neurological examination. Additionally, this encounter will include the MACE screening results.

Joint Theater Trauma System (JTTS) Clinical Practice Guidelines (CPG), "Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting," November 2008

This document provides updated guidance for the diagnosis, evaluation, treatment, follow-up and return to duty of mild traumatic brain injury patients.

5. Evaluation and Management of Concussion in the Deployed Setting
   a. Treatment of concussion in the deployed setting

   2) Headache Management
   - Acutely, use acetaminophen
   - Avoid the use of Tramadol, NSAIDs, ASA, or other platelet inhibitors for the first forty-eight hours or until neuroimaging demonstrates the absence of intracranial pathology
   - Avoid narcotics as these are not indicated for the management of posttraumatic headaches
   - After 1 week, consider nortriptyline or amitriptyline, 25mg po qhs for headaches occurring > 2 times/week. It is recommended that only 7-10 pills are dispensed at a time.

   b. Assessment and Treatment of Acute Mild TBI

   (1) The following three algorithms (Appendices A, B and C), offered as clinical practice guidelines, should not be interpreted as a substitute for sound clinical judgment. The Military Acute Concussion Evaluation (MACE) serves as a standardized tool for the evaluation of symptoms and cognitive deficits that may

follow concussion. MACE scores do not diagnose concussion. Concussion remains a clinical diagnosis.

JTTS CPG for mTBI Appendix D: Concussion Patient Information Sheet

5. Does medicine help?

The treatment for concussion is limited duty and rest. If you have a headache, you can usually take acetaminophen (brand name: Tylenol). Non-steroidal medications like aspirin and ibuprofen (Advil, Motrin) may increase the risk of bleeding; therefore these medications should only be taken upon the advice of a medical provider. Narcotics may cause significant sedation and interfere with your ability to perform; therefore narcotics like hydrocodone (Vicodin) or oxycodone (Percocet) should be avoided unless you have another medical reason to take them. Over-use of any of these medicines may lead to rebound headaches, making you feel worse.

6. Warning Signs

Certain signs and symptoms of a concussion require immediate care. If you experience any of the following go immediately to the nearest aid station or emergency room, at any time of day or night:

- Progressively declining level of alertness
- Seizures
- Double vision
- Slurred speech
- Unable to recognize people and places
- Unequal pupils
- Repeated vomiting
- Worsening headache
- Weakness or numbness in arms or legs
- Unsteadiness on feet

Appendix G. Management Comments

Under Secretary of Defense for Acquisition, Technology, and Logistics

RESEARCH AND ENGINEERING

ASSISTANT SECRETARY OF DEFENSE
3030 DEFENSE PENTAGON
WASHINGTON, DC 20301-3030

FEB 0 8 2011

MEMORANDUM FOR DEPUTY INSPECTOR GENERAL, SPECIAL PLANS AND OPERATIONS, DoDIG

THROUGH: DIRECTOR, ACQUISITION RESOURCES AND ANALYSIS 2/11/11

SUBJECT: Response to DoD IG Draft Report on Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D000SPO-0242.00)

As requested, I am providing USD(AT&L) responses to recommendations C5.1, C5.2, C6.1 and C6.2 contained in the subject report. Each of the responses to the four recommendations involves updating DoD Directive (DoDD) 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research." This DoD policy is being updated as DoD Instruction (DoDI) 3216.02. A copy of draft DoDI 3216.02 that was submitted for formal coordination is at Tab A. Many of the DoD Components have provided their formal coordination (Mr. Randolph Stone coordinated without comment on behalf of the Inspector General on December 3, 2010.) If all the DoD Components concur with the draft, recommend only minor modifications, and comply with the established timelines for processing DoD Instructions, DoDI 3216.02 should be signed by May 31, 2011. It is anticipated the Military Services will update their policy(s) for protecting human subjects when DoDI 3216.02 is signed. My office will review any significant changes to DoD Component level policies to ensure the DoD Components remain compliant with the DoD level policy.

Recommendation C.5.1: The OIG recommended the USD(AT&L) "review and update DoDD 3216.02 to ensure there is appropriate reference to identifying deployed personnel as a group or potential research subjects that could be vulnerable to coercion or undue influence. Additionally, this directive should include a description of additional protections needed to ensure that the rights of research subjects that are deployed are safeguarded."

Response: Partially Concur. I concur with the need to update the DoDD 3216.02 with respect to obtaining informed consent by subjects that is free of coercion or undue influence. However, there is no evidence that deployed service members are more vulnerable to coercion than non-deployed service members or other DoD personnel. The draft DoDI includes a section describing additional requirements for populations needing additional protections (Section 7 of Enclosure 3 of the draft DoDI). One subsection describes additional protections for all DoD personnel (Paragraph 7.e. of Enclosure 3). In addition to retaining requirements in the current DoDD 3216.02 (e.g., prohibition of superiors influencing the decision of subordinates to volunteer and prohibition of supervisors attending recruitment sessions), the draft DoDI requires the Institutional Review Board (IRB) to discuss the need to appoint an ombudsman to monitor the recruitment process to ensure the subject's enrollment is both voluntary and informed. (The IRB must review and approve all research involving human subjects as described in 32 Code of Federal Regulations Part 219.) The draft DoDI better explains the requirements of protecting all Military Service members from coercion or undue influence.

Recommendation C.5.2: The OIG recommended the USD(AT&L) "ensure that in-theater research oversight authorities receive training regarding additional safeguards that should be considered to protect the rights of research participants who are deployed to a combat zone."

Response: Concur. The draft DoDI has sections regarding education and training requirements for DoD personnel involved human subject research. The draft DoDI requires the DoD Components to ensure all DoD personnel receive initial and continuing education commensurate with their duties and responsibilities (Section 5 of Enclosure 3 of the draft DoDI at Tab A). The draft DoDI assigns the Assistant Secretary of Defense for Research and Engineering (ASD(R&E)) the responsibility for developing a framework for educational training requirements (Paragraph 1.f. of Enclosure 2). The DoD Components have informally coordinated on a draft framework that lists minimum education topics for different roles that personnel have in protecting human subjects and for different types of research. We expect this action to be complete by June 30, 2011. My office will work with the DoD Component as they update and implement their policy(s) for protecting human subjects to ensure personnel involved in the oversight of in-theater research have appropriate training.

Recommendation C.6.1: The OIG recommended the USD(AT&L) "coordinate with the Military Services to develop, update and align DoD and Service level policies related to the investigation of medical research misconduct in a joint-service, deployed environment."

Response: Concur. I concur with the need to update the DoDD 3216.02 with respect to clarifying investigation of research misconduct in a collaborative environment. The recommendation will include all the DoD Components supporting human subject research and cover all DoD conducted research, regardless of the location of the research. Since DoDD 3216.02 was last signed in 2002, DoDI 3210.7, "Research Integrity and Misconduct," (Tab B) was published to provide guidance on addressing allegations of research misconduct. DoDI 3210.7 has coverage of both the potential need to assign joint responsibility (paragraph 6.2.3 of Tab B), as well as a section on non-compliance by DoD Components concerning intramural research (paragraph E3.1.11 of Enclosure 3 of Tab B). Similarly, the draft DoDI 3216.02 has a section about noncompliance with the Instruction (Section 16. of Enclosure 3 of the draft DoDI at Tab A). When more than one DoD Component is involved in an allegation, the draft DoDI directs the DoD institutions to jointly determine and assign responsibilities for responding to the allegation. This should close any perceived gap between the issuances for human subject research and research misconduct as both address this topic. As long as a DoD Component is complying with DoDI 3210.7 and DoDI 3216.02 as drafted, no additional requirements are needed if the allegation involves personnel at a deployed location.

