Appendix 1: Statement of Work and Milestone Payment Schedule
Proposal Number: MTEC-20-12-COVID-19-Diagnostics-010

Organization: Sempulse Corporation

Title: Wearable Physiologic Monitor with Real-time Continuous Data Acquisition and Analysis for Early Detection of COVID 19 Infection

ACURO and/or HRPO approval needed: HRPO approval needed

Background

In the current global COVID 19 pandemic, with more than 4.1 million cases and 285,000 deaths worldwide and 1.3 million cases and 79,000 deaths in the United States to date, viral transmission by asymptomatic or pre-symptomatic carriers threatens the ability of medical, first responder, and military communities alike to continue functioning in their essential roles and endangers the general population. As the RPP states, "There is a dire and urgent need for development of rapid, accurate wearable diagnostics to identify and isolate pre-symptomatic

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Scope/Project Objective

This proposal is submitted in response to Request for Project Proposals for MTEC-20-12-COVID-19-Diagnostics W81XWH-15-9-0001 for a non-invasive, accurate wearable diagnostic tool for identifying and isolating pre-symptomatic COVID-19 cases for preventing the spread of the virus. Current Team Sempulse capabilities support the RPP requirements for wearable physiologic monitoring with (b) (4) and analysis for early detection of COVID 19 infection. Team Sempulse will provide: 1(b) (4)

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(b) (4) Our objective is to provide early detection of COVID 19 infection using wearable physiologic monitoring wit (b) (4)

(b) (4) combined dynamically emerging "best evidence" rule-based screening logic, and machine learning-enabled predictive analytics.

Requirements

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(b) (4) New software adaptations will be incorporated into existing clinical decision support protocols and AI driven predictive algorithms, based on machine learning with case data for ~ 2000 COVID 19 patients. The adapted monitoring platform will be tested in a prospective clinical trial for assessment of its ability to diagnosis COVID 19 infection earlier, in pre-symptomatic individuals, than current diagnostic protocols do, and guide treatment of COVID 19 infections to improve outcomes and preserve scarce medical resources.

At project kick-off, the research team will complete a set of specifications for COVID 19 early detection and alerting as well as quantitative goals for the test of the solution in an operational point-of-care environment. Collaborative team agreements, healthcare business associate agreements, and data sharing agreements will be completed, and an application will be started for FDA Emergency Use Authorization for Sempulse PMP (the wearable device and software and VFusion CDS (early detection and alerting software.

Task 1. (b) (4) (b) (4) sepsis data analytics and prototype user interface display (Figure 3) previously are essentially ready "out-of-the-box". Our software engineers will (b) (4)

(b) (4)

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Sempulse (b) (4) deployed in the HITRUST/FedRAMP-certified AWS GovCloud region that can be configured to connect to virtually any data source. Immediate alpha testing can be performed using expert clinician-guided COVID-19 logic, (b) (4) IRB-approved patient de-identified COVID-19 data, and (b) (4) in a high-fidelity remote patient monitoring "simulation" mode. During testing our expert clinicians would use historic COVID-19 data to iteratively "tune" EW logic to achieve optimal alerting sensitivity/specificity. Our (b) (4) factors SMEs will work with our team of critical care clinicians and software engineers to iteratively refine EW alerting behavior and presentation to maximize effectiveness.

Task 2. Rapid Deployment and Beta Testing:

With live data-feeds and refined interfaces having been established in Task 1, our software engineers will focus on scaling and evaluating the performance of Sempulse (b) (4) and beta

testing with personnel and live patient data. Sempulse(b) (4) is designed for horizontal scalability and AWS provides SLAs for its various services at greater than 99.9% availability, with virtually unlimited scale. We will collect and evaluate all system availability and performance metrics to refine our deployment and sustainment plans. Meanwhile, our clinical and human factors SMEs will obtain feedback on system performance and usability via user direct observation, interviews, and surveys. (b) (4)

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(b) (4) CDS web-based alerting user interface is highly intuitive and will not require formal training. As appropriate, we will make refinements to the EW system knowledgebase and user interfaces based on Beta feedback, and we will produce final training plans and documentation.

Task 3. Automated Improvements (b) (4)

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(b) (4) Working with clinician personnel, our experts will develop and update ML models that take advantage of the newest data available as the pandemic evolves over time, to optimize discrimination and prediction of criticality and deterioration of COVID-19 patients.

