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TITLE: Combat Ready Exposure Device (CRED): Validation of a Portable Exposure Biomarker Device for Lead and Other Heavy Metal Exposures

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CONTRACTING ORGANIZATION: The Henry M, Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD

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14. ABSTRACT

The objective of this research project is to validate a portable all-in-one tool that will produce valid, comparable results to currently available technology for measurement of multiple biomarkers specific to different time frames of exposure from heavy metals. The research for the project will be conducted over two years and consists of two phases, each with a specific aim. Specific aim 1 involves the development, calibration, and validation of the portable x-ray fluorescence prototype device for human measurement of heavy metal body burden in the laboratory based setting (Phase 1, Year 1); and specific aim 2 focuses on the validation of the device for in vivo lead and toenail heavy metal measurements and heavy metal measurements using blood from a single finger prick compared to gold standard methods in a cohort of Soldier participants (Phase 2, Year 2). Over Year 1, significant efforts have been made towards the fabrication, calibration, and validation of the prototype device. Preparation of the human subjects protocol is well underway.

15. SUBJECT TERMS

Heavy metals, environmental assessment, exposure dosimetry, x-ray fluorescence (XRF), biomarkers, military, combat readiness

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1. INTRODUCTION

The research project is a collaborative effort between the US Army Research Institute of Environmental Medicine, whose mission is the delivery of biomedical solutions to Warfighter performance and readiness, and the Harvard T.H. Chan School of Public Health, with expertise in heavy metal research and exposure assessment tools. The research objective of this project is to validate a portable all-in-one tool that will produce valid, quantifiable, and comparable results to currently available technology for the measurement of multiple biomarkers specific from heavy metal(s). The research for the project will be done over two years, and consists of two phases, each with a specific aim. Specific aim 1 involves the development, calibration, and validation of the portable x-ray fluorescence (XRF) prototype device in the laboratory setting (Phase 1, Year 1); and specific aim 2 focuses on the validation of the device via the measurement of *in vivo* bone Pb and toenail Pb, Hg, Mn, Cu, and W; and of blood Pb, Hg, Mn, Cu, and W from a single finger prick compared to gold standard methods in a cohort of Soldier participants (Phase 2, Year 2).

2. KEYWORDS

Heavy metals, environmental assessment, exposure dosimetry, x-ray fluorescence (XRF), biomarkers, military, combat readiness

3. ACCOMPLISHMENTS

3.1 What were the major goals of the project?

As described in the approved Statement of Work (see Table of Tasks below), the major goals during the Year 1 of this project are highlighted in yellow.

		Timeline (Months)
Year 1	**Major Task 1:** Phase I testing: Development and calibration of device	
	Subtask 1: Obtain project support approvals, which includes initiating contacts with transition partners (see Subtask 8 below)	1-2
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	requirements for validation of devices in humans. Obtain approvals.	
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* Milestone order was switched to better depict the Year 1/Year 2 calendar timeline.

3.2 What was accomplished under these goals?

In Year 1, substantial progress was been made towards Major Tasks 1-3. Below is a bullet list of the projected goals and accomplishments over this Year 1 study period:

Major Task 1: Subtask 1: *Obtain project support services' approvals* [COMPLETED]

We have completed a three-way Cooperative Research and Development Agreement (CRADA) between the Henry M. Jackson Foundation (HJF), the US Army Research Institute of Environmental Medicine (USARIEM), and The Harvard T.H. Chan School of Public Health (Harvard). (Fully executed: 11 March 2021)

Major Task 1: Subtask 2: *Initiate fabrication and modification of KXRF device* [IN PROGRESS]

- Our Harvard partners (Drs. Marc Weisskopf and Aaron Specht) have tested different detectors, including sodium iodide, silicon based, and cadmium zinc telluride (CdTe). Their findings have led to the optimization of a detector setup using the K shell x-ray of lead as the prototype. The advantage of this detector is that it can be optimized for our measurements of bone *in vivo*.

- As we will be validating our portable Combat Ready Exposure Device (CRED) device by comparing our results from the CRED prototype device to findings from the gold standard technology (Cd-109 x-ray fluorescence (XRF) device), we have initiated the acquisition of the Cd-109 radioisotope source through an institution (Purdue University) that holds a Nuclear Regulatory Commission board scope license. Through communications with Purdue University's Radiation Safety Officer, we have made the initial arrangements for the purchase and storage of the source early in Year 2.

Milestone 1: Completion of pre-calibrated prototype device for measuring heavy metals in a lab-based setting [IN PROGRESS]

- Work is progressing; we anticipate completion by the end of Year 2 Q1 of the project. See Sections 3.5 and 5.2 below.

