

AD\_\_\_\_\_

**AWARD NUMBER: W81XWH-16-2-0058**

**TITLE: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments**

**PRINCIPAL INVESTIGATOR: Melissa McDiarmid, M.D., MPH, DABT**

**RECIPIENT: University of Maryland  
Baltimore, MD 21201**

**REPORT DATE: October 2018**

**TYPE OF REPORT: Annual**

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

**DISTRIBUTION STATEMENT: Approved for public release; distribution is unlimited**

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

<b>REPORT DOCUMENTATION PAGE</b>				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. <b>PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</b>					
<b>1. REPORT DATE</b> Oct 2018		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 30 Sep 2017-29 Sep 2018	
<b>4. TITLE AND SUBTITLE</b>  Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments				<b>5a. CONTRACT NUMBER</b>	
				<b>5b. GRANT NUMBER</b> W81XWH-16-2-0058	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b> Melissa McDiarmid, M.D., MPH, DABT email: mmcdiarm@som.umaryland.edu				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  University of Maryland  Baltimore, MD 21201				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b>  The 'signature' wound of current and recent conflicts in both Iraq and Afghanistan is that incurred via contact with improvised explosive devices (IEDs) and other high kinetic energy weapons. Beyond the traumatic injury inflicted, health risks from wound contamination with toxic metals must be managed, even as risk from these contaminants is not fully known. To provide a scientific evidence base to refine the clinical management of these patients, a multidisciplinary approach using animal models and patient data will be used. A laboratory rat model system (Project 1) will provide bio-kinetic and toxicological data on a variety of military-relevant metals implanted in the rats. (Project 2) will identify biomarkers of early effect in tissues and body fluids of the implanted animals. Using an existing national VA Embedded Fragment Registry of such injured patients, (Project 3) will assess kidney injury --the presumed target of toxic metal exposure-- and (Project 4) will assess pulmonary injury in these Veterans from both systemic metal absorption and presumed blast-induced -baro-trauma at the time of injury.					
<b>15. SUBJECT TERMS-</b> Embedded metal fragments, health effects, military-relevant metals, laboratory rat, toxic metals, transcriptome, registry, exposure					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  UU	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC
<b>a. REPORT</b> U	<b>b. ABSTRACT</b> U	<b>c. THIS PAGE</b> U			<b>19b. TELEPHONE NUMBER</b> (include area code)

## TABLE OF CONTENTS

	<u>Page</u>
1. Cover	1
2. Report Documentation Page	2
3. Table of Contents	3
4. Introduction	4
5. Keywords	4
6. Accomplishments	5-10
7. Impact	10
8. Changes/Problems	10-14
9. Products	14-17
10. Participants & Other Collaborating Organizations	18-22
11. Special Reporting Requirements	23
12. Appendices	24-90

- 1. INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The 'signature' wound of current and recent conflicts in both Iraq and Afghanistan is that incurred via contact with improvised explosive devices (IEDs) and other high kinetic energy weapons. Beyond the traumatic injury inflicted, health risks from wound contamination with toxic metals must be managed, even as risk from these contaminants is not fully known. To provide a scientific evidence base to refine the clinical management of these patients, a multidisciplinary approach using animal models and patient data will be used. A laboratory rat model system (Project 1) will provide bio-kinetic and toxicological data on a variety of military-relevant metals implanted in the rats. (Project 2) will identify biomarkers of early effect in tissues and body fluids of the implanted animals. Using an existing national VA Embedded Fragment Registry of such injured patients, (Project 3) will assess kidney injury --the presumed target of toxic metal exposure-- and (Project 4) will assess pulmonary injury in these Veterans from both systemic metal absorption and presumed blast-induced -barotrauma at the time of injury.

- 2. KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Embedded metal fragments, health effects, military-relevant metals, laboratory rat, toxic metals, transcriptome, registry, exposure

### 3. ACCOMPLISHMENTS:

What were the major goals of the project?

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

#### **Major Task 1**

Experimental Preparation

Year 1/Month 1 to Year 1/Month 6, 100% completed.

#### **Major Task 2**

Animal Ordering and Pellet Implantation Surgeries

Year 1/Month 6 to Year 3/Month 8, 100% completed.

#### **Major Task 3**

Animal Health Assessments and Urine Collections

Year 1/Month 9 to Year 3/Month 9, 90% completed.

#### **Major Task 4\***

Euthanasia and Tissue Collection; Transfer of Research Samples to University of Kentucky

Year 2/Month 8 to Year 3/Month 9, 75% completed.

#### **Major Task 5**

Histopathology and Immunohistochemical Analyses

Year 2/Month 5 to Year 3/Month 11, 11.5% completed.

#### **Major Task 6**

Metal Analysis and Tissue Imaging

Year 3/Month 1 to Year 4/Month 12, 10% completed.

#### **Major Task 7**

Data Compilation, Statistical Analysis, and Preparation of Final Report

Year 4/Month 1 to Year 5/Month 12, 2% completed.

\*(See pg. 8)

**\*\*All Year 1 sub-tasks are complete**

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**  
***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

#### **Major Task 1**

Experimental Preparation

Year 1/Month 1 to Year 1/Month 12, 100% completed.

#### **Major Task 2**

3M Experimental Group Microarray analyses

Year 2/Month 4 to Year 3/Month 10, 50% completed.

#### **Major Task 3**

12M Experimental Group Microarray analyses

Year 2/Month 8 to Year 4/Month 4, 0% completed.

**Major Task 4**6M Experimental Group Microarray analyses

Year 3/Month 5 to Year 4/Month 10, 0% completed.

**Major Task 5**1M Experimental Group Microarray analyses

Year 3/Month 9 to Year 5/Month 4, 50% completed.

**Major Task 6**Data Compilation, Statistical Analysis, and Preparation of Final Report

Year 5/Month 5 to Year 5/Month 12, 10% completed.

**PROJECTS 3 & 4:****Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3*****"Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans"*****Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4*****"Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals"***

The Major Tasks for Year 2 are shared by Projects 3 and 4.

**Major Task 1**Questionnaire development

Year 1/Month 1 to Year 1/Month 12, 100% completed.

**Major Task 2**Obtain regulatory approvals

Year 1/Month 1 to Year 2/Month 1, 100% completed.

**Major Task 3**Recruitment and questionnaire administration

Year 1/Month 1 to Year 4/Month 9, 15% completed.

**Major Task 4**Questionnaire analyses

Year 2/Month 1 to Year 5 Month 12, 7% completed

**Major Task 5**Collection and analyses of urine specimens

Year 1/Month 1 to Year 4/Month 7, 20% completed.

**Major Task 6**Collection analyses of PFT and IOS findings

Year 1/Month 1 to Year 4/Month 6, 20% completed.

**Major Task 7**Summarize Metal and Renal Findings

Year 2/Month 1 to Year 5/Month 12, 10% completed.

## Major Task 8

### Summarize PFT and IOS Findings

Year 2/Month 1 to Year 5/Month 12, 5% completed.

**\*\*All Year 1 and 2 sub-tasks are complete**

## What was accomplished under these goals?

### John F. Kalinich, Ph.D., Principal Investigator, Project 1

#### *“Health Effects of Embedded Fragments of Military-Relevant Metals”*

During Year 2 of this project, the remaining rats in the 3 month cohort were implanted and subsequently euthanatized at their experimental endpoints. All rats in the 1 month cohort were also implanted and euthanized. The rats in the 12 month cohort reached their experimental endpoint and were humanely euthanized. All rats in the 6 month cohort were surgically implanted with the appropriate metal. At euthanasia, tissues were collected and processed. Designated tissues from the 1, 3, and 12 month experimental groups were packaged and shipped to the University of Kentucky for further analysis (Project 2). Throughout Year 2, weekly health assessments of the rats in all experimental groups were conducted and urine collected for analysis at various time points. Euthanasia of rats in the 6 month experimental groups has commenced and will be completed in Year 3.

Body weight change, over time, of the various metal-implanted groups is shown in Figure 1 of the Appendices. For the most part, all groups gained weight at a similar rate, although weight gain in the aluminum, iron, lead, and cobalt groups trended lower as the rats aged. Hematological assessments of the 1, 3, and 12 month cohorts showed only transient deviations from normal values. Serum chemistry analysis also showed some significant differences from control for some, but not all of the tests conducted. However, until all of the experimental groups are analyzed and statistically evaluated, no definitive conclusions can be made. Hematological and serum data can be found in the Appendices in Tables 1 and 3.

Upon euthanasia, a variety of tissues are collected and weighed. Normalizing tissue weight to overall body weight of the animal is a standard assessment of organ toxicity. As seen in Table 2 (Appendices), only minor statistically significant differences are seen, and then only for copper, depleted uranium, and aluminum for spleen, liver, and kidney, respectively. The finding of no significant differences in any of the normalized tissue weights at 12 months suggests that there is no overt long-term metal toxicity issues with the implanted metals. During this year, tissue samples from the 1 and 3 month animals have been processed for metal analysis and the 3 month metal analysis complete, but the data have not as yet been analyzed. Tissue processing for histopathological assessment has been initiated under the guidance of the Institute’s recently arrived veterinary pathologist. Metal analysis of the urine samples of the 1 month cohort are shown in Fig. 2 (Appendices) and are expressed as ng of metal per mg of urinary creatinine. As seen, in all cases, implanted metals solubilize and are excreted in the urine of the rats at levels higher than found for the tantalum control rats. Most of the analyzed urinary metals for the control rats are below the limits of detection except for a few (iron, copper, lead, aluminum) that would most likely be the result of water ingestion.

Representative photographs of tumors discovered at necropsy are shown in Fig. 4 (Appendices). Both nickel and cobalt induced tumors at the pellet implantation sites, with nickel implantation resulting in 100% tumor incidence. These tumors are rapidly growing and necessitate the humane euthanasia of the animal by 7 months post-implantation. Pathological identification of the collected tumor tissue will be undertaken in Year 3 of the project. One interesting finding in Year 2 was the expulsion of the implanted copper pellets from the implantation sites through the skin. In most cases, this occurred within 6 weeks of implantation. We are currently investigating this finding.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

During Year 2 of this project we completed microarray analysis of gene expression on 1 and 3 month skeletal muscle samples for each of the 8 metals and the control metal (tantalum). The initial bioinformatic analyses of the microarray data revealed in 1 month samples, only nickel and lead showed differentially expressed genes (DEG); nickel had 100 DEGs with 59 gene upregulated and 41 genes down-regulated. Lead showed 155 DEGs with 40 genes upregulated and 115 genes down-regulated. Gene ontology analysis of upregulated DEGS in the lead group showed that ~30% were related to DNA damage. Ndufa3 (NADH:ubiquinone oxidoreductase subunit A3), a subunit of mitochondrial complex 1, was the only gene that was common between nickel and lead samples. In the 3 month samples, the number of DEGs in the nickel group increased to 612 genes with cobalt now showing 901 DEGs; lead no longer showed any DEGs at 3 months. Interestingly, gene ontology of the nickel group revealed that 25% of the down-regulated DEGs were associated with skeletal muscle differentiation and 20% with “transcriptional activator activity”. In contrast, almost all of the up-regulated DEGs in the cobalt group were related to “regulation of the immune response”. At 3 months, nickel and cobalt groups shared 127 DEGs that were upregulated and 114 DEGs that were down-regulated. Although it is too early to draw any firm conclusions, these initial findings indicate that nickel and cobalt will likely have the most dramatic effect on skeletal muscle gene expression. Please see appendix for figures showing the results of the bioinformatics analyses of skeletal muscle samples.

In addition to the microarray analyses, we have optimized the isolation of exosomes from urine. We also validated that collecting urine using LabSand is just as effective as using metabolic cages. Importantly, we found that exosomes isolated from urine collected using LabSand or metabolic cage are not different in terms of size and concentration. Finally, we also confirmed that we are able to isolate a sufficient quantity of exosomal RNA from urine exosomes to perform microRNA microarray analysis. Developing these techniques and assuring quality control took longer than anticipated, but we should complete year 2 urine analysis by the end of the calendar year.

**PROJECTS 3 & 4:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator Project 3 “Biomarker Assessment of Kidney Injury from Metal Exposure in Embedded Fragment Registry Veterans”**

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator Project 4**

***“Respiratory Health in a Cohort of Embedded Fragment Registry Veterans Exposed to Blasts and Metals”***

This project consists of two different populations of Veterans who are selected from the VA Toxic Embedded Fragment Registry to either receive an invitation to complete a questionnaire (Study Population #1), or to participate in a clinical assessment visit (Study Population #2).

**Study Population #1 – Questionnaire Only Group**

During Year 2, final approval from DoD Human Research Protections Office was obtained and the first Continuing Review was completed. New agreements were established to work the VA Albuquerque Cooperative Studies Program (CSP) and VA Automated Information and Technology Center to create the on-line survey. This on-line survey was tested and the questionnaire databases were finalized. In addition, agreements were established with a new partner, the VA Perry Point CSP to assist in the production of the paper-based questionnaires and use of “Datafax” to scan and verify the data from paper-based questionnaires into a database. The first batch of 1000 invitations and questionnaires were mailed to a randomly selected population.



### Study Population #2 – Clinical Assessment Group

During Year 2, final approval from DoD Human Research Protections Office was obtained and the first Continuing Review was completed. The database to capture questionnaire data was finalized and a system to perform quality control checks was established. Recruitment was initiated at all of the partner locations and 110 Veterans were enrolled. Quarterly videoconferences were held with all VA collaborators to review the study protocol and discuss recruitment and any questions that arise. Bi-weekly conference calls were established between all site research coordinators and Dr. Gaitens or Hines to increase communication and troubleshoot any challenges that arise. In addition, the Baltimore research team conducted a site visit to the San Antonio, the site with the largest planned recruitment volume, to identify solutions for overcoming challenges in recruitment/enrollment.

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

We have added a post-doctoral research fellow to the team (at no cost), Dr. Danielle Glick, who is currently enrolled in a Pulmonary and Critical Care fellowship training program at University of Maryland Medical Center. Dr. Glick will acquire unique expertise and skills in impulse oscillometry testing that she would not have received in her fellowship training otherwise, that she will be able to apply through the rest of her career. Dr. Glick has developed an interpretation template for use with impulse oscillometry that can be used by any VA clinician tasked with reviewing impulse oscillometry results. This potentially could be used at VA medical centers throughout the country.

Additionally, impulse oscillometry refresher training videos were created in year 2, that were available to all study team members.

### **How were the results disseminated to communities of interest?**

Nothing to report.

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

#### **John F. Kalinich, Ph.D., Principal Investigator, Project 1**

##### ***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

During Year 3 of the project, the remaining rats in the 6-month cohort will be humanely euthanized and samples collected. Samples from all 6-month groups will be shipped to the University of Kentucky (Project 2) for analysis. Health assessment data for the 6-month rats will be compiled and statistically analyzed. Sample processing and metal analysis of tissue samples will continue. A post-doctoral fellow will be hired to assist with the metal imaging studies. Histopathology assessments on collected tissue will begin, as will immunohistochemical analysis.

#### **Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

##### ***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

During Year 3 of the project, we will isolate total RNA from 6 and 12 month skeletal muscle samples and perform microarray analyses. Once we have the microarray data, we will perform an initial bioinformatic analyses to identify differentially expressed genes at each time point and for each metal sample. We also will isolate exosomes from urine from control (pre-implantation), 1 month and 3 month samples, isolate exosomal RNA and then determine exosomal microRNA abundance by microarray analyses.

## PROJECTS 3 & 4:

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

In Year 3, for Study Population #1 we will continue to mail invitations and questionnaires to randomly selected Veterans from the Toxic Embedded Fragment Registry and enter data into the study databases.

For Study Population #2, we will continue recruitment and enrollment of Veterans to complete the expanded questionnaire and participate in clinical assessments. This includes collecting and prepping urine specimens, sending urine specimens for metal and renal marker analyses, and performing PFT and IOS testing at VA recruitment sites. Additionally, available imaging records will be reviewed to determine if fragments have been documented.

## 4. IMPACT:

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

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

The initial microarray analyses indicate that nickel and cobalt have the most significant impact on skeletal muscle gene expression. While these findings need to be confirmed by qPCR, they do suggest that these metals are likely to have the greatest effect on warriors harboring such embedded metals. Nothing to report.

**What was the impact on other disciplines?**

Nothing to report.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

Nothing to report.

## 5. CHANGES/PROBLEMS:

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report.

### **PROJECTS 3 & 4:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

During Year 2, there were several protocol deviations involving 3 sites using bronchodilators during the pulmonary function testing, which is often the standard of care during performance of PFTs. Another site reported a scheduling error that resulted in two study participants performing PFTs prior to being consented. (See details below under “Significant changes in use or care of human subjects”)

These issues have been reported and acknowledged by both VA C-IRB and DoD HRPO.

**Actual or anticipated problems or delays and actions or plans to resolve them.**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report.