COVID-19 (b) (4) **.** In our prior sepsis work, in a 5-month pilot study at a rural community hospital of 14,392 patient encounters in the trial period, (b) (4) 1,648 cases of sepsis, and 1,225 cases of severe sepsis. In addition to (b) (4) early detection of sepsis, ML models for predicting "sepsis" (Sepsis-2 and Sepsis-3 definitions were both used in final diagnosis) using first 6 hours of ED encounter data. When compared to (b) (4), ML techniques are known to be less sensitive to missing data. Table 1 illustrates experiments where we used subsets of data to evaluate predictive robustness to sparse or missing feature datasets. (b) (4)

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(b) (4) With the availability of this data we will perform (b) (4) analytics and derive (b) (4) in support of improved COVID-induced ARDS and/or sepsis predictive analytics. (b) (4)

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Test materials

Our engineers will scale and deploy Sempulse/(b) (4) to support the required number of sites to provide EW screening support to users and provide 24x7 monitoring and technical support. Clinical Sites will facilitate the IRB approved prospective risk detection and early warning phase of the proposed project at community-based facilities. During testing our expert clinicians work to (b) (4)
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(b) (4)
performance, system efficacy, and user-provided feedback and update the algorithms and operational characteristics of the system as appropriate IAW emerging guidance and data, and in consultation with the Government. We expect to make improvements to data capture protocols reflecting specific formats and clinical practices of users as may be needed for effective EW analytics and in accordance with COVID-19 management guidelines (e.g. frequency of vitals monitoring, clinical data types, etc.).

Task 4. Prospective Study Phase--Deployment and Enhancement

A prospective clinical trial will be conducted to test performance in field conditions.
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matter experts.

Clinical Trial Description

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Patients consenting to participate in this trial will be provided Sempulse monitoring equipment
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will be used to detect and/or predict early signs of established COVID-19 illness and present alerts to clinicians that may lead to a decision to request patient to re-test and/or self-quarantine/isolate.

(b) (4)

(b) (4)

Given that the incubation period is thought to be within 14 days of exposure, with most cases occurring approximately four or five days after exposure1, the per patient study timeframe is 14 days. Current recognized symptoms in adults include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea2. Similar symptoms tend to be less severe in children with mild forms of the disease and may additionally include behavioral changes (e.g. frequent crying, moodiness, anxiety). Children are also less likely to report symptoms, making early detection more challenging in this population3.

Inclusion criteria: All consenting adults and/or guardians of children that presented to a participating ED or clinic with one/or more COVID-19 symptoms that were sent home without a test or were given a test with negative result.

Exclusion criteria: Any participant that does not provide or withdraws consent, has a skin condition that prevents (b) (4) Sempulse (b) (4), presence of a pacemaker or cardiac defibrillator, inability to cooperate or communicate with clinical research team

(b) (4) participants across participating institutions. *Note: Extensive consideration was given to the issue of conducting a randomized vs non-randomized trial. It was determined that because the focus of the MTEC-20-12-COVID-19_Diagnostics solicitation is on demonstrating effective early detection and/or prediction of COVID-19, and not the evaluation of interventional therapies, having a control group for comparing health outcomes was not required. Using (b) (4) via wearable device, the study aims to accurately detect COVID-19 among all enrolled participants.*

- Observational model: Cohort
- Time perspective: Prospective
- Study Period: 90 days
- Estimated clinical trial start date: 2/14/2021
- Estimated clinical trial completion date: 5/15/2021

Primary Outcome Measure (b) (4)
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(b) (4)

Ethics issues

All study participants will be provided with information about the purpose and scope of the study, and will have the opportunity to choose to participate or not, without any effect on the standard of care that they will receive. The clinical trial coordinator will meet with each potential participant to explain the study and to obtain written informed consent.

The risks to patients participating in this study are minimal, as the wearable device being studied is

[1]

(b) (4) and is not being used for diagnostic or treatment purposes for these patients. The very minor physical risks that exist are: potential sensitivity to the adhesive used to attach the monitor and minor discomfort (b) (4). Mitigating these risks is the fact that the adhesive used is a medical grade adhesive commonly used in clinical practice, and the fact that study participants may withdraw from the study at any time. The privacy risk to the patient is the other people may notice that the participant is wearing the device, and will therefore know that the patient is participating in a study. Mitigation against any data breaches that would violate human subject privacy and security regulations or HIPAA are the secure, encrypted software used for storing and transmitting patient vital signs, and the clinical study sites' long experience with securing handling patient data during clinical trials that involve far more sensitive patient data.