Major Task 2: Subtask 1: *Test prototype system with Pb, Hg, Mn, Cu, and W-doped phantoms and in standardized reference blood and cadaver bones.* [IN PROGRESS]

- We received approval for cadaver activity (31 Dec 2020) for the protocol from U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP) to use cadaver bones for calibration of the CRED device in the laboratory component of the study.

- To measure and verify the varying levels of lead using the prototype CRED device in the laboratory-setting, our Harvard partners have created plaster-of Paris standards (phantoms) and have initiated steps for using the cadaver samples. Our Harvard partners have completed the verification of lead levels in 13 tibia and fibula cadaver bone pairs of various level exposure using laser ablation inductive coupled plasma mass spectrometry (ICP-MS). They have also verified the lead levels in the doped phantoms using ICP-MS

Major Task 2: Subtask 2: *Calculate the detection limit of the prototype through optimization of x-ray settings and geometry experimentally* [IN PROGRESS]

- To estimate a detection limit of the CRED prototype, our Harvard partners have conducted initial testing using an x-ray tube and detector set-up simulating the new CRED prototype.
  For each measurement, they used a 200kV x-ray tube running at 1mA with substantial collimation and optimized shielding for the pencil beam for 120 seconds each. Using various doped phantoms, the Harvard partners estimated the minimum detection limit to be 0.2ppm within two-minute measurement, which was considerably lower than what was anticipated from the Monte Carlo stimulations. And, the detection limit is considerably lower than other XRF devices.

Major Task 2; Subtask 3: *Quantify the final radiation dose of the CRED prototype device* [IN PROGRESS]

- Since current available high energy x-ray tubes generally rely on large and diffuse x-ray beams, our Harvard partners have designed an initial collimator and shielding for the x-ray tube which is needed to create a narrow x-ray pencil beam. The Harvard team is currently running through simulations evaluating this design with the proposed collimator and shielding to ensure that they are controlling and lowering the x-ray scattering from the beam that would be hitting the human subject's tibia bone. They are working to optimize the radiation dose to the human subject to be no more than background radiation levels by limiting the pencil beam area from the targeted area of the beam.

Milestone 2: Complete steps required for lab validation of CRED prototype device capable of measuring heavy metals in blood and in vivo

- Work is progressing; we anticipate completion by the end of Year 2 Q1 of the project. See Sections 3.5 and 5.2 below.

Major Task 3: Subtask 1: *Submit protocol for IRB approval for validation of devices in humans* [IN PROGRESS]

- We have prepared the IRB application and gathered all the supporting documents. Submission of the protocol is planned for Sep 2021.

Major Task 3: Subtask 2: *Initiate recruitment of 50 human subjects from active military installations* [IN PROGRESS]

- During Q4, the PIs (Drs. Proctor and Taylor) initiated recruitment efforts by providing the Army National Guard and Active Duty Soldiers the opportunity to consider participation in the study. Specifically, we have reached out to the Ohio National Guard Surgeon's office, who is in the process of identifying specific unit POCs for the team. Additionally, we have made connections with the Army Environmental Science and Engineering Officer (ESEO) Consultant and the OTSG Co-chair of the Army Heavy Metals Working Group. We have also identified a group of ESEO POCs from several different Army posts (i.e. Fort Stewart, Fort Riley, and Joint Base Lewis-McCord), who have expressed interest in working with us on recruitment for the study.

Major Task 3: Subtask 8: *Initiate transition partner planning and execution* [ONGOING]

- The PIs have continued transition partner planning to ensure appropriate transition mechanisms are in place at the conclusion of the project.

3.3. What opportunities for training or professional development has the project provided?

- A HJF personnel (Ms. Ashley Hebert), who is the Research Assistant on this study and has been onsite at USARIEM since March 2021, has spent efforts towards the set-up of data management and analytic tasks. This includes becoming familiar with building programs to create SAS datasets from databases while following the study's protocol.

3.4. How were [are] the results [being] disseminated to communities of interest?

- Nothing to report at this point.

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

Over the next 12 month reporting period (Year 2), we will do the following:

Major Task 1: Subtasks 1-2

- We anticipate that by the end of Year 2, Q1, the fabrication of the prototype CRED device will be completed in the laboratory setting by our Harvard partners (Milestone 1). This includes designing the shielding of the x-ray source, filtering and collimating the beam, and repeating the dosimeter measurements.

