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TITLE: A Closed-Loop Neural Prosthesis for Restoration of Function After Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Pedram Mohseni, PhD

CONTRACTING ORGANIZATION: Case Western Reserve University
Cleveland, OH 44106

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Pedram Mohseni, Randolph J. Nudo, David J. Guggenmos

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5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Case Western Reserve University
10900 Euclid Avenue
Cleveland, OH 44106

Univ. of Kansas Medical Center Research
3901 Rainbow Boulevard, MSN 1039
Kansas City, KS 66103

8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT

Significant progress has been made in developing activity-dependent stimulation (ADS) microdevices for use in both rodent and non-human primate (NHP) models of traumatic brain injury (TBI). Specifically, microdevices have been successfully assembled, benchtop tested for functionality, and deployed in a rodent model of TBI to determine the optimal time window for delivery of the therapy. Our preliminary results from a completed cohort of rodents indicate that we can delay ADS treatment for 1, 2 or 3 weeks after injury and still observe improvement in motor performance.

Moreover, the functionality and versatility of software for the NHP microdevices has been successfully upgraded by adding several new features such as stimulus rate monitoring. In parallel, the design of the substrates for the head-mounted (rigid-flexible) and backpack (all-rigid) portions of the NHP microdevice has been greatly advanced.

15. SUBJECT TERMS
Activity-dependent stimulation; Implantable microsystem; Neuroplasticity; Rehabilitation, Traumatic brain injury

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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TABLE OF CONTENTS

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

The goal of this project is to use an implantable brain-machine-brain interface (BMBI) to facilitate functional reorganization in spared cortico-cortical connections and enhance behavioral recovery after traumatic brain injury (TBI) in both rodent and non-human primate (NHP) models, which will remarkably advance the neurorehabilitation field at the level of functional neurons and networks.

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

Activity-dependent stimulation; Implantable microsystem; Neuroplasticity; Rehabilitation; Traumatic brain injury

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Task 1: Develop functional microdevices for rodent studies for Aim 1 – Currently underway
Major Task 2: Conduct preclinical efficacy study for optimal time window in ambulatory rats using rodent microdevice – Currently underway
Major Task 3: Develop functional microdevices for rodent studies in Aim 2 – Currently underway
Major Task 4: Conduct preclinical efficacy study for persistence of therapeutic effects in ambulatory rats using rodent microdevice – Expected to start in Q2 of Year 3
Major Task 5: Develop functional microdevices for non-human primate studies – Currently underway
Major Task 6: Conduct preclinical efficacy study in ambulatory non-human primates – Starts in Year 3

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

In Year 2, the CWRU team worked on **Major Task 1:** *Develop functional microdevices for rodent studies in Aim 1,* **Major Task 3:** *Develop functional microdevices for rodent studies in Aim 2,* and **Major Task 5:** *Develop functional microdevices for non-human primate [NHP] studies* in Aim 3.

Subtask 2 – **Major Task 1** & **Subtask 1** – **Major Task 3**: *Microdevice assembly and testing*.
Significant progress was made in developing the rodent microdevices. Specifically, the substrate for the rodent microdevices was re-designed to account for a change in the wiring configuration of the stimulating microelectrode array (the change was made by the electrode supplier), and the new substrate was fabricated. All electronic components necessary for rodent microdevice construction were also obtained. Overall, 22 rodent microdevices in total were fully assembled and benchtop tested for functionality in support of **Major Task 2**. Remedial modifications (a combination of adding additional bypass capacitors and changing the type of the battery voltage supply) were also performed in the assembly of a few of these microdevices in order to mitigate problems that were observed at KUMC with unexpected noise and artifacts in the recorded neural signals during wired operation. Left unaddressed, the noise/artifacts would have adversely affected our ability to discriminate spiking activity. At this time, additional rodent microdevices can be assembled and delivered to the KUMC team at anytime upon request in support of **Major Tasks 2** and **4**.

Subtask 1: *Microdevice assembly and testing* (Major Task 5)

Significant progress was made in developing the software and hardware for the NHP microdevices as well. The functionality and versatility of the software was upgraded by successfully incorporating a programming code to calculate the average stimulus rate in both activity-dependent and open-loop stimulation modes. Changes were also made to the overall user interface, microdevice monitoring features, and firmware control blocks. Specifically, the user interface was redesigned for easier access to different settings and implemented a copious amount of automation to help make programming and microdevice monitoring more efficient. For microdevice monitoring, major glitches were resolved concerning the stimulus rate monitoring by modifying the MCU firmware to address meta-stability issues. Additionally, a new feature was added to enable the user to change the microdevice identifier name via BLE, which will serve as an important tool in multiple microdevice deployments.