### **PROJECTS 3 & 4:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

During Year 2, we experienced delays in commencing recruitment of Study Population #1 as our original research survey contractor was unable to process the paper-based surveys and administer the electronic survey in a manner that met all of the regulatory and privacy requirements of the VA for research. We were able to overcome this challenge by finding two partners (one to handle the processing of the paper-

based questionnaires and the other to handle the administration of the electronic questionnaire). Agreements were established with the new partners and modifications were made to our protocol accordingly. Although this significantly delayed the start of recruitment for Study Population #1, we do not anticipate that this delay will affect our ability to reach our targeted enrollment during our projected timeline.

In Year 2 we also experienced delays in commencing recruitment for Study Population #2 due to the length of time it took to obtain all necessary IRB/HRPO approvals and the time it took to hire key staff at all partner sites. Despite this initial delay in recruitment, we anticipate reaching our total targeted recruitment number by slightly increasing our targeted numbers per quarter. To ensure that everyone stays on track with recruitment, we have instituted biweekly research coordinator calls with the Project leads to review each site's progress and discuss any challenges encountered. In addition, enrollment was off to a slow start at the San Antonio VA, the site with the largest planned recruitment volume. The Project leads conducted a site visit there in late July to meet with the local research staff to discuss and identify solutions for overcoming challenges in recruitment and enrollment. Since that site visit, the San Antonio research team enrolled 11 study participants.

#### **Protocol Deviations: (Study Population #2)- Protocol #A-19735.2**

There were three protocol deviations that occurred at two sites (one at Gainesville and two at Oklahoma City) related to performance of post-bronchodilator spirometry during pulmonary function testing. None of the participants experienced adverse effects from the testing.

Two deviations involving the scheduling of research participants occurred at the San Antonio site. In both instances, the participant consented to participate in the research study over the telephone. The research team scheduled the participants for their study visits, where the formal written informed consent, pulmonary function testing, and other study activities were to have occurred. Consults for pulmonary function testing were entered in CPRS by the research team according to protocol. However, the PFT lab staff independently contacted the Veterans to schedule the PFTs on dates prior to the scheduled study visit. Consequently, both participants performed the tests at the PFT lab prior to being formally consented for the study.

**Details of these events, including dates of the events, dates of submissions to VA C-IRB and DoD HRPO, their outcomes and determinations can be found in the "Deviations Tracking Table" in the appendices.**

#### **Changes that had a significant impact on expenditures**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***"Health Effects of Embedded Fragments of Military-Relevant Metals"***

Nothing to report

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**  
***"Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds"***

Nothing to report.

#### **PROJECTS 3 & 4:**

Changes in 'routine' clinical care provided to Veterans with embedded fragments resulted in a significant cost savings for our project as the clinical protocol for urine metal analyses for those enrolled in the

Embedded Fragment Registry now only requires a spot urine collection (instead of a 24-hour specimen). This change has allowed us to use the samples collected as part of our research protocol to be submitted through the pathway used for 'routine' clinical care resulting in a \$255,911 cost savings over a 3-year period. This savings will be offset by additional costs of increased payment to study participants (per IRB reviewers' recommendation), increased urine supplies and shipment costs due to changes in the assessment of renal injury markers protocol, addition of a site visit to assist one of the VA partners with recruitment/enrollment challenges, increased PFT/IOS technical support to facilitate standardized reporting of study results, and replacement of outdated computers for study staff.

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

**Significant changes in use or care of human subjects:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***"Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans"***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***"Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals"***

#### **Amendments submitted to IRB and USAMRMC HRPO**

##### **(Study Population #1)- Protocol #A-19735.1**

- Modification 1 submitted to University of Maryland HRPO (prior to approval by subsequent IRBs), and approved on 9/1/2017. This modification was submitted due to a change in letterhead logos on recruitment letters and was included in the initial USAMRMC HRPO submission form.
- Modification 2 submitted to University of Maryland HRPO (prior to approval by subsequent IRBs), and approved on 3/28/2017. This modification was submitted due the change from use of VA REDCap to VA Cooperative Studies Program-Austin Information Technology Center (CSP-AITC) for capture of electronic survey data. Modification 2 was submitted to USAMRMC HRPO on 3/28/2018.
- Modification 3 submitted to University of Maryland HRPO on 6/1/2018. This modification included a slight change to the appearance of the cover letter accompanying the questionnaire providing a better visual representation of instructions for completing the questionnaire online, and information about how an access code and PIN number will be used to log onto the electronic survey site. This modification was submitted to USAMRMC HRPO on 6/5/18 and acknowledged on 6/13/18. Modification 4 submitted to University of Maryland HRPO on 7/20/2018 and approved on 7/30/2018. This modification was submitted to replace CTRIC and VA Teleforms with the VA Perry Point Cooperative Studies Program and Datafax for the paper questionnaires. Modification 4 was submitted to USAMRMC HRPO on 8/3/2018. \*Please see the "Submissions Tracking Table" in the appendices for a summary of these amendments

#### **Amendments submitted to IRB and USAMRMC HRPO**

##### **(Study Population #2)- Protocol #A-19735.2**

- Modification 1: Submitted to VA C-IRB on 6/5/2018; Approved 6/19/18; Submitted to DoD HRPO 6/25/18 and approved on 6/26/18. This modification grants some flexibility in the event that all study procedures cannot be completed during a single visit. In such an event, (i.e. equipment malfunctions in the pulmonary function lab and test not able to be completed), we will be able to bring participants back to complete the protocol. This modification also allows for additional travel pay for the second visit and includes language in the consent form describing this.
- Modification 2: Submitted to VA C-IRB on 8/15/18; Status: Pending. This modification will allow the participant to opt to be re-contacted for future studies that he or she is eligible for.
- Modification 3: Submitted to VA -CIRB on 9/4/18; Status: Pending. This modification was submitted per the IRB's recommendation in the determination of a deviation that occurred at the San Antonio site. This deviation stemmed from a scheduling error which resulted in a study participant performing a research PFT

prior to being consented. In this modification, the HIPAA authorization was revised to indicate that PHI will be used to schedule pulmonary function tests prior to obtaining consent and HIPAA.

\*Please see the “Submissions Tracking Table” in the appendices for a summary of these amendments

**Significant changes in use or care of vertebrate animals:**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report.

**Significant changes in use of biohazards and/or select agents**

Nothing to report.

**6. PRODUCTS:**

- **Publications, conference papers, and presentations**

**Journal publications:**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Assessing the health effects of embedded metal fragments using a rat model. AFRRRI Seminar Series, Dr. Jessica Hoffman, 23 February 2018.

Hydrophobic sand: a novel method of urine collection for biomarker and metal analysis in the rat. National Capital Area Branch of the American Association for Laboratory Animal Science, Dr. Jessica Hoffman, 14 June 2018.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report

**PROJECTS 3 & 4**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

”Depleted Uranium and Toxic Embedded Fragment Programs.” Presentation to VA Central Office leadership from Office of Post-deployment Health Services regarding how Projects 3 and 4 stem from the VA’s existing registry programs, as a demonstration of a whole government approach to care and research, Baltimore VAMC, Dr. Melissa McDiarmid, 19 January 2018.

**Books or other non-periodical, one-time publications.**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**  
***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**  
***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

Nothing to report.

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**  
***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

Nothing to report.

**Other publications, conference papers and presentations.**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**  
***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**  
***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

Nothing to report.

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

Nothing to report.

- **Website(s) or other Internet site(s)**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

Nothing to report.

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

Nothing to report.

- **Technologies or techniques**

*Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.*

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report



**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**  
***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

Nothing to report.

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**  
***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

Nothing to report.

- **Inventions, patent applications, and/or licenses**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

Nothing to report.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2**  
***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Nothing to report

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**  
***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

Nothing to report.

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**  
***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

Nothing to report.

- **Other Products**

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**  
***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

Impulse oscillometry refresher training videos were created in year 2, that were distributed to all study team members.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

### **Melissa McDiarmid, M.D., Principal Investigator:**

***“Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments”***

**Name:** Melissa McDiarmid, M.D.  
**Project Role:** Principal Investigator  
**Nearest Person Month worked:** 2.40  
**Contribution to Project:** Dr. McDiarmid oversaw conduct and progress of all four study projects and participated in quarterly project team call.

**Name:** Rachel Coates-Knowles, MSM  
**Project Role:** Finance Manager  
**Nearest Person Month worked:** 6.6  
**Contribution to Project:** Maintained and processed all financial transactions and reporting.

**Name:** Clayton Brown  
**Project Role:** Statistician  
**Nearest Person Month worked:** 2.35  
**Contribution to Project:** Provided input on data collection tools and data design.

**Name:** Sheila Williams  
**Project Role:** Administrative Assistant  
**Nearest Person Month worked:** 1.20  
**Contribution to Project:** Assist with procurement, travel arrangements, and document preparation.

### **John F. Kalinich, Ph.D., Principal Investigator, Project 1:**

***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

**Name:** John Kalinich, PhD  
**Project Role:** Principal Investigator, Project 1  
**Researcher Identifier:** 0000-0003-1591-9389  
**Nearest person month worked:** 2  
**Contribution to Project:** Responsible for overall functioning of this portion of the project.  
**Funding Support:** Federal Government Employee (Department of Defense)

**Name:** Christine Kasper, PhD RN, FAAN FACS  
**Project Role:** Co-Investigator,  
**Research Identifier:** 0000-0002-7784-2519  
**Nearest person month worked:** 1  
**Contribution to Project:** Responsible for experimental planning  
**Funding Support:** Federal Government Employee (Department of Veterans Affairs)

**Name:** Anya Fan, MS  
**Project Role:** Research Assistant  
**Nearest person month worked:** 12  
**Contribution to Project:** Responsible for implantation surgeries, urine collection, and animal welfare.

**Name:** Raisa Marshall, BS

**Project Role:** Research Assistant  
**Nearest person month worked:** 12  
**Contribution to Project:** Responsible for implantation surgeries and animal welfare. Ms. Marshall has replaced Ms. Neuendorf.

**Name:** Jessica Hoffman, PhD  
**Project Role:** Co-Investigator  
**Researcher Identifier:** 0000-0003-1858-8394  
**Nearest person month worked:** 5  
**Contribution to Project:** Member of the surgical implantation and euthanasia teams.  
**Funding Support:** Federal Government Employee (Department of Defense)

**Name:** William Danchanko, PhD, CDR, USN  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 1  
**Contribution to Project:** Member of the surgical implantation and euthanasia teams.  
**Funding Support:** U.S. Navy (active duty)

**Name:** Vernieda Vergara, BS  
**Project Role:** Research Assistant  
**Nearest person month worked:** 12  
**Contribution to Project:** Responsible for implantation surgeries and animal welfare. Ms. Neuendorf resigned her position on July 24, 2017.

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

***"Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds"***

**Name:** Charlotte A. Peterson, PhD  
**Project Role:** Principal Investigator, Project 2  
**Nearest person month worked:** no change  
**Contribution to Project:** Responsible for overall functioning of this portion of the project.  
**Funding Support:** University of Kentucky

**Name:** John J. McCarthy, PhD  
**Project Role:** Co-Investigator  
**Nearest person month worked:** no change  
**Contribution to Project:** Responsible for experimental planning  
**Funding Support:** University of Kentucky

**Name:** Alexander Alimov  
**Project Role:** Research Scientist II  
**Nearest person month worked:** 12  
**Contribution to Project:** Responsible for exosome isolation and characterization (Western blot analysis) and RNA isolation.

**Name:** Ivan Vechetti  
**Project Role:** Postdoctoral Scholar  
**Nearest person month worked:** 6  
**Contribution to Project:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Lead Investigator/ Local Site PI, Project 3:**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Name:** Joanna Gaitens, PhD, MSN/MPH  
**Project Role:** Project Lead Investigator/ Local Site PI  
**Nearest person month worked:** 2.4 person months  
**Contribution to Project:** Responsible for overall functioning of this portion of the project, including overseeing recruitment, enrollment, data collection, specimen collection, regulatory protocols, and project team meetings.

**Stella Hines, M.D., MSPH, Project Lead Investigator/ Local Site PI, Project 4:**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

**Name:** Stella Hines, MD, MSPH  
**Project Role:** Project Lead Investigator/ Local Site PI  
**Nearest person month worked:** 2.4 person months  
**Contribution to Project:** Responsible for overall functioning of this portion of the project, including overseeing recruitment, enrollment, data collection, pulmonary testing, regulatory protocols, and project team meetings.

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

Drs. Peterson and McCarthy were awarded a 5 year NIH R01DK119619 on Sept 19, 2018. Each will spend 1.2 calendar months on that project but that will not affect the current project. No overlap.

Dr. Hines has been awarded a contract to provide medical director services to the Building Trades Medical Surveillance program. She will spend 0.24 calendar months on this project but that will not affect the current project. No overlap.

**What other organizations were involved as partners?**

**Participant Enrollment Sites – Clinical Collaboration**

**Baltimore VAMC (Site 1)**

Joanna Gaitens and Stella Hines are the Local Site Principal Investigators for the Baltimore recruitment site. Their contributions to the projects are listed above.

**Name:** Kate Agnetti, BS  
**Project Role:** Research Coordinator  
**Nearest person month worked:** 12 person months  
**Contribution to Project:** Interacted with HRPO and regulatory bodies in order to obtain and maintain required approvals; assisted in developing recruitment, enrollment, and scheduling strategies; recruited and enrolled participants, began data and specimen collection; organized and participated in quarterly project team calls and biweekly site calls.

**Nashville (Site 2):**

**Name:** Kerri Cavanaugh, MD MHS  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 1.2 person months

**Contribution to Project:** Acquired and maintained required approvals; oversaw local recruitment, enrollment, specimen collection; participated in quarterly project team calls.

**Name:** William Lawson, MD  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 0.6 person months  
**Contribution to Project:** Acquired and maintained required approvals; participated in quarterly project team call; received Impulse Oscillometry training.

**Name:** Audrey Tesi  
**Project Role:** Local Study Coordinator  
**Nearest person month worked:** 12 person months  
**Contribution to Project:** Acquired and maintained required approvals; participated in quarterly project team calls and biweekly site calls; recruited and enrolled participants and began data and specimen collection; received Impulse Oscillometry training.

### **Gainesville (Site 3):**

**Name:** Pervumba Sriram, MD  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 0.6 person months  
**Contribution to Project:** Acquired and maintained required approvals; oversaw local recruitment, enrollment, specimen collection; participated in quarterly project team calls.

**Name:** Nataliya Kirichenko  
**Project Role:** Local Study Coordinator  
**Nearest person month worked:** 6 person months  
**Contribution to Project:** Acquired and maintained required approvals; participated in quarterly project team calls and biweekly site calls; recruited and enrolled participants and began data and specimen collection.

**Name:** Paige Gustad  
**Project Role:** Local Regulatory Assistant  
**Nearest person month worked:** 3.6 person months  
**Contribution to Project:** Interacted with local HRPO and regulatory bodies

### **Oklahoma City (Site 4):**

**Name:** Lisa Beck, MD  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 1.8 person months  
**Contribution to Project:** Acquired and maintained required approvals; oversaw local recruitment, enrollment, specimen collection; participated in quarterly project team calls.

**Name:** Vickie Phillips  
**Project Role:** Local Study Coordinator  
**Nearest person month worked:** 7.2 person months  
**Contribution to Project:** Acquired and maintained required approvals; participated in quarterly project team calls and biweekly site calls; recruited and enrolled participants and began data and specimen collection.

### **San Antonio (Site 5):**

**Name:** Catherine Do, MD  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 1.2 person months  
**Contribution to Project:** Acquired and maintained required approvals; oversaw local recruitment, enrollment, specimen collection; participated in quarterly project team calls.

**Name:** Antonio Anzueto, MD  
**Project Role:** Local Site Investigator  
**Nearest person month worked:** 1.2 person months annually  
**Contribution to Project:** Acquired and maintained required approvals.

**Name:** Alex Aguilera  
**Project Role:** Local Study Coordinator  
**Nearest person month worked:** 2.4 person months (increased from 1.2 months annually)  
**Contribution to Project:** Acquired and maintained required approvals; participated in quarterly project team calls and biweekly site calls; recruited and enrolled participants and began data and specimen collection.

**Name:** Myra Mireles  
**Project Role:** Local Study Coordinator  
**Nearest person month worked:** 9.6 person months (increased from 6 months annually)

**Contribution to Project:** Acquired and maintained required approvals; participated in quarterly project team calls and biweekly site calls; recruited and enrolled participants and began data and specimen collection.

## 8. SPECIAL REPORTING REQUIREMENTS

### COLLABORATIVE AWARDS:

Nothing to report.



PI: Melissa McDiarmid, M.D., M.P.H.