Recommendation C.6.2: The OIG recommended the USD(AT&L) "coordinate with the Military Services to develop, update and align DoD and Service level policies related to the conduct of clinical research to ensure there is better interoperability among the Services in cases where research may be conducted in a joint-service environment."

Response: Concur. When human subject research is being supported by more than one DoD Component, the draft DoDI encourages communication, coordination, and reliance to avoid unnecessary duplication of requirements for conducting human subject research (Section 3 of Enclosure 3 of the draft DoDI at Tab A). My office will work with the Military Services as they update their policy(s) for protecting human subjects to improve harmonization and reliance when

reviewing and approving collaborative research. In addition there are other complementary mechanisms within the DoD to promote interoperability and coordination of joint research programs, such as the Armed Services Biomedical Research Evaluation and Management Committee and the DoD Force Health Protection Council.

Please contact (Patty Decot at 703-588-7402 or patty.decot@osd.mil) if additional information is required.

for

Zachary J. Lemnios

Attachment:
As stated

3

Department of the Army

DEPARTMENT OF THE ARMY
OFFICE OF THE ASSISTANT SECRETARY
MANPOWER AND RESERVE AFFAIRS
111 ARMY PENTAGON
WASHINGTON, DC 20310-0111

SAMR-MP

MEMORANDUM FOR Inspector General (IG), Department of Defense (DoD), 400 Army Navy Drive, Arlington, Virginia 22202-4704

SUBJECT: Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

1. Reference: Memorandum from the Department of Defense Inspector General to the Deputy Chief Management Officer, subject: same as above.

2. I have reviewed the draft Department of Defense Inspector General report assessing that the Department of Defense's guidance regarding the performance of research on human subjects (in this case deployed, injured U. S. military personnel in Iraq) was violated in a DoD approved clinical research trial evaluating a treatment for mild traumatic brain injury. The Army concurs with comments to the DoD IG draft report. Enclosed are comments from The Army Surgeon General.

3. The Secretariat point of contact is [redacted] at (703) 692-[redacted] or [redacted]@us.army.mil.

Encl

SAMUEL B. RETHERFORD
Deputy Assistant Secretary of the Army
Military Personnel 9 Feb 2011

b(6)

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

FEB 7 2011

DASG-ZA

MEMORANDUM FOR Inspector General (IG), Department of Defense (DoD), 400 Army Navy Drive, Arlington, VA 22202-4704

SUBJECT: Comments in Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

1. I appreciate the DoD IG's comprehensive investigation of this complaint involving clinical research conducted in Iraq with deployed Service members. The U.S. Army is committed to ensuring that research involving human subjects adheres to the highest ethical standards and is conducted in full compliance with federal, DoD and Army regulatory requirements. The recommendations included in this report will assist us in improving our efforts in the protection of human research subjects.

a. As requested, I am providing comments regarding the observations and recommendations in the draft report that are directed to the US Army Surgeon General and the US Army Medical Command (USAMEDCOM), specifically Observations C.1 - 5 and Recommendations C.1.1-C1.5; C.2.1-C.2.5; C.3.1-C.3.3; C.4.1-C.4.3; and C.5.3-C.5.4.

b. Please note that, although the Recommendations Table on Page 5 of the draft report indicates there is a Recommendation C.1.6, no such Recommendation is listed on page 50. Additional administrative correction comments regarding the document have been provided to the DoD IG in a separate communication sent on 9 January 2011 by the Army POC for this action.

2. Observation C.1. The DoD IG observed that "[a]lthough two potential conflicts of interest existed, processes used during the review and approval of medical research were not effective in identifying and addressing them." I concur with this observation. The following are my responses to the five recommendations to the USAMEDCOM that accompany this observation:

a. Recommendation C.1.1. "Review and update AR 70-25 and AR 40-38 to clarify requirements for disclosing potential conflicts of interest during the conduct of clinical research."

Response: Concur. The Army will combine AR-70-25 and AR 40-38 into an updated consolidated Army human research protections regulation that clarifies the requirements for disclosing and managing potential and actual conflicts of interests that occur prior to and during the conduct of research involving human subjects. We expect this regulation to be approved by 30 April 2012. In the interim I will send a targeted message detailing these requirements to all Army Activities that support research involving human subjects by 28 February 2011. I will follow-up with a message to all Army Activities (ALARACT) by 15 March 2011.

DASG-ZA
SUBJECT: Comments in Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

b. Recommendation C.1.2. "Ensure the Review Board's Standard Operating Procedures are updated to clarify requirements for disclosing potential conflicts of interest."

Response: Concur. Note that the Brooke Army Medical Center (BAMC) Institutional Review Board's (IRB) is the Review Board described in this report. See below for a consolidated response to DoD IG Recommendation C.1.2. and Recommendation C.1.3.

c. Recommendation C.1.3. "Implement the use of a 'disclosure form' to be submitted along with research protocols for Review Board consideration, in order to ensure potential conflicts of interest are identified by the investigator and considered by the Review Board."

Response: Concur. The Director, Army Human Research Protections Office (AHRPO), will ensure that the BAMC IRB Standard Operating Procedures (SOPs) are updated to clarify requirements for disclosing potential conflicts of interest. This procedure will include the use of a comprehensive "disclosure form" to ensure potential conflicts of interest are identified by the investigator and considered by the IRB. These SOPs will be updated, reviewed and approved by 28 February 2011.

Note: In Spring 2010, the Institutional Officials of the Multi-National Forces-Iraq (MNF-I) and US Forces-Afghanistan signed Institutional Agreements with the Headquarters, US Army Medical Research and Materiel Command (HQ USAMRMC) adding the HQ USAMRMC IRB to their DoD Assurances for Protection of Human Research Subjects ("Assurances"). The USAMRMC IRB has served as the IRB of record for all new Theatre protocols since 14 June 2010. The HQ USAMRMC IRB Policy regarding conflict of interest is at Tab A. It employs an Investigator Disclosure Form (Tab B).

d. Recommendation C.1.4. "Ensure that there are policies and procedures in place for individuals or teams that are responsible to conduct research study reviews and investigations in a deployed setting. Specifically, ensure that individuals involved in the review must be independent and not previously involved in the research protocol review and approval process."