Progress was also made in the design of the substrates for the head-mounted and backpack portions of the NHP microdevice. The layout for the backpack unit was completed and rapid-prototyped to verify that the unit would fit within the selected housing module. Optimal strategies for connecting the head-mounted portion to microelectrode connectors inside the skull-mounted plastic chamber, as well as connecting it to the backpack portion via a subcutaneously implanted wire were also examined. Changes were made to the skull-mounted plastic chamber to incorporate custom slots that would hold the microelectrode connector for easy connect/disconnect during implantation procedures. The changes were rapid-prototyped through 3D printing and laser printing to ensure stable mechanical design.

In Year 2, the KUMC team worked exclusively on **Major Task 2:** *Conduct preclinical efficacy study for optimal time window in ambulatory rats using rodent microdevice*.

Subtask 2: *Conduct ambulatory experiments for optimal time window (Aim 1)*
The KUMC team optimized a workflow for processing and analyzing the neurophysiological data coming from the microdevices, and then proceeded to conduct the animal experiments. Eight rats successfully completed the experimental protocol. Procedures were followed in an additional six animals, but hardware issues prevented spike discrimination and thus effective ADS treatment. The hardware issues have been addressed adequately, but the data from these rats were eliminated from the analysis.

Preliminary data from the eight rats completing the study are shown in **Fig. 1**. These data largely replicate the effects of the ADS treatment reported in our previous *PNAS* publication in 2013 that demonstrated improved motor performance when ADS was initiated immediately after brain injury occurred. Assuming that these results are similar in the remaining animals, these new data show that we can delay ADS treatment for 1, 2 or 3 weeks after injury and still observe improvement in motor performance.

As the performance in the 1-week-delay group was optimal – nearly reaching normal baseline levels of performance – it would appear that one week would be the preferred time point after injury for implantation of the microdevice and initiation of treatment. This is highly relevant from a clinical perspective, since it would allow time for the individual to be made medically stable and for edema to subside before a neurosurgical procedure is performed. The remaining rats proposed for this task were in various stages of the protocol at the end of Year 2 and will be completed in the next reporting period. A full analysis of these results will be reported at the conclusion of these experiments.

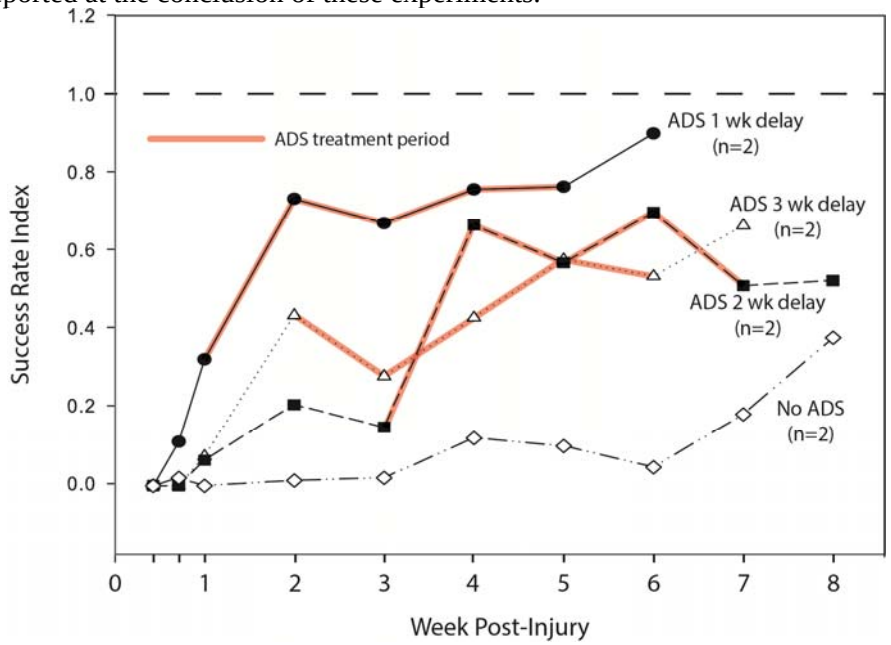

Figure 1: *Motor performance on a skilled reach task in rats with a TBI in the primary motor cortex. ADS treatment was initiated at 1, 2 or 3 weeks after the injury and compared with control rats that received no ADS treatment. Normal baseline index score (1.0) is indicated by the dashed line. Post-TBI index score is zero. As these preliminary data show, each of the ADS groups performed better than the control group, indicating that we can delay treatment for 1-3 weeks post-injury and still observe a substantial improvement in motor performance.*