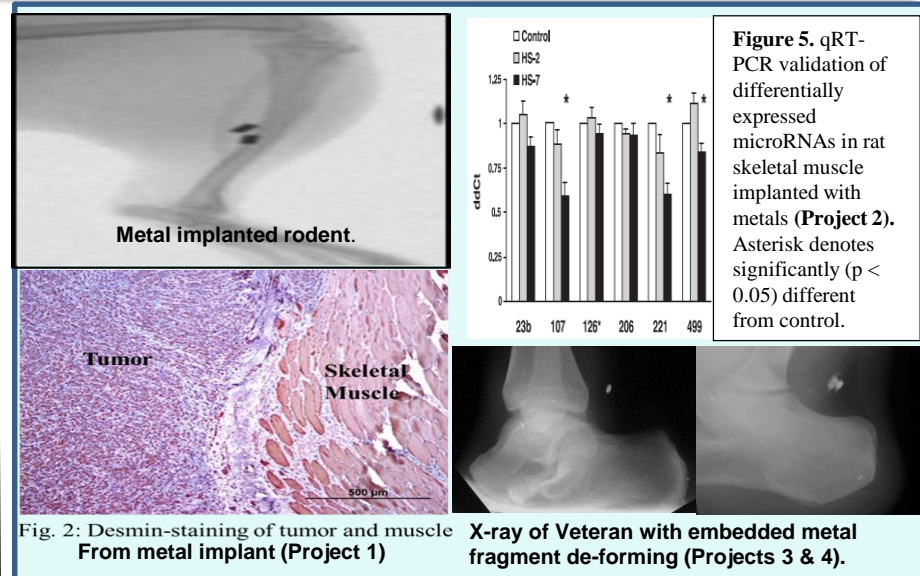
Org: University of Maryland, Baltimore Award Amount: \$7,967,578

**Study/Product Aim(s)**

To provide a scientific evidence base to refine the clinical management of the Veteran or Service member with retained, embedded metal fragments.

**Approach**

A multidisciplinary approach using animal models and patient data will be used. Simulated metal fragment wounds will be studied using rodents surgically implanted with various metals of toxic concern. In **Project 1**, tissues surrounding the implant will be studied for histopathology, immunochemistry and neoplastic change. **Project 2** will attempt to identify early biomarkers of potential malignant transformation in skeletal muscle, urine and serum from these implanted animals. **Project 3** will assess kidney injury (the presumed target of toxic metal exposure) in Embedded Fragment Registry Veterans and **Project 4**, will assess pulmonary injury in these Veterans both from systemic metal absorption and presumed blast-induced –baro-trauma at the time of injury.

**Timeline and Cost**

Activities	CY	2017	2018	2019	2020	2021
PRJ 1: Health Effects of Embedded Fragments of Military-Relevant Metals		100 %	100 %			
PRJ 2: Biomarkers for Assessing Return-to-Duty Potential of Personnel		100 %	85 %			
PRJ 3: Biomarker Assessment of Kidney Injury from Metal Exposure		100 %	25 % *			
PRJ 4: Respiratory Health in Cohort of Embedded Fragment Registry Veterans		100 %	25 % *			
<b>Estimated Budget (\$Mil)</b>		<b>\$1.0</b>	<b>\$1.8</b>	<b>\$1.9</b>	<b>\$1.8</b>	<b>\$1.2</b>

**Goals/Milestones (Example)**

**Project 1:** Animals in all experimental groups have been implanted. Initiated euthanasia at experimental time points.

**Project 2:** All rat samples from all time points following implantation of metals have been received and analyses underway.

**Projects 3 & 4:** Enrolled 110 participants across 5 sites. Established web-based survey platform and paper survey production under new contracts with VA Cooperative Studies Programs. Mailed invitation letters to 1,000 Veterans to participate in survey.

**Comments/Challenges/Issues/Concerns**

- Nothing to report.

**Budget Expenditure to Date (9/30/16 – 9/29/18)**

Projected Expenditure: \$2,882,591

Actual Expenditure: \$1,858,073

## 9. APPENDICES

### **John F. Kalinich, Ph.D., Principal Investigator, Project 1**

#### ***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

1. Figure 1 – Body weight gain (1, 3, and 12M groups)
2. Table 1 – Hematology data (1, 3, and 12M groups)
3. Table 2 – Normalized tissue weight data (1, 3, and 12M groups)
4. Table 3 – Summary of serum chemistry data (1 and 3M groups)
5. Figure 2 – Urinary metal data (1M group)
6. Figure 3 – Tumor development in metal-implanted animals

### **Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

#### ***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Bioinformatic analyses of microarray data from skeletal muscle samples. (Figures 1-9)

### **PROJECTS 3 & 4:**

### **Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

#### ***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

### **Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

#### ***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

1. Datafax Questionnaire: “Self-Reported Health Effects in Veterans with Blast and Embedded Metal Fragment Injuries” (Study Population #1-Questionnaire Only Group)
2. Submission Approvals Table
3. Online Questionnaire (screen shot of login page)
4. Deviations Tracking Table
5. Updated Informed Consent Document



**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***  
**2017 Schedule**

**OCTOBER 2017**

1	2 Implant 1M Ta (8)  Euthanasia 3M (4) – DU	3 Euthanasia 3M (4) – DU  Deliver 1M Rats (8) (Al)  LabSand – 1M Ni (8)	4 Implant 1M W (8)	5  LabSand – 1M Co (8)	6	7
8	9 <b>COLUMBUS DAY</b>	10 Implant 1M Ni (8) Pair house 1M Ta  LabSand – 1M Fe (8)	11 Pair house 1M W  LabSand – 1M Cu (8)	12 Implant 1M Co (8)	13	14
15	16 Implant 1M Fe (8)  LabSand – 1M Al (8)	17 Pair house 1M Ni	18 Implant 1M Cu (8)	19 Pair house 1M Co	20	21
22	23 Implant 1M (8) – Al Pair house 1M Fe  LabSand – 1M Ta (4)	24  LabSand – 1M Ta (4)	25 Pair house 1M Cu  LabSand – 1M W (4)	26  LabSand – 1M W (4)	27	28
29	30 Euthanasia 1M Ta (4) Pair house 1M Al Order Remaining 1M Rats (16) – Pb/DU (6 weeks old) LabSand – 1M Ni (4)	31 Euthanasia 1M Ta (4)  LabSand – 1M Ni (4)				

## NOVEMBER 2017

			1 Euthanasia 1M (4) – W  LabSand – 1M Co (4)	2 Euthanasia 1M (4) – W  LabSand – 1M Co (4)	3	4
5	6 Euthanasia 1M (4) – Ni  LabSand – 1M Fe (4)	7 Euthanasia 1M (4) – Ni  LabSand – 1M Fe (4)	8 Euthanasia 1M (4) – Co  LabSand – 1M Cu (4)	9 Euthanasia 1M (4) – Co  LabSand – 1M Cu (4)	10 <b>VETERANS DAY</b>	11
12	13 Euthanasia 1M (4) – Fe  LabSand – 1M Al (4)	14 Euthanasia 1M (4) – Fe  LabSand – 1M Al (4)	15 Euthanasia 1M (4) – Cu	16 Euthanasia 1M (4) – Cu	17	18
19	20 Euthanasia 1M (4) – Al	21 Euthanasia 1M (4) – Al  Deliver 1M Rats (16) – (Pb/DU)	22	23 <b>THANKSGIVING</b>	24	25
26	27	28	29	30		

## DECEMBER 2017

					1	2
3	4  <b>LabSand – 1M Pb (8)</b>	5	6  <b>LabSand – 1M DU (8)</b>	7	8	9
10	11 <b>Implant 1M Pb (8)</b>	12	13 <b>Implant 1M DU (8)</b>	14	15	16
17	18 <b>Pair house 1M Pb</b>	19	20 <b>Pair house 1M DU</b>	21	22	23
24/31	25 <b>CHRISTMAS</b>	26	27	28	29	30

## JANUARY 2018

	1 <b>NEW YEAR'S DAY</b>	2  LabSand – 1M Pb (8)	3  LabSand – 1M DU (4)	4  LabSand – 1M DU (4)	5	6
7	8 Euthanasia 1M (4) – Pb	9 Euthanasia 1M (4) – Pb	10 Euthanasia 1M (4) – DU	11 Euthanasia 1M (4) – DU	12	13
14	15 <b>MLK DAY</b>	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

## FEBRUARY 2018

				1 LabSand – Cu/12M (6M)	2	3
4	5	6 LabSand – Al/12M (6M)	7 Emergency Euthanasia 12M Ni	9 LabSand – Pb/12M (6M)	9	10
11	12	13 LabSand – DU/12M (6M)	14	15	16	17
18	19 <b>PRESIDENT'S DAY</b>	20	21	22	23	24
25	26	27 Rat Delivery (16)	28			

## MARCH 2018

				1	2	3
4	5	6 Rat Delivery (16)	7	9	9	10
11	12 LabSand – Ta/6M	13 Rat Delivery (16)	14 LabSand – W/6M	15	16	17
18	19 IMPLANT – Ta/6M (8) LabSand – Ni/6M	20 Rat Delivery (16)	21 IMPLANT – W/6M (8) LabSand – Co/6M	22	23	24
25	26 IMPLANT – Ni/6M (8) LabSand – Fe/6M Pair house Ta/6M	27 Rat Delivery (8)	28 IMPLANT – Co/6M (8) LabSand – Cu/6M Pair house – W/6M	29	30	31

## APRIL 2018

1	2 IMPLANT – Fe/6M (8) LabSand – Al/6M Pair house – Ni/6M	3	4 IMPLANT – Cu/6M (8) LabSand – Pb/6M Pair house – Co/6M	5	6	7
8	9 IMPLANT – Al/6M (8) LabSand – DU/6M Pair house – Fe/6M	10	11 IMPLANT – Pb/6M (8) Pair house Cu/6M	12	13	14
15	16 IMPLANT – DU/6M (8) Pair house – Al/6M	17 LabSand – Ta/12M (9M)	18 Pair house – Pb/6M	19 LabSand – W/12M (9M)	20	21
22	23 Pair house – DU/6M	24 LabSand – Ni/12M (9M)	25	26 LabSand – Co/12M (9M)	27	28
29	30					

## MAY 2018

		1 LabSand – Fe/12M (9M)	2	3 LabSand – Cu/12M (9M)	4	5
6	7	8 LabSand – Al/12M (9M)	9	10 LabSand – Pb/12M (9M)	11	12
13	14	15 LabSand – DU/12M (9M)	16	17	18	19
20	21	22	23	24	25	26
27	28 MEMORIAL DAY	29	30	31		



**JUNE 2018**

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

## JULY 2018

1	2	3	4 INDEPENDENCE DAY	5	6	7
8	9	10 LabSand – Ta/12M	11	12 LabSand – W/12M	13	14
15	16 Euthanasia – Ta/12M (4)	17 Euthanasia – Ta/12M (4) LabSand – Ni/12M	18 Euthanasia –W/12M (4)	19 Euthanasia – W/12M (4) LabSand – Co/12M	20	21
22	23 Euthanasia – Ni/12M (4)	24 Euthanasia – Ni/12M (4) LabSand – Fe/12M	25 Euthanasia – Co/12M (4)	26 Euthanasia – Co/12M (4) LabSand – Cu/12M	27	28
29	30 Euthanasia – Fe/12M (4)	31 Euthanasia – Fe/12M (4) LabSand – Al/12M				

## AUGUST 2018

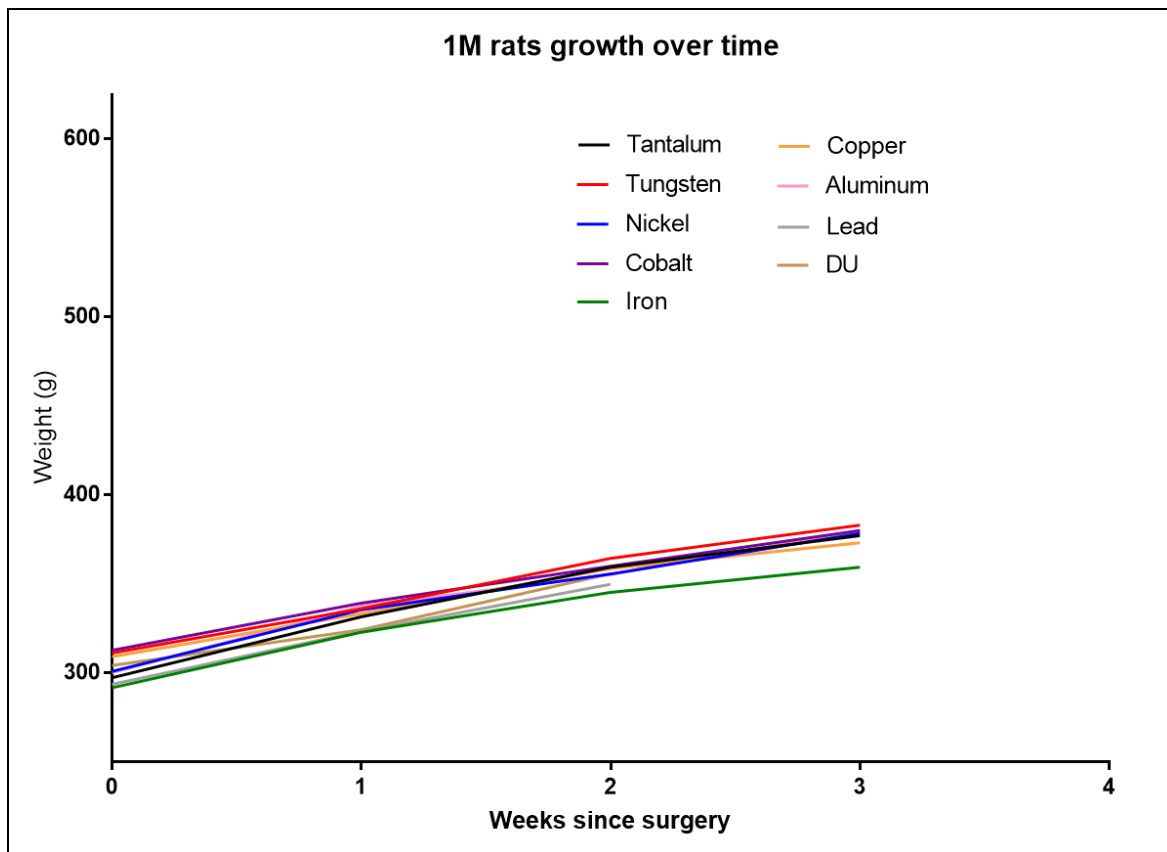
			1 Euthanasia – Cu/12M (4)	2 Euthanasia – Cu/12M (4) LabSand – Pb/12M	3	4
5	6 Euthanasia – Al/12M (4)	7 Euthanasia – Al/12M (4) LabSand – DU/12M	8 Euthanasia – Pb/12M (4)	9 Euthanasia – Pb/12M (4)	10	11
12	13 Euthanasia – DU/12M (4)	14 Euthanasia – DU/12M (4)	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

## SEPTEMBER 2018

1/2	3 LABOR DAY	4	5	6	7	8
9	10	11 LabSand – Ta/6M	12	13 LabSand – W/6M	14	15
16	17 Euthanasia – Ta/6M (4)	18 Euthanasia – Ta/6M (4) LabSand – Ni/6M	19 Euthanasia – W/6M (4)	20 Euthanasia – W/6M (4) LabSand – Co/6M	21	22
23	24 Euthanasia – Ni/6M (4)	25 Euthanasia – Ni/6M (4) LabSand – Fe/6M	26 Euthanasia – Co/6M (4)	27 Euthanasia – Co/6M (4) LabSand – Cu/6M	28	29
30						

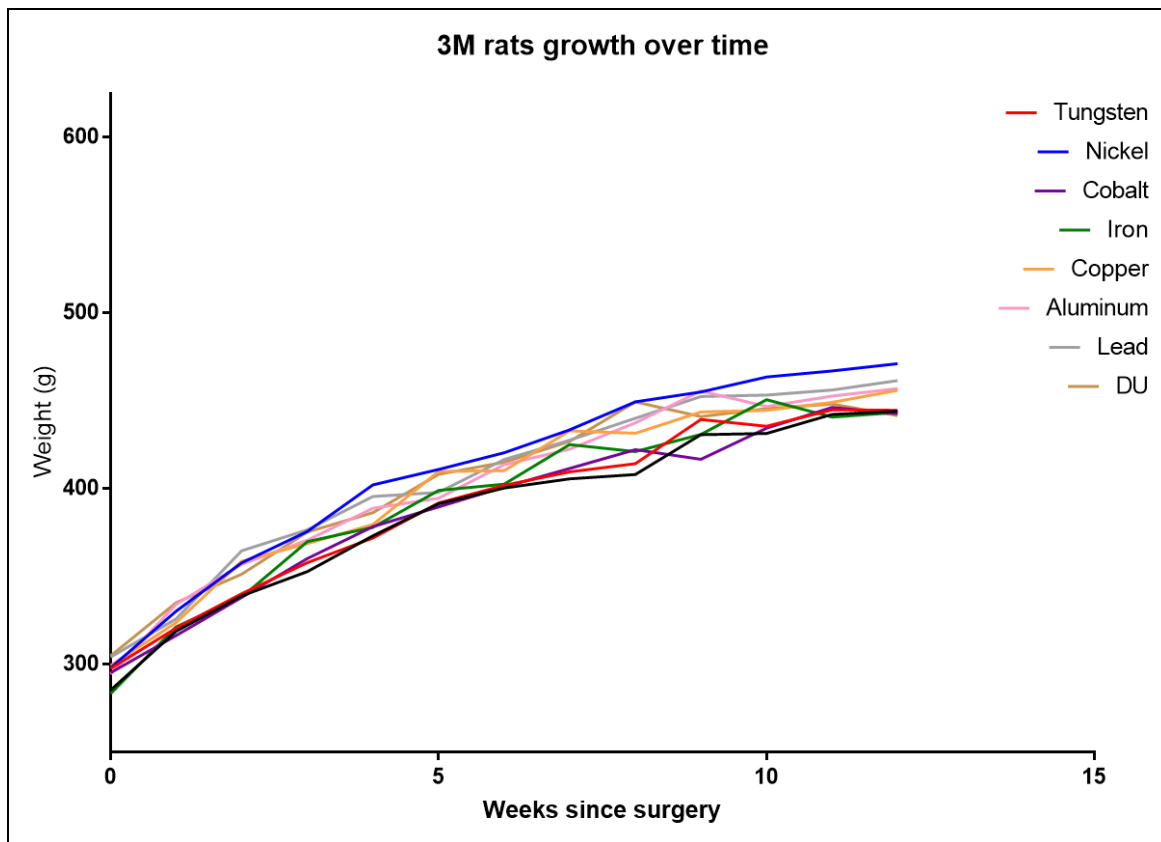
**Figure 1:** Weight gain over time (Panel A: 1M groups; Panel B: 3M groups; Panel C: 12M groups)

