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April 5, 2021

University of California, San Francisco (UCSF)
3333 California St., Ste 315
Campus Box 0962
San Francisco, CA 94143

Attention: (b) (6), Assistant Director, Contracts

Subject: Modification No. 03 to MTEC Research Project Award No. 02; MTEC-20-12-Diagnostics-023

Reference: MTEC Base Agreement No. 2018-674

Dear (b) (6):

In accordance with the terms and conditions of the referenced MTEC Base Agreement, Modification No. 03 hereby amends the Research Project Award No. 02 as follows:

DESCRIPTION OF MODIFICATION

1) **The Term of the Task Agreement clause of the Research Project Award is hereby amended to read as indicated in bold below:**

3. Term of the Task Agreement
The period of performance for this Research Project Award is from July 13, 2020 through February 28, 2022 *(this is a nine month no-cost extension)*.

2) **Attachment A, Statement of Work, of the Research Project Award is hereby amended to read as attached herein.**

Except as provided herein, all Terms and Conditions of the referenced MTEC Base Agreement, Research Project Award, and preceding modifications remain unchanged and in full force and effect.

The Research Project Awardee is required to sign this document and return to Advanced Technology International to finalize this action.

University of California, San Francisco (UCSF)

By: (b) (6)

Name: (b) (6)

Title: Director

Date: 4/7/2021

Advanced Technology International

By: (b) (6)

Name: Subcontracts Administrator I

Title: (b) (6)

Date:

Attachment A
Statement of Work and Milestone Payment Schedule
(Incorporated as of Modification No. 03; changes are indicated in bold italics.)

Project Proposal: MTEC-20-12-Covid19-Diagnostics-023
Organization: The Regents of the University of California, San Francisco
Title: Leveraging Wearable Ring Data for Early SARS CoV-2 Detection
ACURO and/or HRPO Approvals Needed: HRPO approvals needed.

Introduction/Background: The COVID-19 pandemic has highlighted the urgent need, across both military and civilian populations, to develop solutions that identify individuals who may be in the earliest stages of a transmittable disease to target rapid testing that will guide isolation and contract tracing procedures aimed at interrupting transmission. On March 20, 2020, PI Mason launched TemPredict, which enrolled 45,455 participants to provide ambulatory data from Oura smartrings. Oura smartring metrics include temperature, heart rate, heart rate variability, and respiration rate. This sample includes participants who possessed an Oura ring prior to joining the study (n ~43,000) as well as healthcare workers whom TemPredict is providing rings to (2,700 of 3,400 deployed). At present the dataset includes more than 4,000 frontline responders, including those whom TemPredict recruited (existing Oura smartring owners) and those who TemPredict provided Oura smartrings to. The current proposal aims to leverage the initial data collected in TemPredict to perform algorithm development using physiological data from a wearable device (Oura ring) for early detection of COVID-19 disease. A secondary aim is to test use of the physiological data for detection of other illnesses.

Scope/Project Objective: This proposal focuses on wearable technologies for early illness detection, and is broken into 3 major aims:

1. Leverage initial TemPredict data by performing SARS CoV-2 antibody testing in ~10,000 TemPredict participants to provide accurate determination of infection status, including asymptomatic infection for use in algorithm development.
2. Use the initial TemPredict data with antibody testing results to develop algorithms, based on physiological signals (temperature, HR, HRV, and RR), that identify individuals who may have early SARS CoV-2 disease;
3. Develop protocols for, and to conduct initial deployment and testing of, Aim 2 algorithms using the Oura device to trigger: (a) early SARS CoV-2 PCR testing and discriminative influenza testing and (b) early isolation in civilian populations.

Requirements: All necessary facilities for the proposed work are in action already.
Data gathering. TemPredict has deployed ~2,700 smartrings to front line medical personnel, and ~42,000 additional Oura users have joined TemPredict and are filling out (b) (4) questionnaires. UCSF has an established infrastructure for data collection for surveys, enrollment data, and participant tracking for the study, including University-licensed (b) (4) and HIPAA-compliant research data cloud storage systems.

Data management/storage: All data models will be managed at (b) (4) through (b) (4) (b) (4) (b) (6) and (b) (6). Enhanced labeling through serology (Aim 1) will augment these efforts when such data become available.

1. House data at (b) (4) Data pipelines to be established between: a) Oura (b) (4) and (b) (4) (b) (4)) for repeated pushes (2x week for data updates); b) UCSF and (b) (4) survey data and (b) (4) c) (b) (4) and MIT LL.
2. Integrating Aim 1 serology data. This will require completion of the Serology database framework, accumulation of the serology test result data, and establishing a pipeline between (b) (4) and the serology results database.