Major Task 2: Subtask 1-3

- We anticipate that by the end of Year 2, Q1, our Harvard partners will complete the validation the CRED device (Milestone 2). This includes calculating the final radiation dose and detection limit of the device through extensive radiation dosimetry. They will acquire an optically stimulated luminescent dosimeter and plan to also use thermoluminescent dosimeters and stimulation to verify the radiation dose and to complete the dose assessments. Additionally, assessments of the cadaver bone measurements to compare to L-shell measurements, and 2-D laser ablation inductive coupled plasma mass spectrometry (LA-ICP-MS) measurements will be completed. This assessment will be done using the 13 cadaver bones, each with completed LA-ICP-MS and XRF measurements to verify the lead concentration and distributions, which will finally be compared to our experimental and stimulated results. The testing will also determine the device's range for the *in vivo* measurements as well verify the portion of bone being estimated with the CRED device. And, thirdly, we anticipate approval of the prototype CRED device from Harvard's Radiation Safety Office.

- In Year 2, we will co-author a manuscript on the development and validation of the CRED device in the laboratory setting (Milestone 3).

Major Task 3: Subtasks 1-8

- We will obtain approval of the protocol from USARIEM's Scientific Review Committee as well as obtain approval on the IRB application from MRDC IRB and HRPO (Milestone 4).

- For the recruitment phase, the PIs (Drs. Proctor and Taylor) will confirm POCs from active military institutions. Senior leadership will assist us with identifying a group of interested Soldier volunteers within their unit(s).

- In Year 2, Q1, the PIs (Drs. Proctor and Taylor) will initiate the planning and logistics for the recruitment of 50 human subjects from identified military installations.

- The participant Soldiers study visit will be conducted by the PIs and Harvard Investigator(s) at Purdue University. Data collection is anticipated to occur in Year 2 Q2 and Q3 of the project. (Milestone 5).

- Data processing and analyses will occur in the summer 2022.
  - Analyses of Phase 2 of the study will be conducted using SAS. Heavy metal measurements using the CRED device will be compared to the gold standard Cd-109 KXRF device for bone metal measurements, and metal concentrations will be quantified in toenail and blood spot cards using inductively coupled plasma mass spectrometer (ICP-MS). The venous blood samples will be analyzed at the Dartmouth Trace Element Laboratory at Dartmouth College, NH.
  - Interim study results would tentatively be available by the end of summer 2022.

- We will co-author a manuscript on the validation of the CRED device against the gold standard technology (Cd-109 KXRF device) (Milestone 6).

- The PIs (Drs. Proctor and Taylor) will transition the validated portable KXRF device to designated transition partners (Milestone 7).

4. IMPACT

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

- This project, in addition to others previously conducted by the PIs (Drs. Proctor and Taylor) and our Harvard Investigators, are contributing to the knowledge base pertaining to human exposure assessment(s) of heavy metals through environmental and occupational exposures.

4.2 What is the impact on other disciplines?

- Nothing to report at this point.

4.3 What was the impact on technology transfer?

- There are few available validated dosimeters with the capability to measure human absorbed dose to heavy metals in real time. Our goal is that the CRED device will replace the current stationary machine, taking advantage of new developments in x-ray detectors and technology to create a portable, non-invasive method of measuring heavy metal exposure in humans.

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

- While the development and validation of a device capable of measuring metals through bone, nails and blood is important for understanding military exposures to heavy metals and their subsequent health outcomes, this research can contribute to the knowledge base for human exposure and human health policies for the US and the international communities. Largely, this device could be useful in quantifying heavy

metals in occupational groups, including police officers, fire fighters and construction workers that are known to have exposures to heavy metals. Furthermore, this device may be useful for measuring metals in the general population particularly when there is evidence of high levels of exposure(s) to heavy metal(s).

5. CHANGES/PROBLEMS

5.1 Changes in approach and reasons for change

- Nothing to report

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

- The regulations and policies related to access to research laboratory facilities established to mitigate the spread of the coronavirus have limited our Harvard colleagues' progresses towards the completion of Major Tasks 1 and 2. By the end of Year 1 Q4, we had anticipated completing the pre-calibration of the CRED device for measuring heavy metals in the laboratory and steps required for laboratory validation of measuring heavy metals in blood and *in vivo*. While we have not completed milestones 1 and 2, significant progress towards the completion of the device has physically occurred by our Harvard partners in the laboratory setting during months 8-12. We anticipate completing Major Tasks 1 and 2 by end of Year 2 Q1.