Panel A



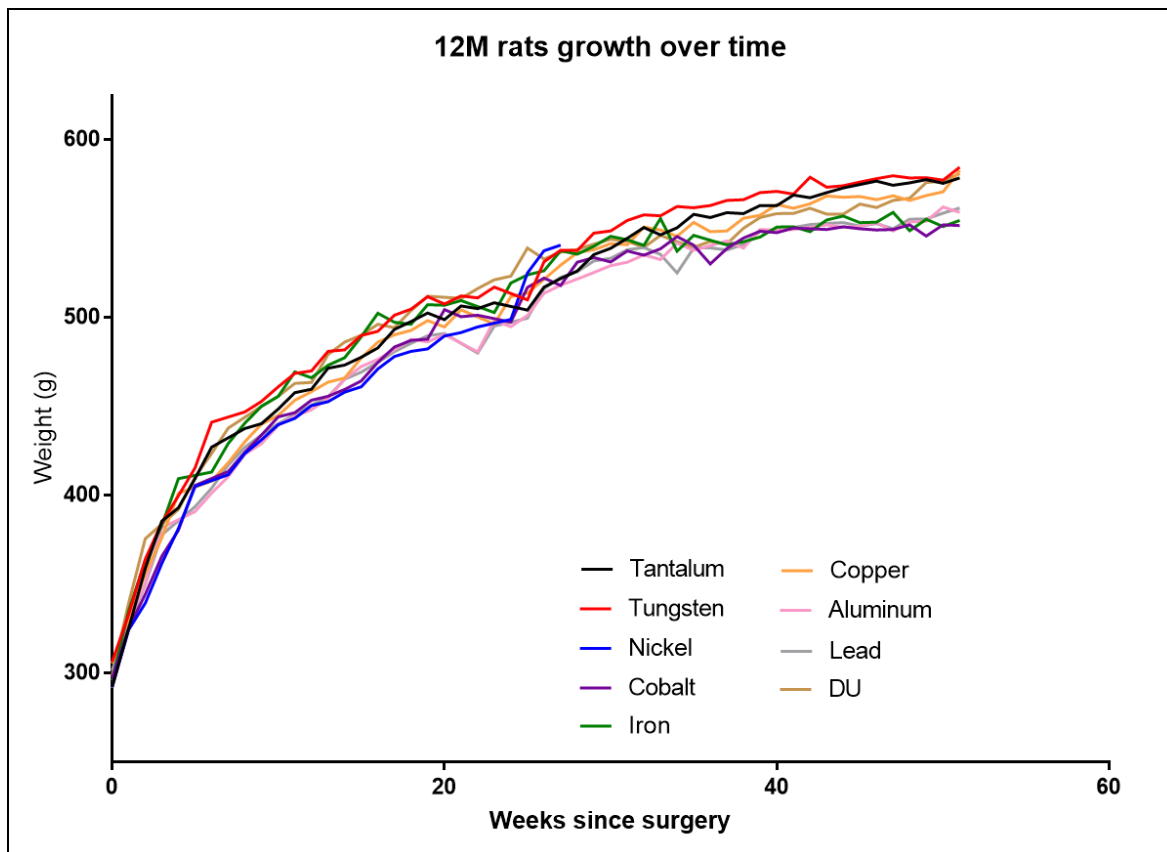
Panel B

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***



Panel C

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***



**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

**Table 1:** Hematology data for 1M, 3M, and 12M groups

<b>1M Rats</b>			
	<b>WBC (<math>10^3/\text{mm}^3</math>)</b>	<b>RBC (<math>10^6/\text{mm}^3</math>)</b>	<b>HGB (g/dl)</b>
	F(8,62)=10.86 *p<0.0001	F(8,62)=1.409 p=0.2108	F(8,62)=4.365 *p=0.0003
<b>Tantalum</b>	9.675 (1.909)	7.045 (2.219)	15.34 (0.809)
<b>Tungsten</b>	9.388 (1.308)	<b>8.126 (0.244)</b>	15.38 (0.315)
<b>Nickel</b>	10.310 (0.807)	7.976 (0.277)	15.16 (0.472)
<b>Cobalt</b>	11.100 (1.857)	7.878 (0.196)	15.00 (0.374)
<b>Iron</b>	9.925 (1.635)	7.999 (0.231)	15.38 (0.602)
<b>Copper</b>	<b>16.130 (2.878)</b>	7.804 (0.266)	14.73 (0.575)
<b>Aluminum</b>	8.950 (2.689)	7.760 (0.211)	14.81 (0.340)
<b>Lead</b>	10.490 (1.070)	7.981 (0.347)	<b>14.55 (0.666)</b>
<b>Depleted Uranium</b>	10.550 (0.921)	7.958 (0.179)	<b>14.30 (0.325)</b>

WBC: Tantalum vs Copper \*p=0.0001  
 (WBC is higher in copper animals compared to tantalum)

RBC: Tantalum vs Tungsten \*p=0.0348  
 (RBC is higher in tungsten animals compared to tantalum)

HGB: Tantalum vs Lead \*p=0.0249  
 (HGB is lower in lead animals compared to tantalum)  
 Tantalum vs DU \*p=0.0015  
 (HGB is lower in DU animals compared to tantalum)

<b>3M Rats</b>			
	<b>WBC (<math>10^3/\text{mm}^3</math>)</b>	<b>RBC (<math>10^6/\text{mm}^3</math>)</b>	<b>HGB (g/dl)</b>
	F(8,63)=1.301 p=0.2596	F(8,63)=0.2315 p=0.9836	F(8,63)=0.1977 p=0.9902
<b>Tantalum</b>	9.913 (3.288)	8.250 (0.310)	15.25 (0.346)
<b>Tungsten</b>	9.325 (1.026)	8.329 (0.284)	15.35 (0.499)
<b>Nickel</b>	8.113 (0.980)	8.329 (0.197)	15.38 (0.453)
<b>Cobalt</b>	9.075 (2.160)	8.201 (0.595)	15.40 (0.984)
<b>Iron</b>	8.263 (1.302)	8.389 (0.330)	15.44 (0.609)
<b>Copper</b>	8.663 (1.391)	8.294 (0.269)	15.29 (0.742)
<b>Aluminum</b>	8.388 (1.198)	8.349 (0.301)	15.53 (0.607)
<b>Lead</b>	8.150 (1.476)	8.353 (0.312)	15.26 (0.403)
<b>Depleted Uranium</b>	7.688 (1.515)	8.346 (0.330)	15.28 (0.358)

No significant differences



12M Rats			
	WBC (10 <sup>3</sup> /mm <sup>3</sup> )	RBC (10 <sup>6</sup> /mm <sup>3</sup> )	HGB (g/dl)
	F(8,57)=1.134 p=0.3550	F(8,57)=1.46 p=0.1925	F(8,57)=2.607 *p=0.0167
Tantalum	6.975 (1.152)	8.136 (0.242)	15.48 (0.523)
Tungsten	6.313 (1.305)	7.925 (0.279)	15.18 (0.392)
Nickel	7.429 (0.660)	8.589 (0.637)	<b>14.47 (0.492)</b>
Cobalt	7.663 (2.232)	8.068 (0.377)	15.18 (0.759)
Iron	7.186 (1.735)	7.991 (0.307)	15.37 (0.556)
Copper	7.033 (1.668)	8.178 (0.231)	15.33 (0.628)
Aluminum	7.275 (0.982)	8.045 (0.258)	15.66 (0.358)
Lead	8.543 (2.469)	7.366 (1.795)	15.14 (0.600)
Depleted Uranium	7.857 (1.382)	8.146 (0.674)	15.67 (0.927)

HGB: Tantalum vs Nickel \*p=0.0136  
(HGB is lower in nickel animals compared to tantalum)

Data presented as mean (SD), bold indicates significant difference when compared to tantalum control group using one-way ANOVA.

**Table 2:** Tissue weight data normalized to body weight for 1M, 3M and 12M groups

1M Rats					
	Thymus	Liver	Spleen	Kidney	Testes
	F(8,63)=0.734 7 p=0.6605	F(8,63)=0.915 6 p=0.5097	F(8,63)=5.336 *p<0.0001	F(8,63)=1.051 p=0.4086	F(8,63)=0.947 5 p=0.4847
Tantalum	0.108 (0.022)	3.618 (0.164)	0.197 (0.017)	0.672 (0.164)	1.023 (0.071)
Tungsten	0.104 (0.020)	3.556 (0.118)	0.181 (0.011)	0.605 (0.032)	0.977 (0.041)
Nickel	0.017 (0.016)	3.614 (0.299)	0.204 (0.016)	0.614 (0.028)	0.985 (0.061)
Cobalt	0.113 (0.009)	3.665 (0.115)	0.196 (0.014)	0.626 (0.036)	0.981 (0.039)
Iron	0.113 (0.031)	3.628 (0.118)	0.202 (0.025)	0.618 (0.029)	1.017 (0.097)
Copper	0.119 (0.012)	3.549 (0.197)	<b>0.221 (0.018)</b>	0.617 (0.029)	1.021 (0.075)
Aluminum	0.121 (0.026)	3.654 (0.249)	0.178 (0.017)	0.612 (0.020)	0.970 (0.043)
Lead	0.119 (0.021)	3.743 (0.199)	0.188 (0.011)	0.653 (0.015)	0.982 (0.040)
Depleted Uranium	0.117 (0.011)	3.719 (0.199)	0.184 (0.017)	0.643 (0.043)	1.010 (0.064)

Spleen: Tantalum vs Copper \*p=0.0282 (spleen is larger in copper animals compared to tantalum)

3M Rats					
	Thymus	Liver	Spleen	Kidney	Testes
	F(8,63)=0.260 1 p=0.9763	F(8,63)=3.885 *p=0.0009	F(8,63)=1.044 p=0.4133	F(8,63)=1.986 p=0.0626	F(8,63)=0.886 3 p=0.5332
Tantalum	0.061 (0.010)	3.034 (0.186)	0.163 (0.012)	0.563 (0.010)	0.924 (0.081)
Tungsten	0.056 (0.009)	3.006 (0.202)	0.168 (0.024)	0.567 (0.042)	0.851 (0.106)
Nickel	0.056 (0.012)	3.089 (0.247)	0.164 (0.014)	0.586 (0.036)	0.894 (0.051)
Cobalt	0.055 (0.007)	3.024 (0.099)	0.165 (0.021)	0.577 (0.018)	0.912 (0.123)
Iron	0.058 (0.016)	3.017 (0.115)	0.146 (0.009)	0.568 (0.025)	0.855 (0.123)
Copper	0.056 (0.013)	3.097 (0.133)	0.162 (0.013)	0.596 (0.045)	0.856 (0.070)
Aluminum	0.057 (0.010)	3.243 (0.184)	0.161 (0.011)	<b>0.611 (0.052)</b>	0.898 (0.080)
Lead	0.058 (0.007)	3.249 (0.235)	0.164 (0.022)	0.578 (0.030)	0.922 (0.046)
Depleted Uranium	0.055 (0.012)	<b>3.334 (0.099)</b>	0.166 (0.025)	0.601 (0.018)	0.891 (0.060)

Liver: Tantalum vs Depleted Uranium \*p=0.0074 (liver is larger in DU animals compared to tantalum)

Kidney: Tantalum vs Aluminum \*p=0.0330 (kidneys are bigger in aluminum animals compared to tantalum)

12M Rats					
	Thymus	Liver	Spleen	Kidney	Testes
	F(8,59)=2.213 *p=0.0390	F(8,59)=2.213 *p=0.0391	F(8,59)=1.043 p=0.4152	F(8,59)=0.754 9 p=0.6432	F(8,59)=1.536 p=0.1644
Tantalum	0.0319 (0.006)	3.248 (0.406)	0.1546 (0.022)	0.6589 (0.172)	0.8553 (0.180)
Tungsten	0.0306 (0.011)	3.075 (0.331)	0.1416 (0.021)	0.5993 (0.050)	0.7648 (0.076)
Nickel	0.0400 (0.008)	3.031 (0.255)	0.1764 (0.072)	0.6170 (0.034)	0.8607 (0.033)
Cobalt	0.0273 (0.006)	3.233 (0.118)	0.1560 (0.016)	0.5974 (0.045)	0.7924 (0.074)
Iron	0.0293 (0.007)	3.557 (0.544)	0.1619 (0.038)	0.5498 (0.219)	0.8139 (0.067)
Copper	0.0261 (0.009)	3.566 (0.548)	0.1709 (0.035)	0.6089 (0.091)	0.7384 (0.070)
Aluminum	0.0283 (0.003)	3.359 (0.265)	0.1659 (0.020)	0.5937 (0.033)	0.7801 (0.074)
Lead	0.0259 (0.007)	3.626 (0.450)	0.1795 (0.021)	0.6083 (0.060)	0.8119 (0.067)
Depleted Uranium	0.0287 (0.011)	3.348 (0.460)	0.1865 (0.057)	0.6803 (0.190)	0.7836 (0.058)

Thymus ANOVA is significant, but no comparisons survived post-hoc analysis

Liver ANOVA is significant, but no comparisons survived post-hoc analysis

Data presented as mean (SD), bold indicates significant difference when compared to tantalum control group using one-way ANOVA.

**Table 3:** Summary of serum chemistry statistically significant differences between experimental groups and tantalum control

**1M significances:**

Sodium: Tantalum vs Tungsten \*p=0.0001 (sodium is lower in tungsten animals compared to tantalum)

Sodium: Tantalum vs Copper \*p=0.0025 (sodium is lower in tungsten animals compared to tantalum)

Calcium: Tantalum vs Iron \*p=0.0121 (calcium is lower in iron animals compared to tantalum)

Total Protein: Tantalum vs Lead \*p=0.0043 (total protein is lower in lead animals compared to tantalum)

Albumin: Tantalum vs Nickel \*p=0.0465 (albumin is lower in nickel animals compared to tantalum)

Albumin: Tantalum vs Copper \*p=0.0238 (albumin is lower in copper animals compared to tantalum)

Albumin: Tantalum vs Lead \*p=0.0001 (albumin is lower in lead animals compared to tantalum)

Lipase: Tantalum vs Copper \*p=0.0472 (lipase is lower in copper animals compared to tantalum)

**3M significances:**

Sodium: Tantalum vs Cobalt \*p=0.0001 (sodium is increased in cobalt animals compared to tantalum)

Chloride: Tantalum vs Cobalt \*p=0.0001 (chloride is increased in cobalt animals compared to tantalum)

Chloride: Tantalum vs Aluminum \*p=0.0124 (chloride is increased in aluminum animals compared to tantalum)

Chloride: Tantalum vs Lead \*p=0.0257 (chloride is increased in lead animals compared to tantalum)

Carbon Dioxide: Tantalum vs Cobalt \*p=0.0395 (carbon dioxide is decreased in cobalt animals compared to tantalum)

Carbon Dioxide: Tantalum vs Lead \*p=0.0019 (carbon dioxide is decreased in lead animals compared to tantalum)

Carbon Dioxide: Tantalum vs DU \*p=0.0448 (carbon dioxide is decreased in lead animals compared to tantalum)

Phosphorus: Tantalum vs Aluminum \*p=0.0165 (phosphorus is increased in aluminum animals compared to tantalum)

Phosphorus: Tantalum vs Lead \*p=0.0142 (phosphorus is increased in lead animals compared to tantalum)

Total Protein: Tantalum vs Cobalt \*p=0.0168 (total protein is increased in cobalt animals compared to tantalum)

Albumin: Tantalum vs Cobalt \*p=0.0065 (albumin is increased in cobalt animals compared to tantalum)

ALKP: Tantalum vs Iron \*p=0.0492 (ALKP is increased in iron animals compared to tantalum)

**3M significances (cont.):**

LDH: Tantalum vs Aluminum \* $p=0.0261$  (ALKP is decreased in aluminum animals compared to tantalum)

LDH: Tantalum vs Lead \* $p=0.0405$  (ALKP is decreased in lead animals compared to tantalum)