Response: Concur. In March, 2009, an independent MNF-I Human Protections Administrator (HPA) position was established. This action was taken in recognition of the potential for conflict of interest that occurred in requiring the Deputy Director of the Army-sponsored Deployed Combat Casualty Research Team (DC2RT) charged with the facilitation of research in Iraq to also serve as the individual with on-site responsibility for ensuring an objective review of the research for compliance with human subjects protection regulatory requirements. The MNF-I HPA reported to the Institutional Official (MNF-I Command Surgeon) and was responsible for the compliance oversight of all human research conducted under the Army approved MNF-I DoD Assurance. An Army Medical Service Corps Colonel was the first officer assigned to that position for one year. That position remained an essential component of the MNF-I Human Research Protection Program (HRPP) until the MNF-I Assurance was replaced in August 2010 by the US Central Command (USCENTCOM) Assurance that now covers the Joint Operating Areas of Iraq, Kuwait and Afghanistan.

The USCENTCOM HRPP Plan (Tab C) serves as the foundation for the current USCENTCOM Army-approved DoD Assurance (Tab D). This HRPP describes the HPA's responsibilities. The

DASG-ZA
SUBJECT: Comments in Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

HPA is independent of the now "Joint" (formerly "Deployed") Combat Casualty Research Team (JC2RT) and reports directly to the In-theatre Institutional Official. The SOP for USCENTCOM HPA monitoring of human research studies was originally developed and implemented in October 2009. The title of the SOP was revised in January 2011 to better reflect its operational independence from the JC2RT (Tab E). HPA monitoring and audit reports are provided to the Institutional Official and to the Director, HQ USAMRMC IRB.

e. Recommendation C.1.5. "Pending the outcome of the U.S. Navy investigation, conduct a review of the process used during the Deployed Research Team's visit to Camp TQ to identify any necessary changes needed to ensure that future reviews are complete and accurate."

Response: Concur. The Director, AHRPO, will review the process used during the DC2RT's visit to Camp TQ to identify any necessary changes needed to ensure that future reviews are complete and accurate. The AHRPO report will be completed by 15 May 2011. These results will be further evaluated upon receipt of the outcome of the U.S. Navy investigation.

3. Observation C.2. The DoD IG observed that "[t]he Research Review Board was not effective in acknowledging or complying with Food and Drug Administration (FDA) regulations for the conduct of clinical trials using Investigational New Drugs (IND)." I concur with this observation. The following are my responses to the five recommendations to the USAMEDCOM that accompany this observation:

a. Recommendation C.2.1. "Conduct a review into the process used by the Review Board which led to the decision to recommend approval for this research protocol without submission of an Investigational New Drug application."

Response: Concur. The Director, AHRPO, will conduct a review into the process used by the BAMC IRB which led to the decision to recommend approval for this research protocol without submission of an IND. AHRPO will also review the current BAMC IRB processes and SOPs to ensure that the system deficiencies that led to the failure to identify the requirement for an IND application in this case have been addressed. This AHRPO review and report to me will be completed by 28 February 2011.

b. Recommendation C.2.2. "Review and update AR 40-7 to clarify requirements regarding use of investigational drugs in medical research, to include intended use of nutritional supplements as experimental drugs. Additionally, identify the U.S. Army Medical Materiel Development Activity Division of Regulated Activities and Compliance as a consulting agency for researchers and institutional review boards regarding interpretation of FDA regulations and Investigational New Drug determinations."

Response: Concur. Army Regulation 40-7, "Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances" was updated on 19 October 2009 (Tab F). The US Army Medical Materiel Development Activity Division of Regulated Activities and Compliance (USAMMDA DRAC) will update AR 40-7 with respect to clarifying, based on FDA regulations and the latest guidance from FDA, requirements for submission of IND applications for studies utilizing nutritional supplements as experimental drugs. The update will include identifying USAMMDA DRAC as the consulting agency for

researchers and institutional review boards for interpretation of FDA regulations and IND determinations. Expected completion of the updated AR 40-7 is by 30 April 2012.

c. Recommendation C.2.3. "Update the Review Board's policies and procedures to ensure compliance with Investigational New Drug considerations and procedures. Additionally, ensure that these policies and procedures include prompt consultation with a subject matter expert for FDA-related matters, particularly for Investigational New Drugs, as well as for any other matters outside the scope of Review Board members' expertise."

Response: Concur. The Director, AHRPO, will ensure that BAMC IRB SOPs are updated to require the comprehensive review of clinical research involving the use of medical products and/or devices to ensure compliance with FDA regulations regarding INDs and Investigational Device Exemptions (IDEs). These SOPs will identify procedures for consulting the USAMMDA DRAC for interpretation of FDA regulations and provision of IND/IDE determinations. The SOPs will include checklists for researchers to use at the time of protocol submission which identify the criteria used in making an IND or IDE determination. These SOPs will be updated, reviewed and approved by 28 February 2011.

Note: The HQ USAMRMC IRB protocol application (Tab G) template currently in use for all new research in Theatre includes two sections to solicit information from the researcher regarding planned use of any investigational or approved drugs, dietary supplements, biologics, or devices in the proposed research [one in Part A (Section 8) and one in Part C (Section 7.2)]. The IND and IDE Checklists used by the HQ USAMRMC IRB support staff in preparing the protocols for IRB review are included at Tab H. This information is used by the IRB in making regulatory determinations and/or requesting subject matter expert consultation to ensure that all requirements for IND considerations are met.

d. Recommendation C.2.4. "Develop a specific checklist for researchers to use at the time of protocol submission which identifies the criteria used in making an Investigational New Drug determination. Additionally, this form could be used by scientific reviewers and the Review Board to ensure that all requirements for Investigational New Drug considerations are met."

Response: Concur, see response to Recommendation C.2.3. In addition, please note that it is the institution engaged in research and the institution's IRB's responsibility to identify the FDA regulatory requirements for the conduct of human subjects research. The Scientific Review Committee's primary responsibility is to assess the scientific integrity of a proposed study. Thus we will not add these FDA regulatory checklists to the Scientific Review Committee SOPs.

e. Recommendation C.2.5. "Ensure that all individuals involved in the submission, review, and approval of clinical research protocols receive training in the use of investigational drugs, Food and Drug Administration regulations and the Investigational New Drug process."

Response: Concur. Both AR 70-25 and AR 40-7 will be updated to include a requirement for individuals involved in the submission, review, and approval of clinical research protocols to receive training in FDA regulations applicable to the conduct of studies involving the administration of medical products and the use of medical devices. We expect these regulations to be updated by 30 April 2012.

DASG-ZA
SUBJECT: Comments in Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

4. Observation C.3. The DoD IG observed that "[e]xisting procedures used during the review of the Research Protocol failed to resolve scientific peer reviewer concerns." I concur with this observation. The following are my responses to the three recommendations to the USAMEDCOM that accompany this observation:

a. Recommendation C.3.1. "Conduct a review into the process used by the HPA and USAISR during the scientific review of the research protocol and identify improvements needed to ensure that future scientific reviews are thorough, accurate and address all concerns necessary for a valid and scientifically sound research proposal."