- In Year 1 Q4, Dr. Specht, Research Investigator at Harvard accepted a faculty appointment at Purdue University and moved there in mid-August 2021. Due to this change in institution, we are submitting a request to USAMRAA to add Purdue University as a new subaward (starting September 1, 2021), and in conjunction, modifying the existing subaward with Harvard. While this is a modification to the subaward, we will still use the available funds in the current award, and no additional funds are being requested. In addition, preparation of a four-way CRADA between Harvard, HJF, USARIEM, and Purdue University is underway. Dr. Weisskopf, the primary Harvard PI, will continue his efforts at Harvard, and Dr. Specht will maintain a visiting professor appointment at Harvard.

- Due to not having our device completed and approved, milestone 4 has not been fulfilled. However, we have finalized the content of the IRB application, and have gathered the supporting documents required for the Scientific Review Committee. We anticipate the submission of the IRB application to the MDRC IRB and HRPO for their approval of the study protocol at the beginning of Year 2.

5.3 Changes that had a significant impact in expenditures

- Nothing to report

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

- Nothing to report

6. PRODUCTS

6.1 Publications, conference papers, and presentations

- On 16 Sept 2021, Drs. Taylor and Proctor presented an overview of the project to the Army Heavy Metals Working Group. They were interested in knowing more about Army research in this area and expressed interest in helping in facilitation of the study and dissemination of findings when complete.

6.2 Website(s) and/or Internet site(s)

- Nothing to report

6.3 Technologies or techniques

- Nothing to report

6.4 Inventions, patent applications, and/or licenses

- We have recently submitted Invention Disclosure documentation for the CRED tool to MRDC for patent consideration (24 Aug 2021). Discussions are ongoing with patent agent and counsel.

6.5 Other products

- Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1 What individuals have worked on the project?

- Over the following Year 1 period, these individuals have worked on the project:
  - ✓ *Name*: Susan P. Proctor, D.Sc.
    Project Role: USARIEM Study PI
    Research Identifier (e.g. ORCID ID):
    Nearest person months worked: 5% of 12 person-months (0.60 person months)
    Contribution to the project: Dr. Proctor handles all PI responsibilities for the project, including interactions with the IRB, the grantee (HJF)), partners (Harvard), Supervisors/Commanders at installations, and USARIEM personnel
    Funding support: HJF

  - ✓ *Name*: Kathryn Taylor, Sc.D.
    Project Role: USARIEM Site PI
    Research Identifier (e.g. ORCID ID):
    Nearest person months worked: 50% of 12 person-months (6 person months)
    Contribution to the project: Dr. Taylor oversees the study, including working with the PIs on protocol development, interacting with grantee and partners, maintaining required documents, and recruiting future participants
    Funding support: HJF

  - ✓ *Name*: Marc Weisskopf, Ph.D., Sc.D.
    Project Role: Harvard Site PI
    Research Identifier (e.g. ORCID ID):
    Nearest person months worked: 4% of 12 person-months (0.48 person months)
    Contribution to the project: Dr. Weisskopf works with the PIs on the protocol development, including the development, calibration and validation of the prototype CRED device as well as data collection and analyses.
    Funding support: HJF

  - ✓ *Name*: Aaron Specht, Ph.D.
    Project Role: Harvard Research Scientist
    Research Identifier (e.g. ORCID ID):
    Nearest person months worked: 50% of 12 person-months (6 person months)

Contribution to the project: Dr. Specht works with the PIs on the protocol development, including the development, calibration and validation of the prototype CRED device as well as data collection and analyses.
Funding support: HJF

- ✓ *Name*: Anne Collaco, MPH
  Project Role: HJF Project Coordinator
  Research Identifier (e.g. ORCID ID):
  Nearest person months worked: 100% of 6 person-months (6 person months) – started in March 2021
  Contribution to the project: Ms. Collaco assists PIs in the day-to-day operations and planning of the project, including IRB tracking, HJF administrative tasks, communications and coordination with project personnel, equipment purchases, and preparation of study related materials
  Funding support: HJF

- ✓ *Name*: Ashley Hebert, MPH
  Project Role: HJF Research Assistant
  Research Identifier (e.g. ORCID ID):
  Nearest person months worked: 100% of 6 person-months (6 person months) – started in March 2021
  Contribution to the project: Ms. Hebert assists the PIs and project coordinator in the development of study related materials, and data management
  Funding support: HJF

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

- Nothing to report

7.3 What other organizations were involved as partners?

- **Organization Name:** Harvard T. H. Chan School of Public Health (Harvard)
- **Location of Organization:** Harvard T. H. Chan School of Public Health, Department of Environmental Health, 667 Huntington Ave, 14th Floor, Boston, MA 02115.
- **Partner's contribution to the project:**
  - **Financial support:**
  - **In-kind support:**
  - **Facilities:**
  - **Collaboration:** Drs. Marc Weisskopf and Aaron Specht, Harvard Investigators have supported the USARIEM PIs (Drs. Proctor and Taylor) and have contributed significant efforts towards fulfilling Major Tasks 1 and 2 during Year 1.
  - **Other:**