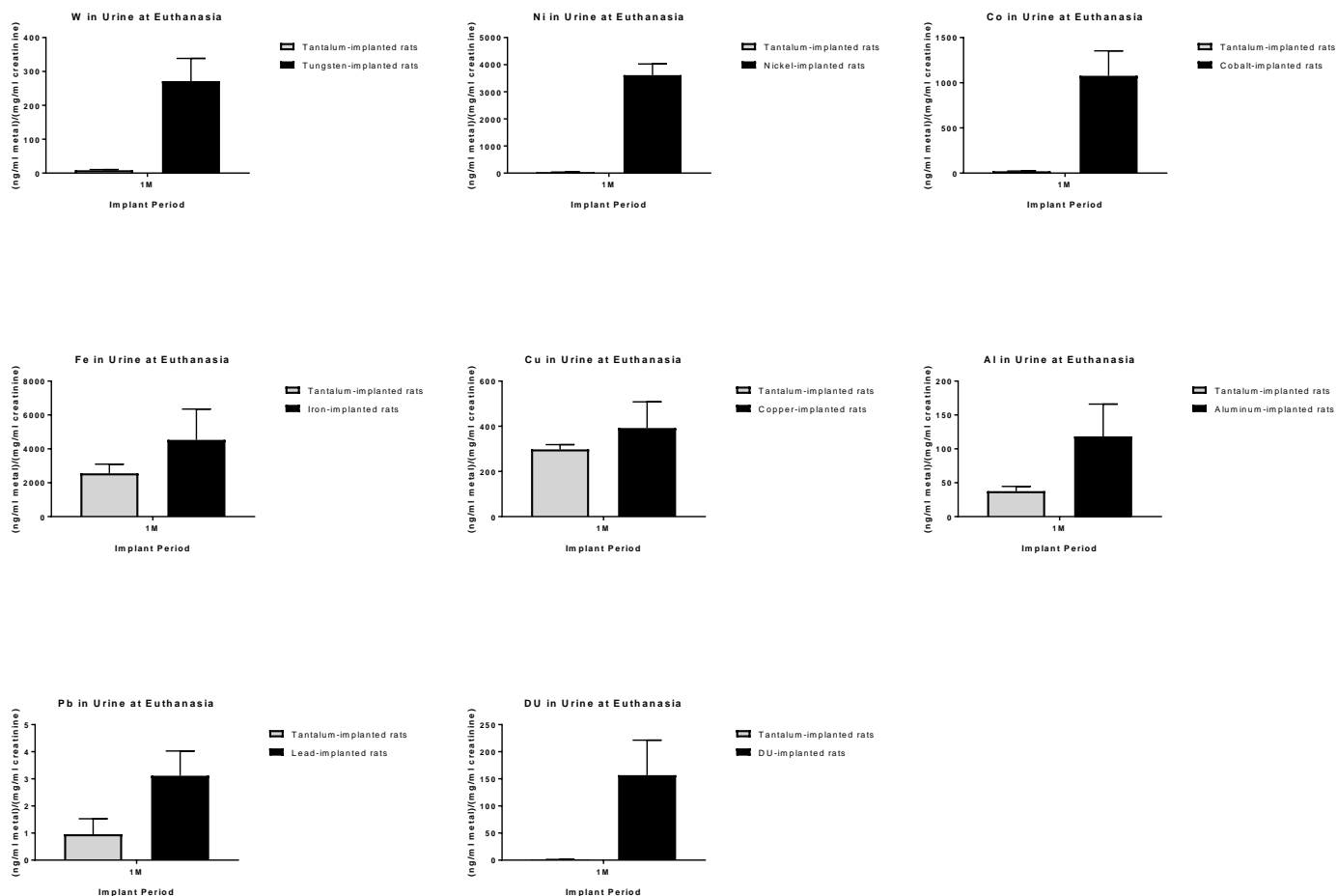
Direct HDLC: Tantalum vs Aluminum \* $p=0.0443$  (Direct HDLC is increased in aluminum animals compared to tantalum)

Direct HDLC: Tantalum vs Lead \* $p=0.0063$  (Direct HDLC is increased in lead animals compared to tantalum)

Direct HDLC: Tantalum vs DU \* $p=0.0238$  (Direct HDLC is increased in DU animals compared to tantalum)

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***

**Figure 2: Urinary metal levels (ng/mg creatinine) in 1M groups**



**Figure 3: Tumor development in metal-implanted rats**



**A) Tumor formation around implanted nickel pellet (6M)**



**B) Tumor formation around implanted cobalt pellet (12M group)**

**John F. Kalinich, Ph.D., Principal Investigator, Project 1**  
***“Health Effects of Embedded Fragments of Military-Relevant Metals”***



**C) Kidney tumor in 12M depleted uranium-implanted rat**



**D) Kidney tumor in 12M lead-implanted rat**

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

Bioinformatic analyses of microarray data from skeletal muscle samples. (Figures 1-9)

**Figure 1.**

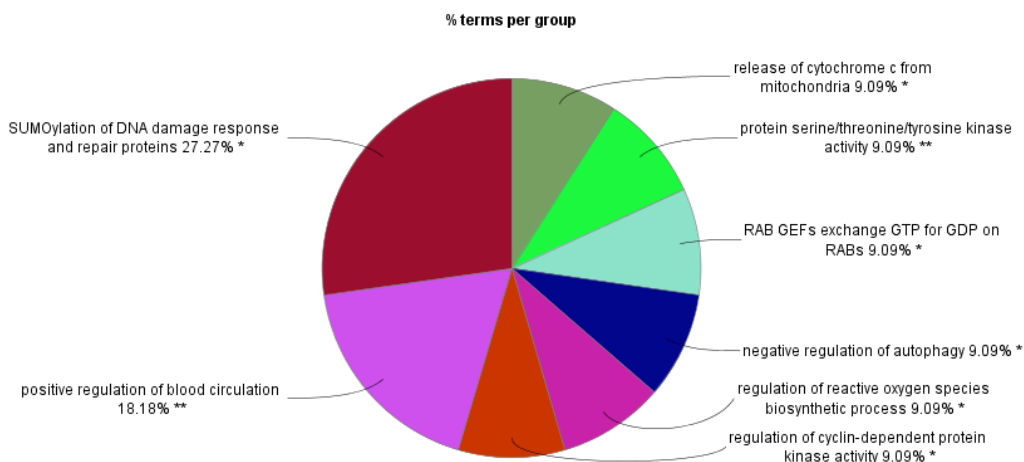
## Microarray Summary for Muscle Samples

		Tungsten	Nickel	Cobalt	Iron	Copper	Aluminium	Lead	Depleted Uranium
1 month	UP	None	59	None	1	3	None	40	3
	Down	None	41	6	10	9	2	115	50
3 months	UP	None	227	499	None	None	None	None	None
	Down	None	385	402	None	None	3	None	None

**Differentially expressed genes:** adjusted p value <0.05; FC 1.5 (UP) or 0.5 (Down) \_ Tantalum used as control

**Figure 2.**

## 1 month: Lead – down-regulated (115 genes)





Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:

*"Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds"*

Figure 3.

## Common Genes – 1 month

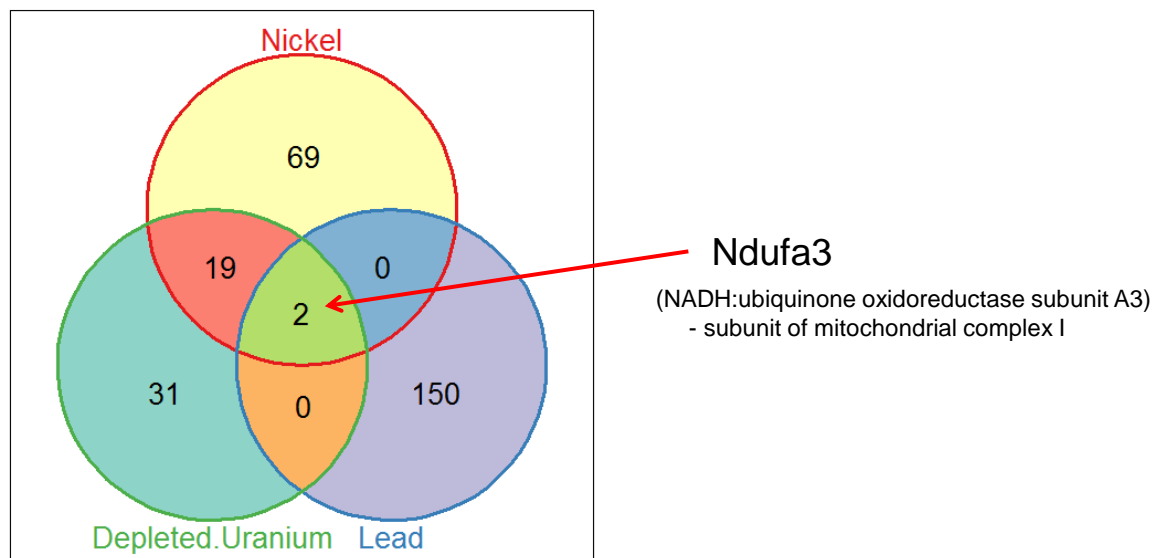
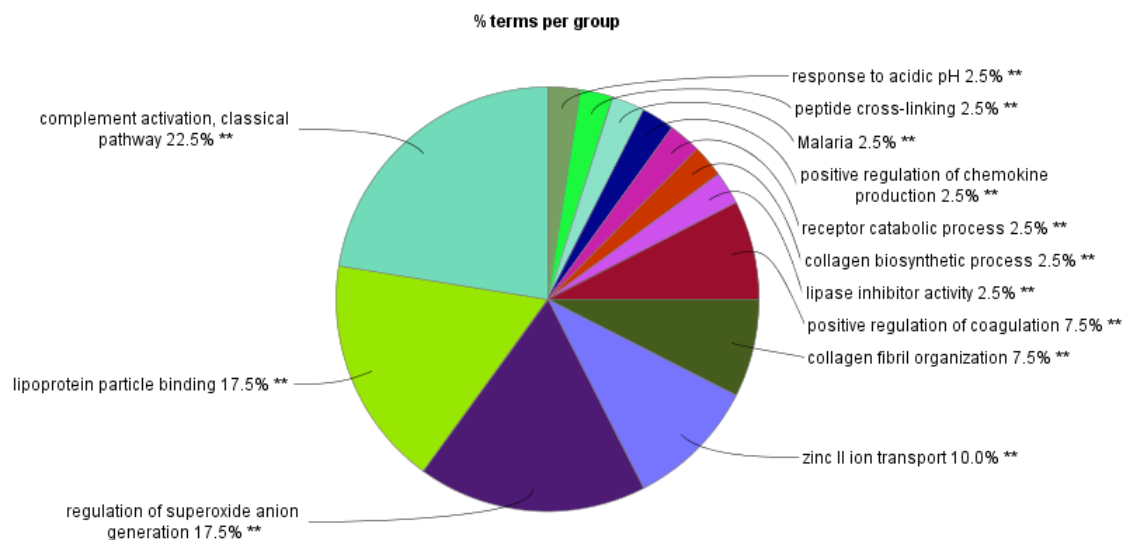


Figure 4

## 3 months: Nickel

### UP-REGULATED

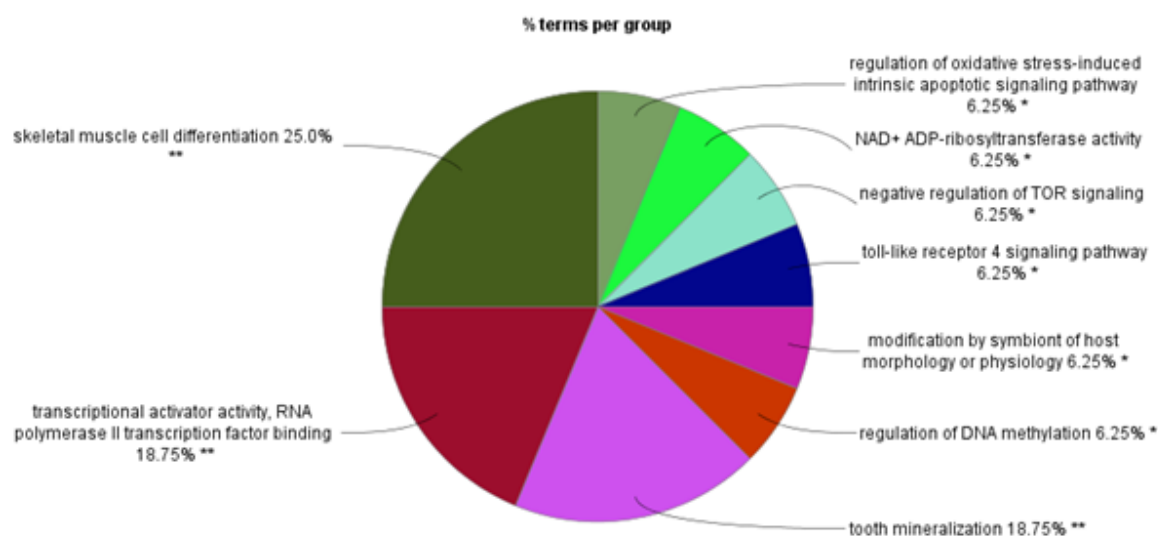


**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

## 3 months: Nickel

### DOWN-REGULATED



**Figure 5.**

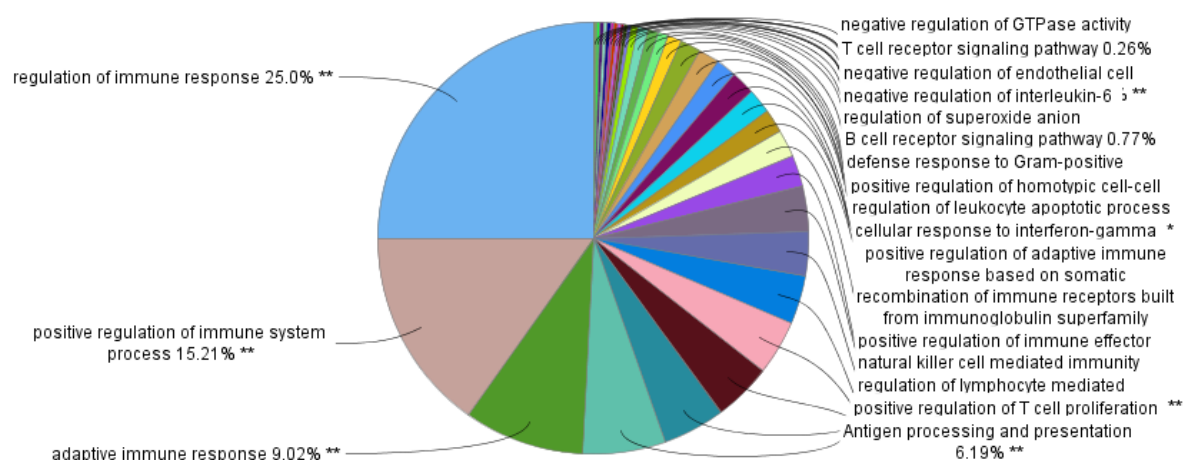
**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

## 3 months: Cobalt

### UP-REGULATED

% terms per group



**Figure 6.**

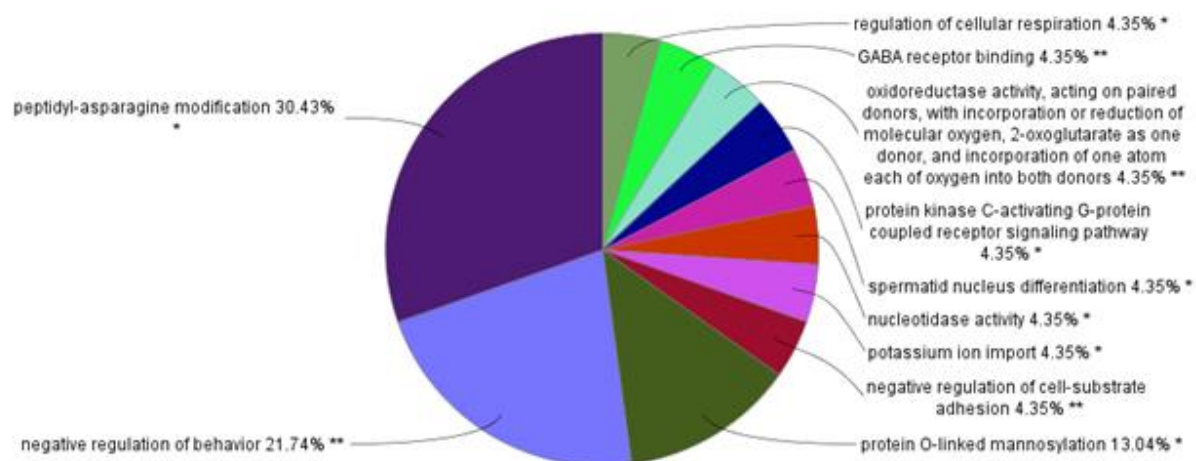
**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

