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AWARD NUMBER: W81XWH-14-2-0161

TITLE: Improving Diagnosis of Sepsis After Burn Injury Using a Portable Sepsis Alert System

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RECIPIENT: The University of Texas Medical Branch at Galveston

REPORT DATE: October 2019

TYPE OF REPORT: Annual

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

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE October 2019		2. REPORT TYPE Annual		3. DATES COVERED 30 Sep 2018-29 Sep 2019	
4. TITLE AND SUBTITLE Improving Diagnosis of Sepsis After Burn Injury Using a Portable Sepsis Alert System				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-2-0161	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Ravi S. Radhakrishnan, MD, MBA, FACS, FAAP Associate Professor, Department of Surgery The University of Texas Medical Branch at Galveston E-Mail: rsradhak@utmb.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Medical Branch at Galveston 301 University Boulevard Galveston, TX 77555-5302				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Background: Sepsis is the leading cause of death after significant burn injury. Severely burned patients (TBSA >20%) have sepsis rates < 40%. Early initiation of antibiotics within 1 hour of recognition of sepsis is the only factor associated with better survival. Diagnosis of sepsis after burn injury is not amenable to standard sepsis criteria. To address this problem, the American Burn Association developed specific criteria to prompt sepsis workup. Despite these guidelines, these findings can be subtle leading to delays in recognition of sepsis. Hypothesis: Best practice guidelines using 'new vital signs' of heart rate variability, regional tissue oxygenation, and noninvasive cardiac output can diagnose burn sepsis earlier, reducing morbidity and mortality. Rationale: Heart Rate Variability (HRV), regional Tissue Oxygenation, and non-invasive Cardiac Output (CO), have shown promise in detecting sepsis in other patient populations. These modalities have not been evaluated for sepsis detection after burn injury. Specific Aims/Study Design: 1. Prospectively collect traditional and 'new vital signs' and compare the diagnostic accuracy, time to diagnosis, and prediction of outcome. 2. Develop a best practice guideline for the early diagnosis and treatment of sepsis in the burn patient, integrating current and new vital signs, and incorporating these into a bedside decision-support tool. 3. Design and conduct a prospective, multicenter, randomized study to test the efficacy of the newly developed bedside tool in detecting sepsis. Relevance: The use of 'new vital signs' will provide an improved assessment of burn sepsis, enabling earlier detection of sepsis. The results of the study may change the standard of burn care if it is found that 'new non-invasive vital signs' can detect sepsis earlier, leading to earlier initiation of antibiotics and improved morbidity and mortality.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

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

Despite multiple advances in critical care and resuscitation, sepsis is the leading cause of death in patients who sustain a significant burn injury. Our over-arching hypothesis is that best practice guideline using ‘new vital signs’ of heart rate variability, regional tissue oxygenation, and noninvasive cardiac output can be used to diagnose sepsis earlier, reducing morbidity and mortality after burn injury.

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

Burn injury, sepsis, mortality, heart rate variability, regional tissue oxygenation, noninvasive cardiac output

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

What were the major goals and objectives 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.

Task 1. Test the efficacy of “new noninvasive vital signs” of HRV, regional tissue oxygenation, and noninvasive cardiac output in detecting sepsis after burn injury. Proposed Timeline: Months 0-18. Patients to be enrolled: 18. Completion date: Month 48.
Task 2. Identify and use best conventional and “new” vital signs for early detection of burn sepsis to create a best practice guideline for identification of burn sepsis. Proposed Timeline: Months 6-40. Adjusted completion date: Month 72.
Task 3. Create decision support tool using best practice guidelines. Proposed Timeline: Months 12-48. Adjusted completion date: Month 72.

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.

Task 1. Test the efficacy of “new noninvasive vital signs” of HRV, regional tissue oxygenation, and noninvasive cardiac output in detecting sepsis after burn injury.