8. SPECIAL REPORTING REQUIREMENTS

8.1 See Appendix for Quad Chart Report

9. APPENDICES

Combat-Ready Exposure Device (CRED): Validation of a Portable Exposures Biomarker Device for Lead and Other Heavy Metal Exposures

Award #W81XWH-20-2-0037/ Log# RC190148

PI: Dr. Susan P. Proctor **Org:** H Jackson Fdn/USARIEM/Harvard T. H. Chan School of Public Health **Award Amount: $982,325**

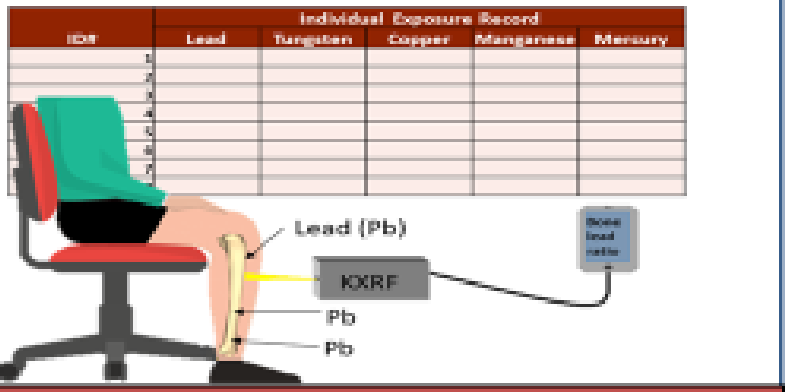
Study/Product Aim(s)

- Warfighters are required to be medically ready to operate in multi-domain, near-peer battlefields (Gaps # 203617, 455212) such dense urban environments
- DoD lacks a fielded capability to determine human exposure risks (MOMRP Joint ICD 2017)
- The end state goal to address the capability gap is to detect and assess exposure risk in a valid and scale-able method
- The functional objective of this project is to produce a non-invasive, portable tool to measure exposure risk to heavy metals (Pb, Hg, Mn, Cu, and W) in vivo (in bone and toenails) to contribute to the DoD Individual Longitudinal Exposure Record (and other big data systems)

Approach

Study to be conducted in two Phases over two years.

- Phase I, Technical Objective 1: Build and laboratory validate a portable KXRF prototype device for human *in vivo* measurement of heavy metal body burden
- Phase II, Technical Objective 2: Validate the device for *in vivo* bone Pb and toenail Pb, Hg, Mn, Cu and W measurement in Soldier participants (compared to existing gold standard methods)



Device Concept: Provide non-invasive, portable assessment of in vivo, heavy metal exposure risk

Accomplishments: Components for the fabrication of the CRED device and calibration and laboratory validation of the device are in the final phases. In addition, the IRB protocol is being finalized for submission and planning for the recruitment phase underway.

Schedule and Funding

Major Milestones	~FY21	~FY22
Phase I testing: Development and testing of device		
Phase I completion: Lab validation of device		◆3
Transition Partner planning and execution		
Phase II testing: IRB approval and data collection		
Phase II completion: Validation of device in human subjects (Army Soldiers)		◆5
Total Funding ($K) =982,325 (6.2) [Of total, $720.3K to HJF; $262K to USARIEM]	**$475**	**$507**

Period for Performance: 1 Sep 2020-31 Aug 2022

◆ Anticipated TRL

Updated: 22 SEPT 2021

Goals/Milestones

FY2021 Goals – Develop and Laboratory test the portable CRED

☑ Project set-up

☐ Complete a calibrated prototype for measuring heavy metals in a lab-based setting

☐ Complete steps required for lab validation of CRED prototype device capable of measuring heavy metals in blood and in vivo

☐ Approval of IRB application from MRDC IRB and HRPO

FY2022 Goals – Human Subject validation of the CRED

☐ Complete preparation of manuscript describing development of device

☐ Completion of human subjects data collection for validation of prototype

☐ Complete manuscript on validation of the CRED in humans against existing gold standards

☐ Transition the validated portable KXRF device to transition partners

Comments/Challenges/Issues/Concerns: N/A

Budget Expenditure to Date

HJF Projected Expenditure: ~$367K (with open commit to Harvard ~$181K)

HJF Actual Expenditure: ~$306K (with open commit subaward- $181K)

[USARIEM Military budget actual expenditure: $101K (of $262K total)]