### 3 months: Cobalt

#### DOWN-REGULATED

% terms per group

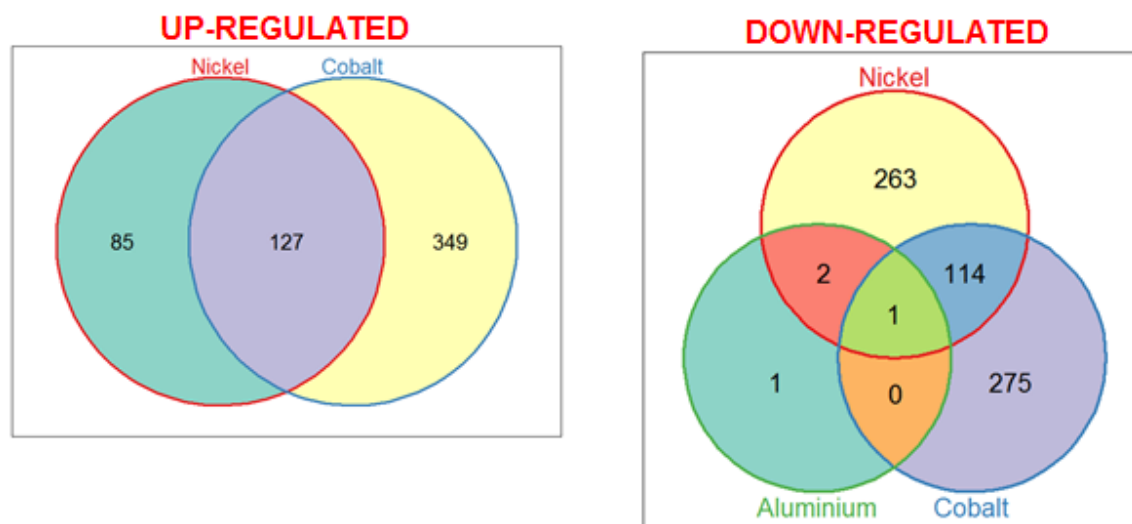


**Figure 7.**

**Charlotte A. Peterson, Ph.D., Principal Investigator, Project 2:**

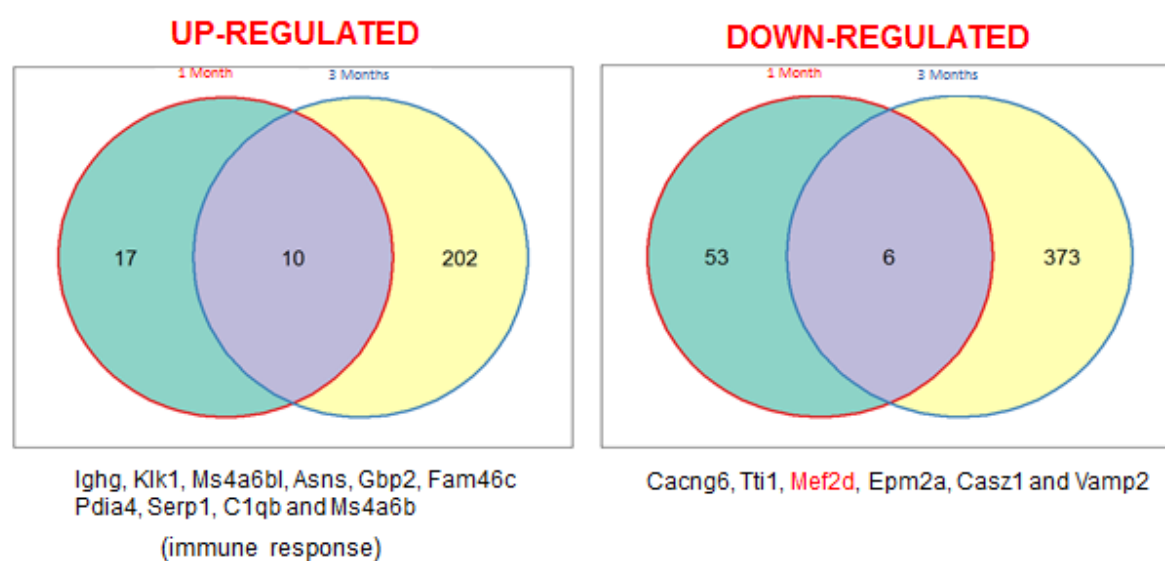
***“Biomarkers for Assessing Return-to-Duty Potential of Personnel with Embedded Metal-Fragment Wounds”***

## 3 months: common genes



**Figure 8.**

# 1 vs 3 months: common genes for nickel



**Figure 9.**

**PROJECTS 3 & 4:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

1. Datafax Questionnaire: “Self-Reported Health Effects in Veterans with Blast and Embedded Metal Fragment Injuries” (Study Population #1- Questionnaire Only Group)



DataFax # 246

Plate # 101

Visit # 001

## Self-Reported Health Effects in Veterans with Blast and Embedded Metal Fragment Injuries

PID#: **101339**

Date Form was Completed (mm/dd/yyyy)

		/			/				
--	--	---	--	--	---	--	--	--	--

### INSTRUCTIONS

- Use a black/blue pen.
- **Please place an "X" in the boxes and do not make any stray marks on this form.**
- Please answer every question as honestly as possible and to the best of your ability, unless you are requested to skip over a question. The questionnaire will take between 20-30 minutes to complete.
- Please feel free to reference any records you may have in your possession.

### Section A: Basic Information

Gender: ☐ Female ☐ Male Current Age:   years

#### 1. Marital Status:

- |  |                                   |
|--|-----------------------------------|
| <input type="checkbox"/> Married       | <input type="checkbox"/> Widowed  |
| <input type="checkbox"/> Separated     | <input type="checkbox"/> Divorced |
| <input type="checkbox"/> Never Married |                                   |

#### 2. Are you Spanish, Hispanic, or Latino?

- ☐ No, not Spanish, Hispanic, or Latino
- ☐ Yes, Mexican, Mexican American, Chicano
- ☐ Yes, Puerto Rican
- ☐ Yes, Cuban
- ☐ Yes, other Spanish, Hispanic, or Latino

#### 3. What is your race? (Choose one)

- |   |   |
|---|---|
| <input type="checkbox"/> White                  | <input type="checkbox"/> Other Asian                    |
| <input type="checkbox"/> Black/African American | <input type="checkbox"/> Filipino                       |
| <input type="checkbox"/> Pacific Islander       | <input type="checkbox"/> Chinese                        |
| <input type="checkbox"/> Japanese               | <input type="checkbox"/> American Indian/Alaskan Native |
| <input type="checkbox"/> Asian Indian           | <input type="checkbox"/> Other: <input type="text"/>    |

#### 4. What is the highest degree or level of school you have completed?

- ☐ Less than high school
- ☐ High school diploma/GED
- ☐ Some college credit, but no degree
- ☐ Associate's degree (e.g., AA, AS)
- ☐ Bachelor's degree (e.g., BA, BS)
- ☐ Master's degree (e.g., MA, MS, MBA)
- ☐ Professional or Doctorate degree



5. Including yourself, how many people currently live in your household?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9+

6. Which income category represents the total income of your household from all sources (before taxes and deductions) during the last 12 months?

☐ Less than \$10,000 ☐ \$40,000 - \$49,999 ☐ \$100,000 - \$149,999  
☐ \$10,000 - \$19,999 ☐ \$50,000 - \$59,999 ☐ \$150,000 or more  
☐ \$20,000 - \$29,999 ☐ \$60,000 - \$74,999 ☐ Prefer not to answer  
☐ \$30,000 - \$39,999 ☐ \$75,000 - \$99,999

## Section B: Uniformed Service Experience

7. In which branch of the service did you serve?

☐ Army ☐ National Guard  
☐ Navy ☐ Merchant Marines  
☐ Air Force ☐ NOAA  
☐ Marine Corps ☐ Public Health Service  
☐ Coast Guard

8. At the time of your injury, please indicate if you were:

☐ Active Duty ☐ Reserves

9. Did you deploy in support of the 1990-91 Gulf War?

☐ Yes ☐ No

10. Were you ever exposed to chemical or biological warfare agents?

☐ Yes ☐ No ☐ Unsure

*The following set of questions is related to your blast/injury experience and will help us assess the significance of the blast or explosion.*

## Section C: Blast/Injury History

11. Did you have any injury(ies) during your deployment from any of the following?

- a. Fragment ☐ Yes ☐ No  
b. Bullet ☐ Yes ☐ No  
c. Vehicular (any type of vehicle, including airplane) ☐ Yes ☐ No  
d. Fall ☐ Yes ☐ No  
e. Blast (Improvised Explosive Device, RPG, Land mine, Grenade, etc) ☐ Yes ☐ No  
f. Other ☐ Yes ☐ No If yes, specify:

12. Following a blast or explosion, did you experience any of the following?

*\*If you did not experience a blast or explosion select N/A for all and skip to number 13.*

- a. Being dazed, confused, or "seeing stars" ☐ Yes ☐ No ☐ N/A
- b. Not remembering the injury ☐ Yes ☐ No ☐ N/A
- c. Losing consciousness (knocked out) for less than a minute ☐ Yes ☐ No ☐ N/A
- d. Losing consciousness for 1-20 minutes ☐ Yes ☐ No ☐ N/A
- e. Losing consciousness for longer than 20 minutes ☐ Yes ☐ No ☐ N/A
- f. Having any symptoms of concussion afterward ☐ Yes ☐ No ☐ N/A
- g. Head injury ☐ Yes ☐ No ☐ N/A

13. Are you currently experiencing any of the following problems that you think might be related to a possible head injury or concussion?

- a. Headaches ☐ Yes ☐ No
- b. Dizziness ☐ Yes ☐ No
- c. Memory Problems ☐ Yes ☐ No
- d. Balance Problems ☐ Yes ☐ No
- e. Ringing in the ears ☐ Yes ☐ No
- f. Irritability ☐ Yes ☐ No
- g. Sleep Problems ☐ Yes ☐ No
- h. Other ☐ Yes ☐ No

If yes, specify:

14. As the result of a blast or explosion, did you experience any of the following?

*\*If you did not experience a blast or explosion, select N/A for all and skip to question 15.*

- a. Pneumothorax (collapsed lung) ☐ Yes ☐ No ☐ N/A
- b. Lung contusion (bruised lung) ☐ Yes ☐ No ☐ N/A
- c. Rib fracture (broken rib) ☐ Yes ☐ No ☐ N/A
- d. Penetrating lung injury (gunshot wound or shrapnel to the chest) ☐ Yes ☐ No ☐ N/A
- e. Ruptured ear drum ☐ Yes ☐ No ☐ N/A
- f. Pain around the cheek bones, above your eyes, or in your teeth ☐ Yes ☐ No ☐ N/A
- g. Nose bleed ☐ Yes ☐ No ☐ N/A
- h. Sinus pressure ☐ Yes ☐ No ☐ N/A

15. Did your injury require surgery? ☐ Yes ☐ No



DataFax # 246

Plate # 104

Visit # 001

PID #

101339

16. Did your injury require amputation? ☐ Yes ☐ No

16a. If so, describe:

17. Immediately following your injury, did you notice blood in your urine?

☐ Yes ☐ No ☐ Unsure

18. Have you ever been told you had a traumatic brain injury (TBI) by a physician?

☐ Yes ☐ No

*The following set of questions will allow us to 1.) describe health conditions that may be associated with retained fragments and 2.) identify other sources of metal exposure.*

## Section D: Fragment and Metal Exposure Questions

19. In what year did you have an injury that led to having an embedded fragment? (If more than one, enter the year of the first injury)

20. Location when you received the injury that resulted in shrapnel or fragments being removed from or remaining in your body:

☐ Afghanistan ☐ Iraq ☐ Other

**The next several questions ask about your embedded fragment injury.**

21. Were you injured by a bullet?

☐ Yes ☐ No

22. Were you injured as a result of a blast or explosion?

☐ Yes (Go on to question 22a) ☐ No (Skip to question 25)

22a. If yes, approximately how many meters were you from the explosion?

 Meters

23. Were you in a vehicle at the time of the blast or explosion?

☐ Yes ☐ No

24. Was the blast or explosion caused by:

a. Improvised Explosive Device (IED) ☐ Yes ☐ No

b. Rocket Propelled grenade ☐ Yes ☐ No

c. Land mine ☐ Yes ☐ No

d. Grenade ☐ Yes ☐ No

e. Enemy fire ☐ Yes ☐ No

f. Friendly fire ☐ Yes ☐ No

g. Unknown ☐ Yes ☐ No

h. Other ☐ Yes ☐ No

If yes, please describe:





DataFax # 246

Plate # 106

Visit # 001

PID #

**101339**

26. Did you have shrapnel, fragments, or bullets removed during surgery?

☐ Yes ☐ No ☐ Unknown

26a. If yes, were the fragments sent to the lab for analysis?

☐ Yes ☐ No ☐ Unknown

27. Do you have retained fragments or shrapnel in your body from bullets or a blast or explosion?

☐ Yes ☐ No ☐ Unknown

27a. If yes, where? *Please "X" the boxes indicating the body part area(s) where the fragments are located. (continued on next page)*

27a. Please "X" the box(es) indicating the body part area(s) where **FRAGMENTS** are located.

**Front** **Back**

☐ 1. Head

☐ 2. Neck

☐ 3. Chest

☐ 4. Abdomen

☐ 5. Groin/Pelvis

☐ 6. Head

☐ 7. Neck

☐ 8. Upper Back

☐ 9. Lower Back

☐ 10. Buttocks

**LOCATION  
OF  
FRAGMENTS**

**Right** **Left**

☐ 11. Shoulder

☐ 12. Upper arm

☐ 13. Lower arm

☐ 14. Hand, wrist & fingers

☐ 15. Upper leg & thigh

☐ 16. Knee

☐ 17. Lower leg

☐ 18. Ankle

☐ 19. Foot & toes

☐ 20. Shoulder

☐ 21. Upper arm

☐ 22. Lower arm

☐ 23. Hand, wrist & fingers

☐ 24. Upper leg & thigh

☐ 25. Knee

☐ 26. Lower leg

☐ 27. Ankle

☐ 28. Foot & toes

28. Where were you treated for this injury?

- ☐ In the field
- ☐ At a Combat Support Hospital
- ☐ At Landstuhl, Germany
- ☐ At a U.S. based Medical Treatment Facility
- ☐ At a VA Medical Center

**The next several questions ask about other sources of metal exposures.**

29. In the past year, have you worked in an occupation or had a hobby that involved the following:

- a. Smelting ☐ Yes ☐ No
- b. Demolition ☐ Yes ☐ No
- c. Mining ☐ Yes ☐ No
- d. Soldering ☐ Yes ☐ No
- e. Welding ☐ Yes ☐ No
- f. Machining, grinding of metals ☐ Yes ☐ No
- g. Sand blasting ☐ Yes ☐ No
- h. Other manufacturing that involves working with metals ☐ Yes ☐ No
- i. Making bullets or shot ☐ Yes ☐ No
- j. Firing range use or maintenance ☐ Yes ☐ No
- k. Working with wood preservatives ☐ Yes ☐ No
- l. Making stained glass ☐ Yes ☐ No
- m. Making fishing weights ☐ Yes ☐ No
- n. Working with anti-foulant (marine) paint ☐ Yes ☐ No
- o. Working with lead paint ☐ Yes ☐ No
- p. Making jewelry or art using metals ☐ Yes ☐ No

30a. In the past year, have you worked in an occupation in which you were exposed to metal dust or fumes in any other way?

☐ Yes ☐ No

If yes, please describe:



DataFax # 246

Plate # 109

Visit # 001

PID #

101339

30b. In the past year, have you had a hobby in which you were exposed to metal dust or fumes in any other way?

☐ Yes ☐ No

If yes, please describe:

31. Do you currently have any of the following:

a. Metal braces on your teeth ☐ Yes ☐ No

b. Tattoos ☐ Yes ☐ No

c. Piercings ☐ Yes ☐ No

32. Do you have any of the following implants/devices in your body?

a. Hip, knee, or shoulder replacement ☐ Yes ☐ No

*Year of first Implant*

*Location in Body*

b. Surgical Clips or wires ☐ Yes ☐ No

*Year of first Implant*

*Location in Body*

c. Metal plates, screws, or rods ☐ Yes ☐ No

*Year of first Implant*

*Location in Body*

d. Stents ☐ Yes ☐ No

*Year of first Implant*

*Location in Body*

e. Pacemaker or defibrillator ☐ Yes ☐ No

*Year of first Implant*

*Location in Body*

f. Dental implants ☐ Yes ☐ No

*Year of first Implant*

*Location in Body*

g. Other ☐ Yes ☐ No Specify:

*Year of first Implant*

*Location in Body*



33. Do you routinely use/take the following?

- a. Vitamins ☐ Yes ☐ No
- b. Ayurvedic medications ☐ Yes ☐ No
- c. Denture cream ☐ Yes ☐ No
- d. Nutritional or dietary supplements ☐ Yes ☐ No
- e. Zinc sunblock ☐ Yes ☐ No

34. What is the primary source of your household water?

- ☐ Community Water System ☐ Well

*Sometimes people have fragments in a part of their body different from the site of their injury. The following questions address both the fragment site and the injury site. Please answer accordingly.*

35. How often do you experience...

- a. ...skin irritation near the site of a fragment?  
☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐ Unsure of fragment location
- b. ...skin irritation near the site of the injury?  
☐ Often ☐ Sometimes ☐ Rarely ☐ Never
- c. ...pain around the site of a fragment?  
☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐ Unsure of fragment location
- d. ...pain around the site of an injury?  
☐ Often ☐ Sometimes ☐ Rarely ☐ Never
- e. ...swelling around the site of a fragment?  
☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐ Unsure of fragment location
- f. ...swelling around the site of the injury?  
☐ Often ☐ Sometimes ☐ Rarely ☐ Never

36. Have you had fragments work their way out of your body (without surgery)?

- ☐ Yes ☐ No

37. Do you have any area on your skin that is discolored (i.e., darkened, tattoo-like appearance) that you believe is related to a fragment?