Response: Concur. Please note that, at the time this event occurred, it was the Deputy Director, DC2RT's, responsibility to forward research protocols from the MNF-I to the USAISR for scientific review. The Deputy Director had assumed an additional duty of serving as the HPA. On 19 June 2010, the USCENTCOM and US Army Institute of Surgical Research USAISR) established a revised process for scientific review and approval of USCENTCOM research protocols. The current SOP for scientific review (Tab I) includes robust procedures to ensure that future scientific reviews are thorough, accurate and address all concerns necessary for a valid and scientifically sound research proposal.

b. Recommendation C.3.2. "Review and update AR 40-7 to include a more detailed description of the process and procedure for communication used during a scientific peer review, to ensure that actions taken are adequate to address any of the reviewers' stated concerns or questions. Consider the encouragement of an open exchange of information among the scientific peer reviewers, the investigator, and the review board to resolve any concerns or differences of opinion."

Response: Concur, however regulation to be updated is AR 70-25. AR 70-25, "Use of Volunteers as Subjects of Research" dated 25 January 1990; AR 40-38; "Clinical Investigation Program", 1 September 1989; and AR 40-7, "Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans including Schedule I Controlled Substances", 10 October 2009, are the current regulations governing the Army conduct of research involving human subjects. AR 70-25 and AR 40-38 will be consolidated into one updated Army regulation governing the conduct of research involving human subjects. This updated regulation will include a more detailed description of the minimum requirements for the scientific review process. It will address procedures for communication used during a scientific peer review. We will also encourage an open exchange of information among the scientific peer reviewers, the investigator, and the IRB to resolve any concerns or differences of opinion. The current AR 40-7 addresses the requirement for scientific review and references AR 70-25 in its discussion of review requirements.

c. Recommendation C.3.3. "Update the Review Board's SOP to include a detailed scientific peer review checklist which includes a section dedicated to medications and considerations for Investigational New Drug determinations."

Response: Concur, however, it is the institution engaged in research and its IRB's responsibility to identify the FDA regulatory requirements for the conduct of human subjects research, the

checklists outlining regulatory considerations for INDs and IDEs will be included in the BAMC IRB SOPs as well as the revised AR 70-25. Please note that the scientific review process is generally a separate activity that involves the assessment of the scientific validity of a proposed study.

5. Observation C.4. The DoD IG observed that "[e]xisting processes and tools used during the review and approval of the Clinical Trial failed to effectively leverage the Medical Monitor role in protecting research participants." I concur with this observation. The following are my responses to the three recommendations to the USAMEDCOM that accompany this observation.

a. Recommendation C.4.1. "Conduct a review into the process used by the Review Board to select an appropriate individual to serve as medical monitor for the Research Protocol. Additionally, identify improvements needed for research studies to involve medical monitors to ensure that there are maximum protections of the rights and welfare of research participants."

Response: Concur. The Director, AHRPO, will conduct a review of the process used by the BAMC IRB to select an appropriate individual to serve as medical monitor for the Research Protocol. Additionally, AHRPO will identify improvements needed for research studies to involve medical monitors to ensure that there are maximum protections of the rights and welfare of research participants. This review will be completed by 15 May 2011.

b. Recommendation C.4.2. "Review and update AR 70-25 to ensure there is appropriate detail regarding roles and responsibilities, as well as qualifications of a medical monitor. Specifically this guidance should require that medical monitor roles and responsibilities be provided in writing in the form of an appointment letter with clearly stated reporting requirements."

Response: Concur. The Army will combine AR-70-25 and AR 40-38 into an updated consolidated Army human research protections regulation that will include appropriate detail regarding medical monitor roles, responsibilities, and qualifications. In addition the requirement for written designation of the medical monitor will be established. We expect this regulation to be published by 30 April 2012.

c. Recommendation C.4.3. "Ensure that the Review Board's Standard Operating Procedures include procedures and/or checklists to ensure all research protocol requirements are met prior to giving approval to initiate the research. Specifically, ensure that criteria are developed to document that a medical monitor was assigned (if required) and appointed in writing including details on their role and responsibilities."

Response: Concur. The Director, AHRPO, will ensure that BAMC IRB SOPs are updated to include procedures and checklists to ensure all research protocol requirements are met prior to giving approval to initiate the research. Specifically, AHRPO will ensure that criteria include documentation that a medical monitor was assigned (if required) and his/her roles and responsibilities were delineated. These SOPs will be updated, reviewed and approved by 28 February 2011.

DASG-ZA
SUBJECT: Comments in Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

6. Observation C.5. The DoD IG observed that "[e]xisting regulations and procedures used by the investigator and research authorities failed to identify and appropriately protect deployed U.S. Service members as a vulnerable human subject group." I concur that the procedures used by the investigator and research authorities failed to adequately identify and appropriately protect the subjects of the research study reviewed by the DoD IG. However, to the extent that these subjects were vulnerable to undue influence or coercion, such vulnerability was not because of their status as deployed US Service Members. Their vulnerability was due to the nature of their injuries and the FRAGO directing movement of patients to Camp TQ. Deployed US Service Members who may participate in research are not inherently more vulnerable to undue influence or coercion than non-deployed US Service Members, and should not be expressly identified as members of a vulnerable group.

Existing regulations (32 CFR 219, DoDD 3216.02 and AR 70-25) identify appropriate "vulnerable" groups (e.g., children, prisoners, pregnant women, mentally or physically disabled persons, and economically or educationally disadvantaged persons) for whom additional safeguards are usually needed, and require additional safeguards to protect rights and welfare of other subjects who do not belong to named vulnerable groups, but who are nevertheless recognized to be vulnerable. The recognition of the potential for participants to be vulnerable to undue influence or coercion is based upon a comprehensive review of all aspects of the proposed study. The IRB is charged with ensuring that safeguards are in place to address any such vulnerability. In addition, DoDD 3216.02 and AR 70-25 discuss protections for all military personnel, deployed and non-deployed, to minimize likelihood of undue influence and coercion.

The following are my responses to the two recommendations to the USAMEDCOM that accompany this observation:

a. Recommendation C.5.3. "Conduct a review into the process used by the Review Board to recommend approval for the Clinical Trial. Additionally, review the report provided by the Deployed Research Team to ensure it was accurate with appropriate recommendations and actions taken."

Response: Concur. The Director, AHRPO, will conduct a review into the process used by the BAMC IRB to recommend approval of the trial and will review the process used during the Deployed Research Team's visit to Camp TQ to ensure it was accurate with appropriate recommendations and actions taken. The report will be completed by 15 April 2011.

b. Recommendation C.5.4. "Review and update AR 70-25 to ensure there is appropriate reference to identifying deployed personnel as a group of potential research subjects that could be vulnerable to coercion or undue influence. Additionally, this directive should include a description of additional protections needed to ensure that the rights of research subjects that are deployed are safeguarded."

Response: Concur. All Soldiers represent a unique category of vulnerability to coercion or undue influence. It is the Army's position that deployed Soldiers will not be considered a subset of this population. The Army is in the early process of combining AR-70-25 and AR 40-38 into an updated consolidated Army human research protections regulation. The Army will ensure that the regulation considers vulnerabilities of all military personnel to undue influence and

DASG-ZA
SUBJECT: Comments in Response to DoD IG Draft Report on Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00) dated December 22, 2010

coercion, and that military-specific protections are included. Identification of vulnerable groups and protections for military personnel will be consistent with the revision of DoDD 3216.02 (being updated as DoDI 3216.02). It is anticipated that protections for military personnel in the DoDI will include prohibition of superiors influencing the decision of subordinates to volunteer, prohibition of supervisors attending recruitment sessions, and a requirement that the IRB discuss the need to appoint an ombudsman to monitor the recruitment process. Thus this updated regulation will not identify deployed personnel as a uniquely vulnerable population and will not describe special safeguards applicable to deployed personnel. We expect the Army regulation to be approved by 30 April 2012.