Antibody testing capabilities: Core research laboratory facilities for this project are based at Vitalant Research Institute (VRI, formerly Blood Systems Research Institute), a division of Vitalant (a non-profit blood bank system) and is housed within the Vitalant blood center in San Francisco, CA. VRI has an affiliation with UCSF. VRI has state of the art equipment to support research related to blood and blood product safety in the areas of molecular biology, immunology, virology, tissue culture, cell processing and epidemiology. VRI staff has 7734 sq. ft. of labs (including a biosafety level 3 lab), and a 3164 square foot freezer room with capacity to store more than one million specimens. This project will utilize two VRI core laboratories, the Core Immunology Laboratory (CIL) and the Viral Reference and Repository Core (VRLRC). This project will also utilize clinical laboratory resources at Creative Testing Solutions (CTS). CTS is the largest nonprofit blood donor testing laboratory organization in the US, and is owned by Vitalant, American Red Cross, and OneBlood, and is a CLIA certified laboratory with high throughput testing capabilities, which include support for research study clinical laboratory testing.

Algorithm development. (b) (4) researchers, together with MIT LL researchers, who have both domain expertise in time series disease modeling, will lead algorithm development efforts for the detection and progression monitoring of COVID-19. (b) (4) has suitable computational resources (b) (4) (b) (4) for managing and analyzing the 500 terabytes of time series and accompanying data. Algorithm development will continue throughout the funding period. Final results (maximum specificity and sensitivity) are unknowable ahead of effort, and so versions will be released as they are developed, with iterative releases improving on specificity and sensitivity. Algorithm development will be initiated as soon as data are gathered from Oura and UCSF (b) (4) as opposed to being delayed until the completion of serology data gathering from Aim 1. Algorithm development is a broad, flexible task which requires upfront investment for hiring postdoctoral researchers who will have 100% effort on these goals. Deliverables will come in the form of algorithms accompanied by manuscripts for scientific publication.

1. Algorithm development between (b) (6) a(b) (4) and MIT LL. Algorithm development proceeds along three parallel paths, all using a framework of ROC curve comparison to evolve higher specificity and sensitivity:
    a. Individualized illness onset detection;
    b. Individualized severity projection;
    c. Individualized recovery confirmation.
2. Hire postdoctoral researcher for dedicated algorithm development and data management.
3. Data model development with (b) (6) at (b) (4). While algorithm development will begin as soon as data gathering to (b) (4) is complete, the analysis of these data will become substantially more efficient with the development of appropriate data models framing these data to allow faster chunking for computation and querying.
4. Hire postdoctoral researcher for dedicated model development and management.

Milestone Deliverable tasks: Below are milestone deliverable tasks that we include in the milestone payment schedule

1) UCSF IRB Submission for Aims 1 & 2
2) HRPO Submission for Aims 1 & 2
3) Aim 1: Validation of dried blood spot antibody testing for SARS CoV-2 antibody detection using well characterized sera.
4) Aim 1: Assessment of the accuracy of antibody assay methods for estimation of the SARS CoV-2 infection period using serial sera with known dates of symptom onset.
5) Aim 1: Determination of SARS CoV-2 infection status of initial 3,000 participants first DBS specimen.

6) Aim 1: Determination of SARS CoV-2 infection status in additional 7,000 participants first DBS specimen
7) Aim 1: Determination of SARS CoV-2 infection status of second DBS specimen in 10,000 participants.
8) Aim 2: Hire postdoctoral researchers
9) Aim 2: Data de-identified, aligned, and curated at (b) (4) Oura and (b) (4) data pushed to (b) (4) (b) (4) ; aligned, de-identified, and moved into (b) (4) as shareable research object
10) Aim 2: Initiate development of full data model for algorithm. MIT LL confirms access to data model housed on (b) (4) coordinated with (b) (6) and (b) (6)
11) Aim 2: Initial algorithm developed for early detection of COVID-19 disease.
12) Aim 3: IRB Approval for Aim 3
13) Aim 3: HRPO Approval for Aim 3
14) Aim 3: complete for Aim 3
15) Aim 3: Data collection prepared for Aim 3: Questionnaires finalized and programmed for participants and specimen collection and testing protocols
16) Aim 3: Data system in place for working with Oura ring data in real time to identify participants with elevated risk of COVID-19 infection.
17) Aim 3: Initial 1,600 participants enrolled for aim 3, from existing TemPredict participant pool (50%)
18) Aim 3: Complete enrollment of ***Aim*** 3 participants (***up to*** 3,200 total)
19) Aim 3: Complete follow-up of ***Aim*** 3 participants, including laboratory tests (initial 1,600 participants)
20) Aim 3: Complete follow-up of ***Aim*** 3 participants, including laboratory tests ***(remaining*** participants)
21) Aim 3: Analysis of sensitivity and specificity of algorithm for Aim 3 participants.
22) ***Prepare initial draft of analyses for initial algorithm submission to a peer-reviewed journal outlet***
23) ***Submit initial algorithm publication to a peer-reviewed journal outlet***
24) ***Develop auto-encoder based dynamic baseline classification models to classify individuals into "types" based on complex physiological features***
25) ***Complete analysis of metagenomic sequencing data***
26) ***Develop algorithm 2.0, competing best approaches from algorithm 1.0, autoencoder-determined baselines, and other machine learning approaches beside the random forest used within algorithm 1.0***
27) ***Split algorithm 2.0 by sex, age, significant confounding conditions (e.g. diabetes), and re-train to quantify increased efficacy per demographic***
28) ***Quantify demographic coverage gaps in support of future efforts to cover diversity appropriately for algorithms to be deployed across more diverse populations***