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Three electrical engineering graduate students at CWRU continued their training on a wide range of salient topics, including the development of a wireless link based on a Bluetooth Low Energy (BLE) module for neural interface microdevices, design of implantable microsystems, and methods of powering/communicating with implantable microsystems. All three students also had professional development opportunities by attending the NIH Neural Interfaces Conference (NIC) in June 2018.
One research analyst and one postdoctoral fellow at KUMC continued their training on creating data management systems and developing data analytic tools, as well as on experimental testing of neural interface microdevices.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period, we will continue to assemble and deliver to KUMC new rodent microdevices in support of Major Tasks 1 and 3. We also plan to finalize the design of the rigid-flex substrate and the bill of electronic materials/components to be able to develop fully functional non-human primate microdevices in support of Major Task 5.
Furthermore, we will continue performing Major Task 2 with neurobiology collaborators at KUMC, with the aim of completing this task by the end of the next reporting period (i.e., Q1 of Year 3). This includes procuring additional rats, training them on the skilled reach task, and performing the surgical procedures to receive a controlled cortical impact (CCI).

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

There were some unforeseen delays in constructing the rodent microdevices, including manufacturer-caused delay in fabricating the substrates and supplier-caused delay in providing one type of Omnetics connector that is used with each rodent microdevice for temporary monitoring/programming. These delays were typically about 2-4 weeks and hence not too significant. In addition, the microelectrode array supplier changed the wiring configuration of their electrodes, necessitating an alteration in the microdevice connections that was quickly implemented with success to construct additional microdevices.

We had an unforeseen number of rodent microdevices fail mechanically during the experimentation phase. Because of the limited supply of microdevices at the time, we reduced the number of concurrent animals being run to ensure that microdevices could be replaced, if they failed. There were many discussions about modes of mechanical failure, and a resolution to make more microdevices and to slightly alter the location of the stainless steel rod mounting on the implant was deemed to effectively address these problems.

Unexpected noise and artifactual signals were also observed in the recorded neural signals during wired operation of a few rodent microdevices, which adversely affected our ability to discriminate spiking activity. Those microdevices and the peripheral equipment were subsequently returned to CWRU to pinpoint the source of the noise/artifacts and determine a solution going forward. The KUMC team suspended all new behavioral testing and microdevice implantations until a solution was found. After 3 weeks of electronic debugging by the CWRU team, the source of these problems was identified and remedial solutions were implemented into the affected microdevices as well as newly assembled batches of microdevices that were subsequently delivered to KUMC to resume the neurobiological experimentations.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution

committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

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

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*

- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*
Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Pedram Mohseni
Project Role: PD/PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-2849-4677
Nearest person month worked: 1.9
Contribution to Project: Dr. Mohseni oversaw the project progress related to the development of microdevices at CWRU, and maintained communications with the collaborating team at KUMC.

Name: Randolph Nudo
Project Role: Subaward PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-4674-0907
Nearest person month worked: 0.9
Contribution to Project: Dr. Nudo oversaw the project progress related to the neurobiological studies at KUMC, and maintained communications with the collaborating team at CWRU.

Name: Nicholas Vitale
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: 12
Contribution to Project: Mr. Vitale has performed work in the area of bidirectional wireless links for the microdevices based on a Bluetooth low energy (BLE) module.

Name: Meysam Azin
Project Role: Independent Contractor for CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: 4
Contribution to Project: Dr. Azin performed work in the area of algorithms and coding as well as verification of experimental setup reliability and stability.

Name: Reza Erfani
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: 1.6
Contribution to Project: Mr. Erfani has performed work in the area of wireless powering of biomedical implants.

Name: Fatemeh Marefat
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: 1.6
Contribution to Project: Ms. Marefat has performed work in the area of integrated circuit development for multichannel biopotential recording.

Name: David Guggenmos
Project Role: Senior Investigator at KUMC
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Dr. Guggenmos coordinated the work at KUMC, including performing implantation procedures, troubleshooting neurophysiological equipment, and assisting in analysis and interpretation of acquired data.

Name: Caleb Dunham
Project Role: Research Analyst at KUMC
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Mr. Dunham was responsible for data processing, analysis, and storage related to neurophysiological data collected during experimentation.

Name: Heather Hudson
Project Role: Post-Doctoral Fellow at KUMC
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Dr. Hudson performed the behavioral training, assisted on surgical procedures, and performed post-operative behavioral assessment and analysis.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc, available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other*

Organization Name: University of Kansas Medical Center
Location of Organization: Kansas City, KS, USA
Partner's contribution to the project: Collaboration

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.