- ☐ Yes ☐ No

38. Can you feel any of the fragments under your skin?

- ☐ Yes ☐ No

39. Do you have a fragment located in a joint space?

☐ Yes ☐ No ☐ Unsure of fragment location

39a. If so, where:

40. Have you ever broken a bone?

☐ Yes ☐ No

40a. If "yes", when?

1. Before fragment injury ☐ Yes ☐ No

2. At the time of fragment injury ☐ Yes ☐ No

3. After fragment injury ☐ Yes ☐ No

41. Have you ever been told that you have a metal allergy or sensitivity?

☐ Yes ☐ No

41a. If "yes", to which metal?

42. Have you ever been told you have contact dermatitis?

☐ Yes ☐ No

42a. If "yes", was it believed to be related to a metal exposure?

☐ Yes ☐ No

43. Have you ever been told that you have eczema?

☐ Yes ☐ No

44. Have you ever been told you had lead poisoning?

☐ Yes ☐ No

*The following set of questions will help us describe your overall health status.*

## Section E: General Health, Activities, and Habits

45. In general, would you say your health is:

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

46. The following items are about activities you might do during a typical day. **Does your health now limit you in these activities? If so, how much?**

46a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

46b. Climbing several flights of stairs?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

47. During the past 4 weeks, have you had any of the following problems with your work or other daily activities as a result of your physical health?

47a. ...accomplished less than you would like?

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

47b. ...been limited in the kind of work or other activities?

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

48. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

48a. ...accomplished less than you would like?

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

48b. ...not done work or other activities as carefully as usual?

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

49. During the past 4 weeks, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ☐ Not at all
- ☐ A little bit
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely



DataFax # 246

Plate # 113

Visit # 001

PID #

101339

**50. How much of the time in the last 4 weeks...**

50a. ...have you felt calm and peaceful?

- ☐ All of the time  
☐ Most of the time  
☐ A good bit of the time  
☐ Some of the time  
☐ A little of the time  
☐ None of the time

50b. ...did you have a lot of energy?

- ☐ All of the time  
☐ Most of the time  
☐ A good bit of the time  
☐ Some of the time  
☐ A little of the time  
☐ None of the time

50c. ...have you felt downhearted and blue?

- ☐ All of the time  
☐ Most of the time  
☐ A good bit of the time  
☐ Some of the time  
☐ A little of the time  
☐ None of the time

**51. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

- ☐ All of the time  
☐ Most of the time  
☐ Some of the time  
☐ A little of the time  
☐ None of the time

**52. How many prescription medications do you currently take on a daily basis?**

- ☐ None   ☐ 1-3   ☐ 4-6   ☐ 7-9   ☐ 10 or more

**53. How many non-prescription medications do you currently take on a daily basis?**

- ☐ None   ☐ 1-3   ☐ 4-6   ☐ 7-9   ☐ 10 or more

PID #

101339

54. Do you take any of the following medications regularly (2 or more times a week)?

a. Aspirin ☐ Yes ☐ No

e. Celecoxib (CeleBREX) ☐ Yes ☐ No

b. Ibuprofen (Motrin) ☐ Yes ☐ No

f. Goody's Pain Relief ☐ Yes ☐ No

c. Naproxen (Aleve) ☐ Yes ☐ No

g. BC Pain Relief Powder ☐ Yes ☐ No

d. Meloxicam (Mobic) ☐ Yes ☐ No

54a. If you checked "yes" to any of the above, approximately how many months have you been taking this medication regularly?

☐ <1 month ☐ 1-6 months ☐ 6-12 months ☐ 12-24 months ☐ >24months

\*Questions 46-52 were taken from The Veterans RAND 12 Item Health Survey (VR-12). The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) which was developed from the MOS RAND SF-36 Version 1.0. It was modified from its original version for the purpose of this study.

*The following set of questions will ask you about other symptoms you may experience.*

## Section F: Organ-Specific Health Questions

*Rate the severity of each of the following symptoms on a scale from 0 (not at all) to 4 (extremely).*

55. Do you often notice a bad taste in your mouth?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

56. Do you experience loss of appetite?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

57. Do you often feel nauseous or sick to your stomach?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

58. Do you vomit frequently?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

59. Do you experience heart burn?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

60. Do you notice abdominal bloating or excessive gas symptoms?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

61. Do you experience diarrhea?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

62. Do you experience constipation?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

63. Did you frequently get hiccoughs ("hiccups")?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
64. Do you experience itching?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
65. Do you often develop hives or any other type of rash?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
66. Do you bruise or bleed easily?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
67. Do you experience a lack of pep or energy?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
68. Do you tire easily or experience weakness?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
69. Do you develop muscle cramps?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
70. Do you often feel faint when you stand up?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
71. Do you find yourself having difficulty falling and/or staying asleep?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
72. Do you find yourself falling asleep during the day?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
73. Do you feel irritable often?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
74. Do you experience decreased alertness?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
75. Do you experience forgetfulness?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely
76. Do you notice that your vision is blurry?  
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4  
Not at all Extremely

PID # **101339**

77. Do you ever notice blood in your urine?

☐ 0      ☐ 1      ☐ 2      ☐ 3      ☐ 4  
 Not at all      Extremely

78. Do you experience swelling or puffiness of the skin, particularly around your eyes?

☐ 0      ☐ 1      ☐ 2      ☐ 3      ☐ 4  
 Not at all      Extremely

79. Do you find yourself getting up to urinate frequently throughout the night?

☐ 0      ☐ 1      ☐ 2      ☐ 3      ☐ 4  
 Not at all      Extremely

***For the following section, please check "yes" or "no" for each item.***

80. I have been **tested** for chronic kidney disease. ☐ Yes ☐ No

81. I have been **told I have** chronic kidney disease. ☐ Yes ☐ No

82. My age is:

82a. Between 50 and 59 years of age. ☐ Yes ☐ No

82b. Between 60 and 69 years of age. ☐ Yes ☐ No

82c. 70 years of age or older. ☐ Yes ☐ No

83. I have or have had anemia. ☐ Yes ☐ No

84. I am diabetic. ☐ Yes ☐ No

85. I have a history of heart attack or stroke. ☐ Yes ☐ No

86. I have a history of congestive heart failure. ☐ Yes ☐ No

87. I have a circulation disease in my legs. ☐ Yes ☐ No

88. I have protein in my urine. ☐ Yes ☐ No

89. I have a history of high blood pressure. ☐ Yes ☐ No

90. I have a history of lupus, scleroderma, or other autoimmune disease. ☐ Yes ☐ No

91. I have a history of recurrent urinary tract infection (UTI). ☐ Yes ☐ No

92. I have a history of recurrent kidney stones. ☐ Yes ☐ No

93. I have a family history of chronic kidney disease. ☐ Yes ☐ No

94. Has a doctor ever told you that you have:

94a. Hypertension (high blood pressure) ☐ Yes ☐ No

94b. Cardiovascular (heart) disease ☐ Yes ☐ No

94c. Kidney cancer ☐ Yes ☐ No

94d. High cholesterol ☐ Yes ☐ No

94e. An infection or inflammation of the kidneys ☐ Yes ☐ No

*The following set of questions will help us assess your lung function.*

### Section G: Lung Function

*For the following section, please check one option for each item.*

95. Do you usually have a cough? (Count a cough with first smoke or on first going out of doors. Exclude clearing of throat.)

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

*If your answer is "No, none of the time" to the above question, check N/A to the following question.*

95a. Do you usually cough as much as 4 to 6 times a day, 4 or more days out of the week?

- ☐ N/A
- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

96. Do you usually bring up phlegm from your chest? (Count phlegm with first smoke or first going out of doors. Exclude phlegm from nose.)

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time







101339

☐ No, none of the time

☐ Yes, a little of the time

☐ Yes, some of the time

☐ Yes, most of the time

☐ Yes, all of the time

PID #

101339

103. During the past 3 years, have you had chest illnesses that have kept you off work, indoors, or in bed?

- ☐ No, none of the time
- ☐ Yes, a little of the time
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

104. Have you ever had any of the following?

104a. Bronchitis?    ☐ Yes    ☐ No

104b. Pneumonia?    ☐ Yes    ☐ No

104c. Hay fever/seasonal allergies?    ☐ Yes    ☐ No

105. Have you ever had chronic bronchitis?    ☐ Yes    ☐ No

*If your answer is "No" to the above question, check N/A to the following questions.*

105a. Do you still have it?    ☐ N/A    ☐ Yes    ☐ No

105b. Was it confirmed by a doctor?    ☐ N/A    ☐ Yes    ☐ No

105c. At what age did it start?    ☐ N/A      Age when started

106. Have you ever had emphysema?    ☐ Yes    ☐ No

*If your answer is "No" to the above question, check N/A to the following questions.*

106a. Do you still have it?    ☐ N/A    ☐ Yes    ☐ No

106b. Was it confirmed by a doctor?    ☐ N/A    ☐ Yes    ☐ No

106c. At what age did it start?    ☐ N/A      Age when started

107. Have you ever had asthma?    ☐ Yes    ☐ No

*If your answer is "No" to the above question, check N/A to the following questions.*

107a. Do you still have it?    ☐ N/A    ☐ Yes    ☐ No

107b. Was it confirmed by a doctor?    ☐ N/A    ☐ Yes    ☐ No

107c. At what age did it start?    ☐ N/A      Age when started

107d. Do you currently require medicine or treatment for asthma?    ☐ N/A    ☐ Yes    ☐ No

DataFax # 246

Plate # 121

Visit # 001

PID #

101339

108. Have you ever had any other chest illnesses? ☐ Yes ☐ No

108a. If "yes", please specify:

109. Have you ever had any chest injuries?

109a. Pneumothorax (collapsed lung) ☐ Yes ☐ No

109b. Lung contusion (bruised lung) ☐ Yes ☐ No

109c. Rib fracture (broken rib) ☐ Yes ☐ No

109d. Penetrating lung injury (gunshot wound or shrapnel to the chest) ☐ Yes ☐ No

110. Have you ever worked for a year or more in a dusty job? ☐ Yes ☐ No

110a. If "yes", please specify industry:

110b. If "yes", was dust exposure: ☐ Mild ☐ Modest ☐ Severe

111. Have you ever been exposed to gas or chemical fumes in your work? ☐ Yes ☐ No

111a. If "yes", please specify industry:

111b. If "yes", was gas or chemical fume exposure: ☐ Mild ☐ Modest ☐ Severe

112. Have you ever smoked cigarettes (NO means less than 100 cigarettes in your lifetime)? ☐ Yes ☐ No

*If your answer is "No" to the above question, check N/A to the following questions.*

112a. Do you now smoke (as of one month ago)? ☐ N/A ☐ Yes ☐ No

112b. At what age did you start? ☐ N/A Age when started

112c. If you have stopped smoking cigarettes completely, how old were you when you stopped? ☐ N/A Age when stopped

112d. On average of the entire time you smoked, how many cigarettes did you smoke per day?

☐ N/A ☐ 0.5-1 pack/week ☐ 1 pack/week ☐ 1-1.5 packs/day ☐ 1.5-2 packs/day ☐ >2 packs/day

113. Have you ever smoked non-tobacco products regularly (i.e. vape, e-cigarettes)? ☐ Yes ☐ No

113a. If "yes", please specify:

**PROJECTS 3 & 4:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

2. Submission Approvals Table

Protocol #A-19735.1					
		IRB		DoD HRPO	
Type of Submission		Date Submitted	Date Approved	Date Submitted	Date Approved
Initial Protocol	UM HRPO	7/21/2017	8/8/2017	9/27/2018	12/14/2018
	VA R&D	8/16/2017	9/14/2017		
Modifications	1	8/18/2017	9/1/2017	9/27/2018*	12/14/2018
	2	3/12/2018	3/28/2018	3/28/2018	4/3/2018
	3	5/11/2018	6/1/2018	6/5/2018	6/13/2018
	4	7/20/2018	7/30/2018	8/3/2018	8/3/2018
Continuing Review	1	7/2/2018	7/12/2018	7/17/2018	7/30/2018

\*This modification was included in the initial protocol submission to DoD HRPO

Protocol #A-19735.2					
		IRB		DoD HRPO	
Type of Submission		Date Submitted	Date Approved	Date Submitted	Date Approved
Initial Protocol	VA C-IRB	3/23/2017	5/22/2017	9/27/2018	12/14/2018
	LSI	8/1/2017	10/4/2017		
	UM HRPO	6/28/2017	6/28/2017		
	VA R&D	8/8/2017	9/14/2017		
Modifications	1	6/5/2018	6/19/2018	6/25/2018	6/26/2018
	2	8/15/2018	pending		
	3	9/4/2018	pending		
Continuing Review	1	3/22/2018	4/29/2018	5/22/2018	6/12/2018

## PROJECTS 3 & 4:

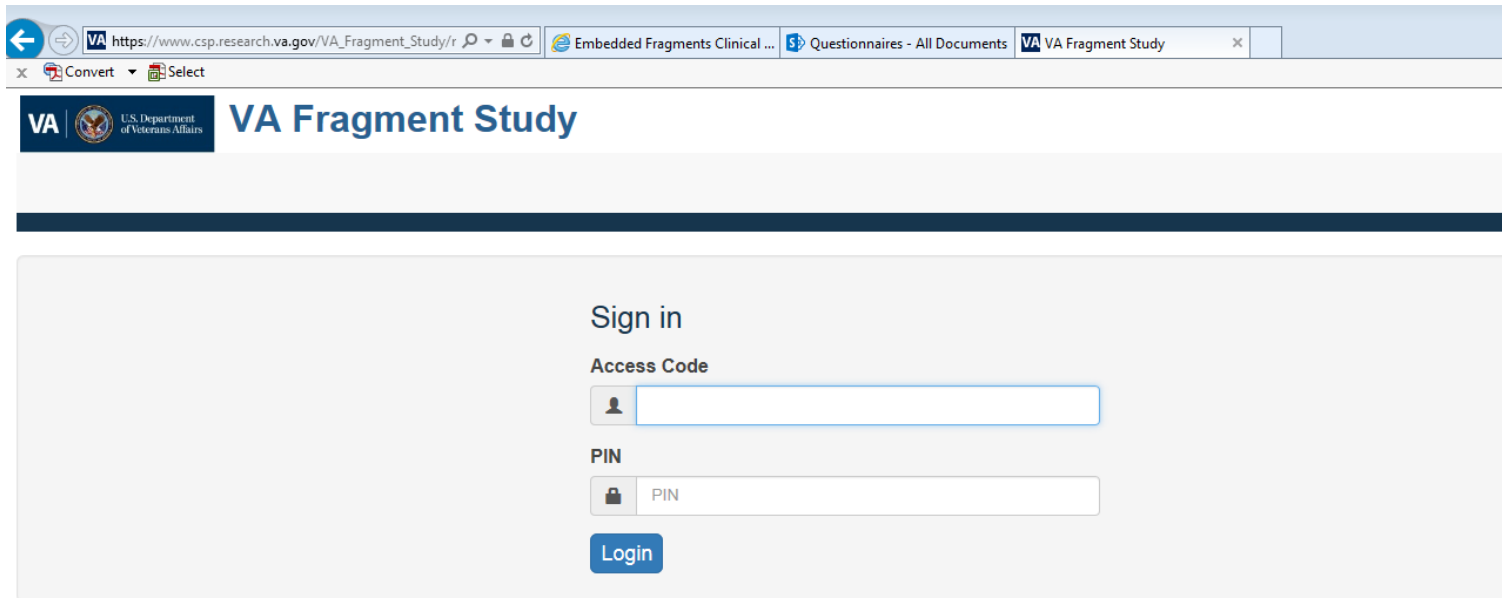
**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals”***

### 3. Online Questionnaire (screen shot of login page)



Sign in

Access Code

PIN

Login

If you have questions about the assessment or need technical assistance please contact the study team at (410) 605-7000 x4858.