7. Please contact [redacted] Acting Director, Army Human Research Protections Office, [redacted]@us.army.mil, 703-693[redacted] (DSN [redacted] if additional information is required.

ERIC B. SCHOOMAKER
Lieutenant General
The Surgeon General and
Commanding General, USAMEDCOM

8

b(6)

Department of the Navy

DEPARTMENT OF THE NAVY
NAVAL INSPECTOR GENERAL
1254 9TH STREET SE
WASHINGTON NAVY YARD DC 20374-5006

IN REPLY REFER TO:
5041/201000537
Ser N64/0076
03 Feb 11

From: Naval Inspector General
To: Inspector General, Department of Defense (Attn: Special Plans and Operations)

Subj: DRAFT REPORT: DODIG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

Ref: (a) DODIG Memorandum of 22 December 2010

Encl: (1) BUMED ltr 7502 Ser M09/UN093000092 of 28 Jan 11

1. Per reference (a), enclosure (1) is forwarded on behalf of Chief, Bureau of Medicine and Surgery.

2. My point of contact for this case is [redacted] United States Navy. [redacted] may be contacted at commercial (202) 433-[redacted] DSN 288-[redacted], or via e-mail at [redacted]@navy.mil

ANDREA E. BROTHERTON
Deputy

Copy to: (w/o enclosures)
BUMED (M09)

b(6)

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DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY
2300 E STREET NW
WASHINGTON DC 20372-5300

7502 IN REPLY REFER TO
Ser M09/UN093000092
JAN 2 8 2011

From: Chief, Bureau of Medicine and Surgery
To: Office of the Inspector General, Department of Defense (Attn: Special Plans and Operations)
Via: Naval Inspector General

Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

Ref: (a) DOD IG Memorandum of 22 Dec 2010

1. Per reference (a) and in accordance with DoDD 7650.3, the following comments/ recommendations are forwarded for your consideration prior to finalizing the subject report.

a. General Comments: A review of the draft report identified terminology that was used incorrectly. Specifically, on page 6 of the report and throughout the document, the term "research misconduct" is incorrectly used. The matters discussed do not meet federal-wide and agency-specific definitions of research misconduct. OSTP 2000 Federal Policy on Research Misconduct, 42 CFR 50 and 93, and DoDI 3210.7 strictly define research misconduct as falsification, fabrication, or plagiarism. Recommend the following corrections be made:

A.1.1, delete "research misconduct;" substitute with "violation of research integrity and ethics standards." Correct section throughout. Correct remainder of document as relevant.

A.2.1, delete "research misconduct;" substitute with "regulatory non-compliance." Correct section throughout. Correct remainder of document as relevant.

A.3.1, delete "research misconduct;" substitute with "regulatory non-compliance and violations of human research protections." Correct section throughout. Correct remainder of document as relevant.

A.4.1, delete "research misconduct;" substitute with "regulatory non-compliance and violations of human research protections." Correct section throughout. Correct remainder of document as relevant.

A.5.1, delete "research misconduct;" substitute with "violations of research ethics and human research protections. Correct section throughout. Correct remainder of document as relevant.

Regarding A.6/A.6.1 and the term research misconduct: The issue of exaggeration of claims indeed may be interpreted as falsification since the claim of "cures" was not verifiable. The term "research misconduct" should be retained, in this case alone, in the recommendation and throughout. Other direction regarding A.6 is found below.

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ENCLOSURE (1)

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Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

Observation A Title on page 6 should be reworded as: "Potential Research Ethics Violations." Correct remainder of document as relevant.

b. The following comments/recommendations address specific recommendations and observations assigned to U.S. Navy Surgeon General:

For the Recommendation A.1.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Non-concur. Recommend that this be reassigned to U.S. Army Medical Command.

Rationale: Though a Navy physician, the investigator was deployed outside the continental United States (OCONUS) during the entire course of the study under U.S. Central Command (CENTCOM)/Army authority. He did not conduct the project under Navy human research or research ethics authorities. The Navy physician conducted his efforts under the Army human research assurance issued to CENTCOM served by the Army's then Institutional Review Board (IRB) of record for that location, namely Brooke Army Medical Center (BAMC) with subsequent headquarters level administrative review by U.S. Army Medical Research and Materiel Command (USAMRMC). Navy had no authority regarding this specific project nor would it have had any cognizance of its conduct or progress. The project was under the sole direction and authority of the Army BAMC IRB and USAMRMC.

Recommend investigation of these allegations be assigned to U.S. Army Medical Command who had the responsibility for approvals and oversight.

For the Recommendation A.2.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Concur, with comment.

Comments: Naval Medical Center San Diego (NMCSD) initiated an investigation into allegations surrounding the source of funding for research study MNC-Iraq-08-040 on 28 July 2010. The investigation results are currently pending and are expected 7 February 2011.

Recommendation: It is recommended that U.S. Army Medical Command also conduct an investigation into the funding source for this research project. They alone would have access to specific information regarding use of time, effort or resources in the CENTCOM area of responsibility (AOR).

For Recommendation A.3.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Non-concur. Reassign to U.S. Army Medical Command.

Rationale: Though a Navy physician, the investigator was deployed OCONUS during the entire course of the study under CENTCOM/Army authority. He did not conduct the

Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

project under Navy human research or research ethics authorities. The Navy physician conducted his efforts under the Army human research assurance issued to CENTCOM served by the Army's then IRB of record for that location, namely BAMC with subsequent headquarters level administrative review by USAMRMC. Navy had no authority regarding this specific project nor would it have had any cognizance of its conduct or progress. The project was under the sole direction and authority of the Army BAMC IRB and USAMRMC. Recommend investigation of these allegations be assigned to U.S. Army Medical Command who had the responsibility for approvals and oversight.

For Recommendation A.4.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Non-concur. Reassign to U.S. Army Medical Command.

Rationale: Though a Navy physician, the investigator was deployed OCONUS during the entire course of the study under CENTCOM/Army authority. He did not conduct the project under Navy human research or research ethics authorities. The Navy physician conducted his efforts under the Army human research assurance issued to CENTCOM served by the Army's then IRB of record for that location, namely BAMC with subsequent headquarters level administrative review by USAMRMC. Navy had no authority regarding this specific project nor would it have had any cognizance of its conduct or progress. Further, consistent with the information provided to the subjects during informed consent and beyond as well as elements of information control required by all Federal agencies by The Common Rule, there are promised restrictions in regard to who has access to the records of data and documentation developed as part of the study. These data and the guidance provided by the IRB are part of records that are not available to the US Navy, but are appropriately available to and reposit with the IRB of record. The project was under the sole direction and authority of the Army BAMC The project was under the sole direction and authority of the Army BAMC IRB and USAMRMC. Recommend investigation of these allegations be assigned to U.S. Army Medical Command who had the responsibility for approvals and oversight.