During the past year, we have continued to screen patients from the Blocker Burn Unit in Galveston as well as include eligible patients from the Shriners’ Hospital in Galveston. In the reporting period, we have screened 73 patients and identified 13 patients who met eligibility requirements for the study. The Shriners’ Hospital IRB and UTMB IRB committees had frozen all patient accrual into studies pending review of the entire portfolio of research protocols. We have completed external review with

	Screened	Eligible for Study	Enrolled in Study
# of Patients (total)	112	38	18 (2 enrolled at Shrine and will be removed bringing total to 16)
# of Patients (reporting period)	0	0	0

Task 2. Identify and use best conventional and “new” vital signs for early detection of burn sepsis to create a best practice guideline for identification of burn sepsis.

Task 3. Create decision support tool using best practice guidelines.

For the reporting period, we have been placed on administrative hold by the Shriners’, UTMB and DoD IRBs. We have received approval from the DoD to continue our work for an additional NCE year. We are currently responding to the UTMB IRB requests for additional information and expect to submit for HRPO approval by January, 2020. Work will commence on tasks 2 and 3 once HRPO approval obtained.

In September, 2019, the PI met with Ankura consulting to review their recommendations for improvement based on their audit of all burn research at UTMB. They found the following:

1. Dates were written on 7 of the 13 informed consent forms and one consent was missing the signature of the study team member.
 - a. Action taken: All study team members have retaken CITI training to learn proper procedure for informed consent.
2. A log of all patients who were screened and enrolled or not enrolled was needed as well as the timepoints that data was collected from the patient. Inclusion/exclusion criteria were not available in study binder.
 - a. Action taken: Inclusion and exclusion criteria were placed in study binder. Log was created to show what times data was collected from patients and patient log was updated to reflect enrollment or non-enrollment.
3. No documentation of scientific review prior to DoD submission
 - a. Action taken: Documentation of prior scientific review conducted at UTMB has been obtained and placed in study binder as well as scientific literature used to support grant proposal.

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.

Nothing to Report.

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.

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

Continue work on tasks 2 and 3 using previously enrolled patients from Blocker Burn Unit.

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.

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 Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.

No progress made in last reporting period due to administrative hold placed on all burn studies at our institution. Hold has been lifted and await UTMB IRB approval, and subsequent HRPO approval, to begin work on tasks 2 and 3.

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.

On December 1, 2018, all burn related research at UTMB was placed on hold pending an investigation into patient enrollment methodology. While this hold has been lifted, all IRB protocols were required to be withdrawn and resubmitted for full review. We are currently in the process of getting our protocol approved by UTMB and will submit to DoD for HRPO approval. All work on this project has been halted since Dec 1, 2018 for this reason.

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.

No recent changes that have had significant impact on expenditures.

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

Have dropped the 2 patients enrolled at the Shriner's Hospital from analysis. Will proceed with 16 previously enrolled patients from Blocker Burn Unit.

Significant changes in use or care of vertebrate animals.

Not applicable.

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. In addition to a description of the technologies or techniques, describe how they will be 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. State whether an application is provisional or non-provisional and indicate the application number. 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;*
- *biospecimen 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: Ravi Radhakrishnan
Project Role: PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Dr. Radhakrishnan began work on data analysis and was working on patient enrollment prior to administrative hold being placed.

Name: Min Zhu
Project Role: Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Dr. Zhu was working with our collected data with Dr. Radhakrishnan to refine decision support algorithm development prior to administrative hold being placed.

Name: Claire Cummins
Project Role: Research Associate/Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Dr. Cummins has worked on patient enrollment, ensuring that data is collected appropriately from patients, assisting bedside nursing with adherence to data collection protocols, and ensuring that sensors are in proper position for data collection prior to administrative hold.

Name: Jian-Jun Wen
Project Role: Research Associate
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Dr. Wen was brought into the lab on 11/2017 to assist with patient enrollment and data collection and was working with Dr. Zhu on these tasks prior to the administrative hold being placed..

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.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating 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.

Attachment 2: Quad Chart

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.