[https://www.csp.research.va.gov/VA\\_Fragment\\_Study/main.cfm/participant\\_logins/welcome](https://www.csp.research.va.gov/VA_Fragment_Study/main.cfm/participant_logins/welcome)

**PROJECTS 3 & 4:****Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3*****“Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans”*****Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4*****“Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals***

## 4. Deviations Tracking Table

Number of participants enrolled at each site (as of 9/30/2018) TOTAL: 110				
Baltimore	Oklahoma City	San Antonio	Gainesville	Nashville
6	42	11	30	21

Site where event occurred	Date of event	Date event was discovered	Date reported to VA C-IRB	Date reported to DoD	Date acknowledged by VA C-IRB	Date acknowledged by DoD	Date VA CIRB determination was received	Date determination was sent to DoD	Description of event/ Action taken by study team
Oklahoma City	6/7/18	6/26/18	6/28/18	7/15/18*	8/8/18	9/4/18	8/28/18	8/31/18	Bronchodilators used during PFT. <b>Corrective Actions:</b> Specific language added to the PFT orders that instruct technicians not to use bronchodilators, reminding them that these are research subjects. For more details, see document entitled “Unanticipated Problem_OKC_2034”
Oklahoma City	6/26/18	6/26/18	6/28/18	7/15/18*	8/8/18	9/4/18	8/28/18	8/31/18	(Same as above) For more details, see document entitled “Unanticipated Problem_OKC_2019”
San Antonio	7/10/18	8/1/18	8/6/18	8/6/18	8/8/18	9/4/18	8/27/18	8/31/18	Participant was called and scheduled by PFT lab staff and performed PFT test prior to being consented by research team. <b>Corrective Actions:</b> Study team will schedule the research visit and PFT appointment based on available dates provided in advance by the PFT lab staff, and not rely on the PFT lab staff to schedule the participant for the PFT. The study team will put in the order for the PFT in CPRS (required to facilitate appointment

Site where event occurred	Date of event	Date event was discovered	Date reported to VA C-IRB	Date reported to DoD	Date acknowledged by VA C-IRB	Date acknowledged by DoD	Date VA CIRB determination was received	Date determination was sent to DoD	Description of event/ Action taken by study team
									booking) with specific to alert PFT lab staff that this test is for research and must not be done without consent first. For more details, see document entitled "RNI_VA CIRB form 119_San Antonio_3122"
Gainesville	7/2/18	8/20/18	8/24/18	8/24/18	8/24/18	9/4/18	9/19/2018	9/24/2018	Bronchodilators used during PFT due to error in CPRS orders and new technician performing test. <b>Corrective Actions:</b> Staff to review orders in CPRS for accuracy prior to the study visit and remind PFT lab staff of research protocol. For more details, see document entitled "RNI_VA CIRB form 119_4203"
San Antonio	9/7/18	9/7/18	9/14/18	9/17/18	9/15/18	9/17/18	10/10/2018	10/10/2018	Participant was called and scheduled by PFT lab staff and performed PFT test prior to being consented by research team. <b>Corrective Actions:</b> LSI and clinical scheduling leadership, and clinical research unit are developing a new strategy to grant research staff to schedule PFTs. For more details, see document entitled "RNI_VA CIRB form 119_San Antonio_3019"

\*These deviations were submitted as part of the DOD Quarterly Report on 7/15/18.



**PROJECTS 3 & 4:**

**Joanna Gaitens, Ph.D., MSN/MPH, RN, Project Leader/Principal Investigator, Project 3**

***"Biomarker assessment of kidney injury from metal exposure in embedded fragment registry veterans"***

**Stella Hines, M.D., MSPH, Project Leader/Principal Investigator, Project 4**

***"Respiratory health in a cohort of embedded fragment registry veterans exposed to blasts and metals"***

## 5. Updated Informed Consent Document



Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal FragmentsPrincipal Investigator: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MDPrincipal Investigator for Multisite Study: Dr. Melissa McDiarmid**INTRODUCTION**

You are being invited to take part in a research study that is being funded by the Department of Defense. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

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

**BACKGROUND AND PURPOSE**

The conflicts in Iraq and Afghanistan have resulted in a large number of blast and/or explosion injuries among Service members. Many of these injuries occur from contact with improvised explosive devices (IEDs). These injuries can result in retained metal fragments being embedded in the body as well as damage to the lungs. The long-term health effects associated with embedded fragments and blast injuries are not well understood. Previous studies have shown elevated levels of metals in people who have retained metal fragments. This suggests that the metals enter the blood stream and can affect body organs far from the site of the retained fragment. One organ system that many heavy metals tend to target is the kidney. This study is designed to examine the effects of blast injuries and embedded metal fragments on kidney and lung function within Iraq and Afghanistan Veterans.

This study is being conducted by the Department of Veterans Affairs and a team of researchers from the University of Maryland, Baltimore. It is being paid for by a Grant issued by the Department of Defense (DoD) for purposes of studying Veterans with embedded fragments.

You have been asked to participate in this study because you have been identified as having an embedded fragment based on information collected in the VA's Embedded Fragment Registry.

**SUBJECT'S IDENTIFICATION**VA Form **10-10-86**

MAR 2006

**FOR VA CENTRAL IRB USE ONLY****PI/SC Approval Date:** 06/19/18**LSI Approval Date:** N/A**LSI Verification Date:** 06/20/18



Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Principal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MD

Principal Investigator for Multisite Study: Dr. Melissa McDiarmid

A total of 421 participants will be enrolled in this study from five participating VA sites. The list below shows the five participating sites and the number of participants that are expected to be enrolled at each site.

- South Texas Veterans Healthcare System – 119 participants.
- VA North Florida/South Georgia Veterans Health System – 101 participants.
- Oklahoma City VA Healthcare System – 94 participants
- VA Central Tennessee Valley Healthcare System – 72 participants
- VA Maryland Healthcare System – 35 participants

### DURATION OF THE RESEARCH

This research study is expected to take approximately 5 years to complete. Your individual participation in the study will take a total of 1.5 to two hours.

### STUDY PROCEDURES

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

You will be asked to participate in a one-time study visit at the participating VA site that is closest to you. During this visit, you will be asked to:

- Complete a written injury and metal exposure questionnaire.
- Complete a more detailed demographic and health questionnaire.
- Submit a urine sample to test for:
  - metal exposure
  - kidney injury
- Complete lung function tests.
- Allow researchers to access your medical record to review imaging (i.e., x-rays) results that show or describe the presence of retained fragments.

The completion of an injury and metal exposure questionnaire and submission of a urine sample to test for metal exposure are activities that are offered as part of routine care provided to any Iraq and Afghanistan Veteran who has an embedded fragment. Usually these routine care activities are coordinated with your VA health care provider. If you have completed these activities in the past, you will be asked to submit another injury and exposure question and urine sample for metal testing as repeated follow-up is also an important part of clinical care. However, for this study, the study team will assist in coordinating these efforts. Your VA health

### SUBJECT'S IDENTIFICATION

#### FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18

**RESEARCH CONSENT FORM**

Version Date: March 10, 2017

Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal FragmentsPrincipal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MDPrincipal Investigator for Multisite Study: Dr. Melissa McDiarmid

care provider will be sent a copy of the results. All other activities, including completing a detailed demographic and health questionnaire, testing of your urine sample for kidney injury markers, lung function tests, and review of your imaging records, are included solely as part of this research study and will be overseen by the study team.

If all study activities are unable to be completed during one visit due to unforeseen circumstances, you may be asked to return on another day to complete the testing.

**Completion of Questionnaires**

*Injury and Metal Exposure questionnaire.* This questionnaire is a standard clinical form used for evaluation of Veterans who have retained embedded fragments. It asks details about where, when, and how you were injured. It also asks about the presence and location of retained fragments, where you were treated for your injury, and other possible sources of metal exposure.

Any Iraq and/or Afghanistan Veteran who has a retained fragment is asked to complete this form as part of routine clinical care. All responses will be captured in the VA's Embedded Fragment Registry as this is part of routine clinical care and surveillance efforts. In addition, your responses from this questionnaire will be captured in our research database. However, your name, address, phone numbers, and social security number (SSN) will not be included in our research database.

*Demographic and Health Questionnaire.* This questionnaire includes basic demographic information and additional injury and exposure questions. It also asks about your past and current medical history, overall health status, and fragment/injury related symptoms. This information is collected solely for research purposes and does not contain personal identifiers such as name, date of birth, or SSN. Questionnaires will be identified through a unique subject ID number known only to the study project team.

Completion of both sets of questionnaires may take up to 20-30 minutes. You are free to skip any questions that you do not want to answer. If, after reviewing the forms you have filled out, any information is unclear, we may ask you to clarify the information.

**Submission of Urine Sample**

You will be asked to provide a urine sample. The amount of urine needed for the various tests is at least 75mL, or approximately 5-6 tablespoons. This sample will be split into two samples. One portion will be used to test for metal levels. The other will be used to test for kidney injury markers. Once your urine sample is collected it cannot be withdrawn.

**SUBJECT'S IDENTIFICATION**

VA Form 10-10-86

**FOR VA CENTRAL IRB USE ONLY****PI/SC Approval Date: 06/19/18****LSI Approval Date: N/A****LSI Verification Date: 06/20/18**



Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Principal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MD

Principal Investigator for Multisite Study: Dr. Melissa McDiarmid

*Urine metal testing.* This sample will be sent to the VA's Toxic Embedded Fragment Surveillance Center (TEFSC) at the Baltimore VA. The urine sample will be tested to determine creatinine and metal levels following the standard protocol that is used as part of routine care offered to all Veterans who have retained fragments. You and your VA health care provider will receive a letter explaining the results and recommended follow-up from the TEFSC program. Your results will also be included in the VA's Embedded Fragment Registry for clinical purposes. All of these activities are done as are part of standard care for any Veteran who has a retained fragment. In addition, your urine metal results, with personal identifiers removed, will be captured in our research study database.

*Kidney injury markers testing.* A portion of your urine will be tested for several kidney injury markers. Measurement of these markers is done only for research purposes. This sample will be coded so that your name cannot be readily identified. It will be sent to a laboratory outside of the Department of Veterans Affairs which is better equipped to accurately analyze the sample. As many of these markers are not routinely used in clinical care, individual test results can be difficult to interpret. Therefore, you will not receive the results of this testing.

#### Lung Function Tests

You will be asked to complete pulmonary (lung) function Testing will be performed by trained technicians and should take approximately 20-30 minutes. During the tests, you will be in a seated position and wearing nose clips. You will be asked to breathe into a machine that will measure lung function. Study staff will enter your lung function test results into a research study database and into the VA's electronic medical record system.

#### Review of Medical Records

As part of this research, the study team will review your available VA medical records to obtain additional fragment related details from imaging (i.e., x-ray) reports. Coded data from these reports will be captured in the research database.

If you chose to enroll in this study, it is expected that you will:

- Keep your study appointment.
- Complete questionnaires as instructed.
- Follow instructions for collecting your urine.
- Follow instructions provided during the lung function tests.
- Ask questions as you think of them.
- Tell the investigator or research staff if you change your mind about completing the protocol.

#### SUBJECT'S IDENTIFICATION

#### FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18



Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Principal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MD

Principal Investigator for Multisite Study: Dr. Melissa McDiarmid

### POSSIBLE RISKS OR DISCOMFORTS

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

A potential risk of the collection of your personal health data is loss of confidentiality. Access to this information will be limited to the staff of the study. The study records will be kept confidential as far as possible within Federal law; however, breach of confidentiality is a potential risk. Loss of confidentiality will be minimized by storing data in a secure location such as a locked office and locked cabinet or electronic data base which will be password-protected.

Lung function tests measure the amount of air you have in your lungs and how well you can move that air by forcefully blowing 3 or more times into a spirometer (lung function machine). You may become short of breath or experience chest tightness while doing the spirometry tests. This is not uncommon during lung function testing and typically resolves after completion of the test.

Some of the questionnaires may have personal questions. The questions might be uncomfortable to answer. You may skip any questions you do not want to answer.

### POTENTIAL BENEFITS

You will not benefit directly from your participation in this study. The main benefit for participating in this study is the ability to contribute to the knowledge of how retained metal fragments and blast injuries may affect kidney and lung function. This information gained from a population-level can help inform medical management guidelines related to care of blast-injured Veterans who have retained fragments.

### ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH

This is not a treatment study. Your alternative is to not take part. If you choose not to take part, your healthcare at the VA will not be affected.

### SUBJECT'S IDENTIFICATION

VA Form 10-10-86

#### FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18





Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Principal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MD

Principal Investigator for Multisite Study: Dr. Melissa McDiarmid

### CONFIDENTIALITY

Taking part in this study will involve collecting private information about you. The information collected for this study will be kept confidential. Your information collected for this study will be shared with other researchers involved in this study.

A code number will be assigned to your information. Only personnel for this study will be authorized to link the code number to you. Other researchers who may receive your specimens for testing outside of the study team and VA system will be given only a code number. They will not be given any other information to link the code back to you.

All electronic research data will be stored on a secure VA server. Paper copies of information will be kept in a locked file cabinet in a locked office at the VA. Your research records and/or identifiers will be retained in accordance with the VA records control schedule. The "records control schedule" is a set of rules set by the federal government that states when federal agencies are allowed to dispose of records. The VA and VHA must follow these rules.

Your social security number is collected on the exposure questionnaire. This form is used for routine care provided to Veterans who have retained fragments. This allows your clinical information to be linked to your medical record. In addition, your social security number is collected for payment purposes. Your social security number will not be used or stored in the research database.

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

People designated from the Department of Veterans Affairs and the University of Maryland, Baltimore study team will be allowed to inspect sections of your medical and research records related to the study. Everyone reviewing these records will work to keep your personal information confidential. Your personal information will not be given out unless required by law or authorized by you in your site's "HIPAA Authorization to Obtain, Use and Disclose Protected Health Information for Research". However, if your information is disclosed to other entities, the Department of Veterans Affairs no longer has control of that information. Please see the HIPAA Authorization for this study for further details.

There are times when we might have to show your records to other people. For example, someone from the Department of Defense, Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of

### SUBJECT'S IDENTIFICATION

#### FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18



Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Principal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MD

Principal Investigator for Multisite Study: Dr. Melissa McDiarmid

Research Oversight, the VA Central IRB, our local Research and Development Committee, the University of Maryland IRB and other study monitors may look at or copy portions of records that identify you.

The results of your urine metal and lung function tests will be included in your medical record. Efforts will be made to limit access of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Your medical and research records will be kept strictly confidential to the fullest extent permitted by law.

### **COSTS TO PARTICIPANTS AND PAYMENT**

#### **Costs to Participants**

You will not be charged for any procedures that are part of this study.

#### **Payment Offered for Participation**

You will be paid \$50 after completing all of the study procedures (questionnaires, urine sample, lung function tests). You will also receive \$50 as reimbursement for travel related expenses after completion of study procedures. If you do not complete all of the study procedures, you will not be paid. You will receive both of these payments for a total of \$100 in the form a check which will be mailed to you within 4 weeks of you completing the protocol.

Every effort will be made to complete all study procedures in one visit. If all study activities are unable to be completed during one visit due to unforeseen circumstances, you may be asked to return on another day to complete the testing. In this case, after completing all study activities, you would be reimbursed an additional \$50 for travel.

If you are active duty military, in addition to being a Veteran, you may not receive any payment for participation in this research study unless you are off duty or on leave during the time you are participating in the protocol.

### **MEDICAL TREATMENT AND COMPENSATION FOR INJURY**

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to

### **SUBJECT'S IDENTIFICATION**

#### **FOR VA CENTRAL IRB USE ONLY**

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18





Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Principal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MD

Principal Investigator for Multisite Study: Dr. Melissa McDiarmid

you unless the injury was due to your not following the study procedures. This care may be limited by local or federal law.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call: *Dr. Stella Hines at (410) 706-7464. If calling after normal business hours (8:30-5pm EST), tell the answering service that you are part of the "Embedded Fragment Study and wish to have Dr. Stella Hines paged.*

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

#### **PARTICIPATION IS VOLUNTARY**

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

If you do withdraw, we will not collect any more information about you. However, we will keep and use the data that we already collected before you withdrew your consent.

If you decide to stop taking part, if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator: *Dr. Stella Hines at (410) 605-7373.*

There are no adverse consequences (physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the study.

#### **RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION**

Your participation in this study is voluntary and will continue until you withdraw or the program is ended by the sponsor. The person in charge of the program or the study sponsor can remove your data from grouped analyses without your approval if you do not meet an eligibility criterion for inclusion. For example, individuals are not eligible if they report not having an embedded fragment.

#### **SUBJECT'S IDENTIFICATION**

VA Form 10-10-86

#### **FOR VA CENTRAL IRB USE ONLY**

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18

**RESEARCH CONSENT FORM**

Version Date: March 10, 2017

Participant Name: \_\_\_\_\_ Date: \_\_\_\_\_

Title of Study: Assessing the Health Effects of Blast Injuries and Embedded Metal FragmentsPrincipal Investigators: Dr. Joanna Gaitens and Dr. Stella Hines VA Facility: Baltimore, MDPrincipal Investigator for Multisite Study: Dr. Melissa McDiarmid**PERSONS TO CONTACT ABOUT THIS STUDY**

If you are a veteran wanting to confirm that this study is in fact IRB approved and is being Conducted at your local VA, you may contact: *Jessica Mendoza, Human and Animal Research Protections Officer for the Baltimore VA at 410-605-7000 extension 6512.*

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

**AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY**

Dr./Mr./Ms. \_\_\_\_\_ the research coordinator or local Principal Investigator has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

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

**I agree to participate in this research study as has been explained in this document.**

_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date

**SUBJECT'S IDENTIFICATION**

VA Form 10-10-86

**FOR VA CENTRAL IRB USE ONLY**

PI/SC Approval Date: 06/19/18

LSI Approval Date: N/A

LSI Verification Date: 06/20/18