For Recommendation A.5.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Non-concur. Reassign to U.S. Army Medical Command

Rationale: Though a Navy physician, the investigator was deployed OCONUS during the entire course of the study under CENTCOM/Army authority. He did not conduct the project under Navy human research or research ethics authorities. The Navy physician conducted his efforts under the Army human research assurance issued to CENTCOM served by the Army's then IRB of record for that location, namely BAMC with subsequent headquarters level administrative review by USAMRMC. Navy had no authority regarding this specific project nor would it have had any cognizance of its conduct or progress. Further, consistent with the information provided to the subjects during informed consent and beyond as well as elements of information control required by all Federal agencies by The Common Rule, there are

Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

promised restrictions in regard to who has access to the records of data and documentation developed as part of the study. These data and the guidance provided by the IRB are part of records that are not available to the US Navy, but are appropriately available to and reposit with the IRB of record. The project was under the sole direction and authority of the Army BAMC IRB and USAMRMC. Recommend investigation of these allegations be assigned to U.S. Army Medical Command who had the responsibility for approvals and oversight.

For Recommendation A.6.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Non-concur. Reassign to U.S. Army Medical Command.

Rationale: Though a Navy physician, the investigator was deployed OCONUS during the entire course of the study under CENTCOM/Army authority. He did not conduct the project under Navy human research or research ethics authorities. The Navy physician conducted his efforts under the Army human research assurance issued to CENTCOM served by the Army's then IRB of record for that location, namely BAMC with subsequent headquarters level administrative review by USAMRMC. Navy had no authority regarding this specific project nor would it have had any cognizance of its conduct or progress. Further, consistent with the information provided to the subjects during informed consent and beyond as well as elements of information control required by all Federal agencies by The Common Rule, there are promised restrictions in regard to who has access to the records of data and documentation developed as part of the study. These data and the guidance provided by the IRB are part of records that are not available to the US Navy, but are appropriately available to and reposit with the IRB of record. The project was under the sole direction and authority of the Army BAMC IRB and USAMRMC. Recommend investigation of these allegations be assigned to U.S. Army Medical Command who had the responsibility for approvals and oversight.

Additional Remarks for Observation A: Regarding claims, data disclosures, etc. discussed specifically in A.6, but throughout all of Observations A, there is a need to ascertain whether the investigator continued any project-related activities after returning from deployment. Such continuations would fall under the authority, responsibility and liability of his parent command and DoD Component, namely Navy. Specifically, and as may be relevant, it must be discovered whether the investigator notified and received approvals from his regular NMCSD IRB and other authorities for such continued activities after his return. It must also be ascertained whether any relevant presentation materials, manuscripts for publication, or other similar materials received requisite reviews and approvals from his Navy chain of command and from Navy Medicine Public Affairs Officials per regulations. Commander NMCSD will take this for action with oversight by appropriate Bureau of Medicine and Surgery (BUMED) subject matter experts.

For Observation B.1. *"Neurological assessments did not adhere to clinical practice guidelines for mTBI"*: Concur, with comment.

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Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

Comment: A Quality of Care review was completed by NMCSD on 30 November 2010. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

[redacted]

Recommendation: [redacted]

"The information provided herein was obtained from records maintained as part of Navy Medicine's Quality Assurance Program and is strictly confidential and privileged. No part of this information may be disclosed, subject to discovery, or admitted into evidence in any judicial or administrative proceeding, except in accordance with 10 U.S.C. section 1102."

For Observation B.2. *"The experimental drug was not approved by the Food and Drug Administration for clinical study"*: Concur, with comments.

Comments: A Quality of Care review was completed by NMCSD on 30 November 2010. [redacted]

[redacted]

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Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

[redacted]

Recommendation: [redacted]

"The information provided herein was obtained from records maintained as part of Navy Medicine's Quality Assurance Program and is strictly confidential and privileged. No part of this information may be disclosed, subject to discovery, or admitted into evidence in any judicial or administrative proceeding, except in accordance with 10 U.S.C. section 1102."

For Observation B.3. "*Medications contraindicated in the treatment of early mTBI were administered*": Concur, with comments.

Comments: A Quality of Care review was completed by NMCSD on 30 November 2010. [redacted]

[redacted]

[redacted]

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Subj: DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

[redacted]

Recommendation: [redacted]

"The information provided herein was obtained from records maintained as part of Navy Medicine's Quality Assurance Program and is strictly confidential and privileged. No part of this information may be disclosed, subject to discovery, or admitted into evidence in any judicial or administrative proceeding, except in accordance with 10 U.S.C. section 1102."

For recommendation C.2.6. *"Review and update BUMEDINST 3900.6B to clarify the use of investigational drugs in medical research, to include intended use of nutritional supplements and other over-the-counter products as experimental drugs"*: Concur

Action: The BUMED Special Assistant for Ethics and Professional Integrity/ Executive Research Integrity Officer will be responsible for revision of BUMEDINST 3900.6B in coordination with the BUMED Office of Special Assistant for Medical Research/Director, Navy Medicine Research and Development Center. Estimated completion date is 31 December 2011.

For recommendation C.2.7. *"Ensure that all individuals involved in the submission, review, and approval of clinical research protocols receive training in the use of investigational drugs, Food and Drug Administration regulations and the Investigational New Drug process"*: Concur

Action: Pursuant to the revision of BUMEDINST 3900.6B, relevant professional education programs will be identified for incorporation into local command education and training curricula by 31 July 2011. The Director, Navy Medicine Research and Development Center (NMRDC) and relevant NMRDC subject matter experts will have responsibility for this action.

2. My point of contact in this matter is [redacted] and she can be reached at [redacted] or by e-mail at [redacted]

A. M. Robinson, Jr.

A. M. ROBINSON, JR.

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DEPARTMENT OF THE NAVY
NAVAL INSPECTOR GENERAL
1254 9TH STREET SE
WASHINGTON NAVY YARD DC 20374-5006

IN REPLY REFER TO:
5041/201000537
Ser N64/0122
23 Mar 2011

From: Naval Inspector General
To: Department of Defense Inspector General
(Attn: Special Plans and Operations)

Subj: BUMED ADDENDUM TO DODIG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

Ref: (a) DODIG Memorandum of 22 December 2010

Encl: (1) BUMED letter 7502 Ser M09/11 UN093000143 of 23 Mar 2011

1. Per reference (a), enclosure (1) is forwarded on behalf of Chief, Bureau of Medicine and Surgery.

2. If you have any questions or concerns regarding this matter, please do not hesitate to contact me or my point of contact for this case, [redacted] U.S. Navy. [redacted] may be reached by telephone at (202) 433-[redacted] or via e-mail at [redacted]navy.mil.