FDA Interactions

Sempulse has been working for the last year on a FDA 510K submission to the FDA for Sempulse (b) for use in performance training and as a predicate device for future modifications of hardware and software. As the Sempulse (b) (4), it is likely to be considered low risk. Sempulse will apply immediately for an FDA Emergency Use Authorization. We will use documentation and materials developed over the last year for a pending 501K medical device application to apply immediately to the FDA for an Emergency Use Authorization for the proposed diagnostic screening tool (hardware and software).

Task 5. Analyze and Evaluate Prospective COVID 19 Early Detection And Alerting Performance

Anticipated Outcomes

A COVID 19 early detection and alerting platform based on a (b) (4) (b) (4). The platform can be deployed within virtually any point-of-need operating environment (physician office, urgent care, clinics, emergency departments, etc.) and support any standard and secure (HIPPA-compliant) data format.

Project Impact

By retrospective analysis of IRB approved COVID-19 data, using assay positive test results, we will aim to achieve (b) (4) (b) (4)

Technical Maturity and Commercialization Strategy

Wearable Physiological Monitoring Devices

Competitors in this space focus on either of two extremes: fitness wearables with low efficacy or hospital-grade devices that require clean power and conditions. (b) (4) Sempulse (b) (4)

(b) (4)

Commercialization Plan

The wearable vital signs monitoring devices market is very large and growing quickly on a global basis. In the civilian market, virus outbreaks like the current COVID-19 pandemic, an aging population, increasing prevalence of chronic disorders as primary causes of death, and technical advances in medical devices are key drivers responsible for the lucrative growth of the vital signs monitoring market. Chronic disease and pain management require consistent day-to-day actions, rather than visits to the doctor to shape outcomes. There is a growing need for autonomous wearable devices that can supply both clinicians and patients with reliable (b) (4), reminders, alerts, and feedback for use in innovative strategies to manage health, diagnosis, and treatment.

(b) (4) Sempulse (b) (4)

(b) (4) In the U.S., the potential combined civilian and defense markets for the (b) (4) exceeds 21 million units in initial sales, based on current numbers of US active duty military (deployment and reserves); veterans to whom the VA annually mails diagnostic kits for remote care; civilian hospital beds; neonatal ICU patients; telemedicine; EMT, paramedics, and firefighters; and individuals affected by natural disasters. The estimated market for an accurate wearable biometric monitor is $951 billion in emergency room and urgent care settings; $353 billion in post-hospital, nursing facility, and long-term care monitoring; and $16 billion in EMS and first responder applications.

Scaling up manufacturing

Our current manufacturing partner is geared up to produce 8,000 devices per month with minimal lead time. They can expand this by 10% in 6 weeks. We have a second operational manufacturing partner that can produce 15,000 / month in a timeline still measured in weeks and has a higher top end capacity closer to 30,000 / month. Both of these are US facilities. Beyond that we could add a third large facility as needed in a few months as the hardware was designed in part for ease of manufacturing.

Deliverables

Deliverables include: A complete set of specifications for COVID-19 early detection and alerting as well as quantitative goals for the test of the solution in an operational point-of-care environment. (b) (4)

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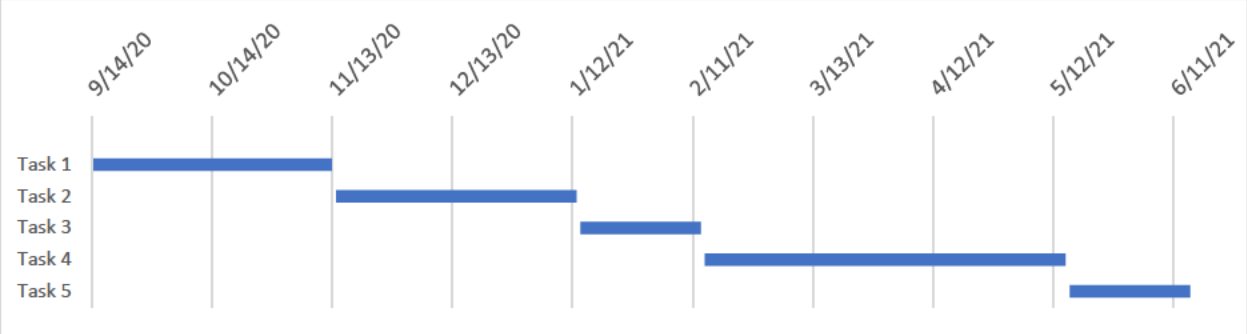
Timeline