Sincerely,

J. A. DELEON
Deputy
Acting

b(6)

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DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY
2300 E STREET NW
WASHINGTON DC 20372-5300

IN REPLY REFER TO
7502
Ser M09/11UN093000143
23 Mar 2011

From: Chief, Bureau of Medicine and Surgery
To: Office of the Inspector General, Department of Defense, Attn: Special Plans and Operations
Via: Naval Inspector General

Subj: ADDENDUM TO CHIEF, BUREAU OF MEDICINE AND SURGERY (BUMED) RESPONSE TO DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

Ref: (a) DoD IG memo of 22 Dec 2010
(b) BUMED memo of 28 Jan 2011

1. This document is submitted to provide additional information in response to reference (a) and as further outlined in reference (b).

2. For the Recommendation A.2.1. *"Allegations of potential medical research misconduct by a U.S. Navy physician were referred to the U.S. Navy for further investigation"*: Concur, with additional comment.

Comments: Naval Medical Center San Diego (NMCSD) completed an investigation into allegations surrounding the source of funding for research study MNC-IRAQ-08-04 on 4 February 2011. Below is a summary of findings and recommendations:

A.2. Findings

- The U.S. Navy physician, Principal Investigator, did not have Office of Naval Research (ONR) funding for the research study MNC-IRAQ-08-04.

- The U.S. Navy physician received Research, Development, Test & Evaluation (RDT&E) 6.4 funds for the project "The Use of Anti-Oxidants to Augment Outcome in Patients with Balance Disorders After Blast Injury and Blunt Head Trauma." This funding came from the BUMED via Naval Medical Research Center to Naval Health Research Center to the Principle Investigator. He used these funds to support the conduct of MNC-IRAQ-08-04 in theater.

- The investigation into the use of these funds for the research study MNC-IRAQ-08-04 revealed a lack of adequate program oversight and financial accountability.

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Subj: ADDENDUM TO CHIEF, BUREAU OF MEDICINE AND SURGERY (BUMED) RESPONSE TO DRAFT REPORT: DOD IG ASSESSMENT OF TRAUMATIC BRAIN INJURY RESEARCH INTEGRITY IN IRAQ (PROJECT NUMBER 2009-DOOSPO-0242-00)

A.2. Conclusion

As strictly defined under federal regulations, research misconduct *per se* was not discovered. Disciplinary action for any individuals identified in this specific funding investigation is not warranted. However, the initial inquiry into the source of funding for MNC-IRAQ-08-04 has identified a requirement for further and more detailed investigation to ascertain the scope and depth of potential regulatory violations or non-compliance with research financial standards.

A.2.1 Recommendations

- BUMED will direct further investigation utilizing external subject matter experts to more thoroughly detail compliance/noncompliance with Research Administration and Management processes to include financial management standards. This shall commence no later than 31 March 2011.

- BUMED will issue regulations for financial management of research funds for immediate local implementation by 30 June 2011. In addition, BUMED will establish a comprehensive Navy Medicine policy and regulation on research administration and management to include financial management standards and oversight. This shall be completed by 31 October 2011.

- BUMED will design, direct and implement comprehensive education and training conferences in research administration and management for research related personnel of all disciplines. A variety of forums may be utilized such as conferences, webinars, and video teleconferences. This shall be completed within 60 days from the establishment of Navy Medicine policy and regulation on research administration and management.

3. My point of contact in this matter is [redacted] and she can be reached at (301) 295-[redacted] or by e-mail at [redacted]@med.navy.mil.

K. A. FLAHERTY
Deputy Chief

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Appendix H. DoD Inspector General Correspondence

Letter to U.S. Navy Bureau of Medicine and Surgery, February 18, 2010

INSPECTOR GENERAL
DEPARTMENT OF DEFENSE
400 ARMY NAVY DRIVE
ARLINGTON, VIRGINIA 22202-4704

February 18, 2010

FOR: Chief, Bureau of Medicine and Surgery

FROM: Deputy Inspector General for Special Plans and Operations
Department of Defense

SUBJECT: Mild Traumatic Brain Injury Clinical Research in Iraq

In reference to the attached correspondence, dated June 11, 2009 and January 15, 2010, we provided a briefing to Rear Admiral (RADM) Thomas Cullison, United States Navy (USN), Deputy Surgeon General on January 19, 2010 and identified three areas of concern: potential clinical research misconduct; possible sub-standard patient care; and weaknesses in the research oversight process.

As discussed during the briefing, we are referring any potential misconduct of the physician researcher, [redacted] and providing relevant documentation to you for investigation and appropriate action.

I want to underscore our concern for the safety and health of the service members who participated in the research study entitled, "The use of anti-oxidants to reduce sequela of Mild Traumatic Brain Injury (mTBI) after blast exposure", conducted at Al Taqaadum, Iraq from November 2008 to March 2009. In the briefing, we specifically requested that you identify the research participants and perform a quality of care review to ensure that these service members received appropriate medical care. Additionally, we recommended that each research subject undergo a health assessment to determine that there were no negative medical outcomes that occurred as a result of their participation in this clinical trial.

In the meantime, we are completing a review of the research process used by the Department of the Army to approve this clinical trial in order to assess potential weaknesses in clinical research oversight.

Please provide a response regarding any preliminary investigative results and a summary of other actions taken within 30 days of receipt of this letter.

If you have any questions, please contact [redacted] at (703) 604-[redacted] DSN 664-[redacted] or [redacted]@dodig.mil.

Kenneth P. Moorefield
Deputy Inspector General
Special Plans & Operations

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Memorandum for Assistant Secretary of Defense for Health Affairs, February 17, 2011

INSPECTOR GENERAL
DEPARTMENT OF DEFENSE
400 ARMY NAVY DRIVE
ARLINGTON, VIRGINIA 22202-4704

February 17, 2011

MEMORANDUM FOR ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

SUBJECT: Mild Traumatic Brain Injury Clinical Research Trial in Iraq

We are requesting your assistance in establishing criteria for and coordinating the implementation of health assessments for 80 U.S. military service members who were participants in a clinical trial conducted in Iraq during the period December 2008 - March 2009.

On May 15, 2009, the Office of Inspector General Defense Hotline received an allegation of suspected medical research misconduct related to this clinical trial. The complainant alleged that, while deployed to Iraq, a U.S. Navy physician conducted sub-standard research in conducting a clinical trial of U.S. military personnel who had suffered mTBI. The purpose was to examine the effectiveness of the substance n-Acetylcysteine (NAC), an over-the-counter nutritional supplement, used in the trial as an experimental drug in treating mTBI.

We initiated an assessment of these allegations in 2009. The results indicated potential research misconduct and possible substandard medical care. In addition, there were concerns identified regarding various medical research oversight matters. Subsequently, we briefed the U.S. Navy Deputy Surgeon General, Bureau of Medicine and Surgery (BUMED), on January 19, 2010, and requested that BUMED conduct an investigation into the various issues.

Furthermore, we recommended that the research participants receive a health assessment to determine whether they had experienced any negative medical consequences as a result of their participation in the clinical trial. BUMED completed their Quality of Care Review in December 2010.

In their response to our draft report which was released December 23, 2010, BUMED concluded that treatments provided to the research participants were not within the standard of care for the treatment of mTBI. They did not, however, conduct any of the health assessments of the service personnel, which are now necessary to determine if there were any adverse medical effects as a result of their participation in the study. According to information collected and reviewed by the Navy during their initial inquiry, there were 80 service members who participated in the mTBI research. These 80 individuals represented a cross section of military services (U.S. Marine Corps – 57; U.S. Army National Guard – 13; U.S. Army – 5; and U.S. Navy – 5.)

Addressing the challenge now presented with respect to identifying and treating any health problems associated with the clinical trial would appear, therefore, to be a joint DoD responsibility. Moreover, DoD and military service regulations are not clear in regards to the authority and responsibilities for conducting a review of medical research and care provided to U.S. service members which occurred in a joint-service environment, as in this case. Our report identified this lack of clarity.

We therefore request that your office conduct health assessments of the 80 military personnel who participated in the mTBI clinical trial. To assist you in conducting this important review, we have provided your office with a copy of our draft report, and our respective staffs have had extensive and productive discussions about this matter, to ensure that your staff has the necessary information to initiate this review. We appreciate the assistance your staff has provided, and their willingness to conduct this review. Because BUMED has further information regarding the identities of the 80 service members and their medical treatment files, we recommend that your staff contact BUMED directly to obtain this information.

We believe you will agree it is essential to conduct accurate, objective, and timely health assessments of these 80 service members, and that such action reflects our Department's strong commitment to take every step necessary to support the health and well-being of these service members.

We would appreciate an estimated timeline for the completion of the requested assessments, at your earliest convenience. If you have any questions, please contact [redacted] at (703) 604-[redacted] DSN 664-[redacted] or at [redacted]@dodig.mil.

Ambassador Kenneth P. Moorefield (Ret)
Deputy Inspector General
Special Plans & Operations

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Memorandum for U.S. Navy Bureau of Medicine and Surgery, February 17, 2011

INSPECTOR GENERAL
DEPARTMENT OF DEFENSE
400 ARMY NAVY DRIVE
ARLINGTON, VIRGINIA 22202-4704

February 17, 2011

MEMORANDUM FOR CHIEF, BUREAU OF MEDICINE AND SURGERY

SUBJECT: Mild Traumatic Brain Injury (mTBI) Clinical Research Trial in Iraq

We appreciate your comments in response to our draft report "Assessment of the Defense Hotline Allegations Concerning Traumatic Brain Injury Research Integrity in Iraq (Project No. D2009-D00SPO-0242.00)."

As discussed in Observation B of our draft report, we recommended that the Navy conduct a Quality of Care Review based on our findings of possible substandard patient care for those service members participating in the mTBI clinical trial at Camp Al Taqaadum, Iraq. The comments to our report acknowledged that the treatments provided to research participants did not meet the standard of care for the treatment of mTBI. Your comments indicated that based on the Quality of Care Review, health assessments of the research participants were needed to determine whether those service members were harmed as a result of their participation in the research.

Information previously provided by Navy Medicine West indicated that there were 80 individuals who participated in this clinical trial, which represents a cross section of military services (U.S. Marine Corps – 57; U.S. Army National Guard – 13; U.S. Army – 5; and U.S. Navy – 5.) Due to our immediate concern for the health and wellbeing of the affected research participants, we have requested that ASD(Health Affairs (HA)) conduct the required health assessments. We asked that Health Affairs contact you to obtain the identities of the research participants and the related medical treatment files used to conduct the Quality of Care Review to aid in Health Affairs' efforts to complete the health assessments.

If you have questions, please contact [redacted] at (703)604-[redacted] DSN 664-[redacted] or [redacted]@dodig.mil

KP Moorefield

Ambassador Kenneth P. Moorefield (Ret)
Deputy Inspector General
Special Plans & Operations

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Memorandum for U.S. Army Medical Command, March 7, 2011

INSPECTOR GENERAL
DEPARTMENT OF DEFENSE
400 ARMY NAVY DRIVE
ARLINGTON, VIRGINIA 22202-4704

March 7, 2011

MEMORANDUM FOR THE COMMANDING GENERAL, U.S. ARMY MEDICAL COMMAND

SUBJECT: Mild Traumatic Brain Injury Clinical Research Trial in Iraq

I am requesting your assistance in completing an investigation into the allegations of potential research misconduct that were identified in our draft report, "Assessment of Allegations Concerning Traumatic Brain Injury Research Integrity," which was released for management comments on December 23, 2010.

As you are already aware, our assessment identified issues specific to possible research misconduct by a Navy physician, concern for the health of the research subjects, as well as weaknesses in the process used to review and approve the mTBI clinical trial conducted at Camp Al Taqaduum (Camp TQ), Iraq.

In response to our request, the U.S. Navy Chief, Bureau of Medicine and Surgery (BUMED) conducted a Research Misconduct Preliminary Inquiry. As a result of their review, BUMED agreed to further investigate the circumstances related to the source of funding which the investigator used to support his research in Iraq (Observation A.2 in our draft report). Also, BUMED has already carried out a Quality of Care Review on those Service personnel who participated in the trial, and the Assistant Secretary of Defense for Health Affairs has agreed to conduct health assessments of the 80 research subjects to determine whether their health was adversely affected by participation in the clinical trial. However, BUMED declined to investigate the remaining allegations of potential research misconduct identified in Observation A, due in part to the fact that the clinical trial was approved under the authority of the Army as was the performance of the research conducted at Camp TQ, Iraq.

Our assessment determined that the U.S. Army Brooke Army Medical Center Institutional Review Board (IRB) was responsible for the review of the clinical trial and therefore was responsible for any oversight of the research in Iraq. Consequently, we believe that the Army is the appropriate authority to conduct the additional investigation needed to determine if research misconduct occurred.

Therefore, we are requesting that you take the lead on the behalf of the Army to investigate matters associated with potential research misconduct. These matters and supporting information regarding financial conflicts of interest, use of investigational drugs, coercion and undue influence, among others, are fully explained in Observation A.1 and A.3 through A.6 of our draft report. We will remain in contact with your staff to provide any additional information required.

Please provide your response by March 14, 2011 and indicate whether you will conduct the requested investigation.

Should you have any questions, please contact [redacted] at: (703) 604[redacted] DSN 664-[redacted] or at [redacted]@dodig.mil.

Ambassador Kenneth P. Moorefield (Ret)
Deputy Inspector General
Special Plans & Operations

Copy to:

Assistant Secretary of Defense for Research and Engineering
Assistant Secretary of Defense for Health Affairs
The Inspector General of the Army
Naval Inspector General
Chief, Bureau of Medicine and Surgery
Department of Defense Hotline

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Special Plans & Operations

Provide assessment oversight that addresses priority national security objectives to facilitate informed, timely decision-making by senior leaders of the DOD and the U.S. Congress.

General Information

Forward questions or comments concerning this assessment and report and other activities conducted by the Office of Special Plans & Operations to spo@dodig.mil

Deputy Inspector General for Special Plans & Operations
Department of Defense Inspector General
400 Army Navy Drive
Arlington, VA 22202-4704

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Report No. SPO-2011-005 March 31, 2011

Inspector General
Department of Defense

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