Major Activity	Period
Task 1. (b) (4) & early warning software initial system configuration & alpha testing	9/14/2020— 11/13/2020
Task 2. Rapid deployment & beta testing	11/14/2020— 1/13/2021
Task 3. Automated improvements (predictive analytics, continuous monitoring devices)	1/14/2021— 2/13/2021
Task 4. Prospective Clinical Trial	2/14/2021— 5/15/2021
Task 5. Final report & technology transfer	5/16/2021— 6/15/2021

Milestone Payment Schedule

Milestone #	Task/Milestone	Description	Due Date	Payment
1	Project kick-off and final planning phase		9/30/2020	$0.00
1.2	Execution of Agreements	(b) (4) Sempulse (b) (4)	10/15/2020	$0.00
1.1	Completed specifications (Deliverable)	(b) (4)	11/15/2020	$358,771.00
1.3	First bimonthly report		11/15/2020	$0.00
2	Start retrospective study phase		11/16/2020	$0.00
2.1	Approved (b) (4)	Approval letter.	11/16/2020	$0.00
2.2	(b) (4)	(b) (4)	12/10/2020	$0.00
2.4	Retrospective analysis of IRB approved COVID-19 data set, using assay positive test results.	Aim to meet or exceed (b) (4) COVID-19 detection performance of (b) sensitivity/specificity with a (b) (4)	12/30/2020	$0.00

Milestone #	Task/Milestone	Description	Due Date	Payment
2.5	Test, tune and validate COVID-19 (b) (4) (Deliverable)	Report on preliminary retrospective study results.	1/15/2021	$706,273.00
2.6	Second bimonthly report		1/15/2021	$0.00
3	Start Integrated solution deployment phase		1/16/2021	$0.00
3.1	Submit prospective research protocol for IRB approval and U.S. Army Human Research Protections Office (HRPO) for ethics review.	Confirmed submissions.	1/30/2121	$0.00
3.2	(b) (4)	Fully functional integrated prototype.	2/13/2021	$0.00
3.3	Deploy the integrated solution into a HIPAA compliant AWS deployment environment. (Deliverable)	Demonstrable deployment in a secure commercial environment.	2/13/2021	$148,010.00
4	Start Prospective clinical trial phase		2/14/2021	$0.00
4.1	IRB/HRPO approvals for Clinical Sites prospective research.	Approval letter.	2/28/2021	$0.00
4.2	Deliver devices for use in prospective trial. (Deliverable)	Complete manufacture and delivery of 250 fully functional units.	3/5/2021	$0.00
4.3	Conduct site training for clinicians, RAs, and protocol monitors. (Deliverable)	Training and readiness reviews confirmed by site-Investigator(s).	3/15/2021	$400,650.00
4.4	Third bimonthly report		3/15/2021	$0.00
4.5	Conduct prospective COVID-19 risk detection and alerting at selected Clinical Sites facilities	Initialization of clinical site participant recruitment.	4/15/2021	$0.00
4.6	Clinician feedback on system operability and early detection performance.	RA capture of feedback through direct observation, interviews, and surveys.	4/20/2021	$0.00
4.7	Complete prospective study phase and submit completion report to IRB (Deliverable).	End of IRB approved study period.	5/15/2021	$140,000.00
4.8	Fourth bimonthly report		5/15/2021	$0.00
5	Analyze and evaluate prospective COVID-19 early detection and alerting performance. (Deliverable)		6/15/2021	$87,774.00
5.1	Final Reports		6/15/2021	$0.00
		Total for Project		**$1,841,478.00**

Data Rights

(b) (4) Sempulse (b) (4) previously developed and funded exclusively at private expense and is such is Restricted in use. The technical data collected and used across the listed aims and milestones during this study, will have Government Purpose Data Rights. The rights of IP held by other parties would continue to be held by respective parties..

Technical Data or Computer Software to be Furnished with Restrictions	Basis for Assertion	Asserted Rights Category	Name of Organization Asserting Restrictions
(b) (4) [redacted]	(b) (4) [redacted]	Government Purpose Rights	[redacted]
(b) (4) [redacted]		Government Purpose Rights	Sempulse Corporation