Milestone Payment Schedule:

MTEC Milestone #	Task #	Significant Event / Accomplishments	Due Date	Government Funds	Cost Share	Total Funding
1	-	Project Kickoff	7/13/20	$40,000		$40,000
2	1	Submission for UCSF IRB Approval, Aims 1 & 2	7/22/20	$30,000		$30,000
3	2	Submission for HRPO Approval, Aims 1 & 2	7/27/20	$30,000		$30,000

4	8	Identify & hire data management and data analyst postdoctoral researchers at (b) (4)	8/5/20	$678,201		$678,201
5	9	Establish secure data repository at (b) (4)	8/12/20	$125,000		$125,000
6	9	Establish pipeline between (b) (4) and Oura (b) (4) - recurring data transfer	8/12/20	$125,000		$125,000
7	3	Validation of dried blood spot antibody testing	8/22/20	$200,000		$200,000
8	4	Assessment of the accuracy of antibody assay methods for estimation of the SARS CoV-2 infection period (Aim 1).	8/22/20	$200,000		$200,000
9	-	Report #1	8/25/20	N/A		N/A
10	Part of 6	Complete collection of additional initial 10,000 DBS cards	9/5/20	NA		N/A
11	5	Determine SARS CoV-2 infection status of initial 3,000 participants (1st DBS specimen, Aim 1).	9/5/20	$125,000		$125,000
12	10	Initiate development of full data model for algorithm	9/5/20	$350,000		$350,000
13	6	Determination of SARS CoV-2 infection status of additional 7,000 participants first DBS specimen.	9/22/20	$275,000		$275,000
14	12	IRB approval for Aim 3	9/22/20	$20,000		$20,000
15	13	HRPO approval for Aim 3	9/28/20	$20,000		$20,000
16	Part of 7	Complete collection of 2nd DBS card, n=10,000	10/6/20	N/A		N/A
17	11	Initial algorithm developed for early detection of COVID-19 disease	10/6/20	$450,000		$450,000
18	15	Data collection prepared for Aim 3 and initiate Aim 3 recruitment	10/13/20	$350,000		$350,000
19	16	Data system in place for working with Oura ring data in real time	10/13/20	$350,000		$350,000
20	-	Report #2	10/25/20	N/A		N/A
21	7	Determination of SARS CoV-2 infection status of second DBS specimen in 10,000 participants	11/5/20	$200,000		$200,000
22	17	Initial 1,600 participants enrolled for aim 3, from existing TemPredict participant pool (50%)	12/1/20	$350,000		$350,000

23	18	Complete enrollment of additional participants for Aim 3, including providing Oura rings (***up to*** 3,200 total)	1/2/21	$350,000		$350,000
24	-	Report #3	12/25/20	N/A		N/A
25	-	Report #4	2/25/21	N/A		N/A
26	19	Complete follow-up of Aim 3 participants, including laboratory tests (initial 1,600 participants)	4/1/21	350,000		$350,000
27	-	Report #5	4/25/21	N/A		N/A
28	20	Complete follow-up of Aim 3 participants, including laboratory tests (***remaining*** participants)	5/1/21	$350,000		$350,000
29	21	Analysis of sensitivity and specificity of algorithm for Aim 3 participants	5/20/21	***$68,360***		***$68,360***
30	***-***	***Report #6***	***6/25/21***	***N/A***		***N/A***
31	***22***	***Prepare initial draft of analyses for initial algorithm submission to a peer-reviewed journal outlet***	***7/1/21***	***$20,000***		***$20,000***
32	***-***	***Report #8***	***8/25/21***	***N/A***		***N/A***
33	***23***	***Submit initial algorithm publication to a peer-reviewed journal outlet***	***10/1/21***	***$20,000***		***$20,000***
34	***24***	***Develop auto-encoder based dynamic baseline classification models to classify individuals into "types" based on complex physiological features***	***10/22/21***	***$20,000***		***$20,000***
35	***-***	***Report #9***	***10/25/21***	***N/A***		***N/A***
36	***25***	***Complete analysis of metagenomic sequencing data***				
37	***26***	***Develop algorithm 2.0, competing best approaches from algorithm 1.0, autoencoder-determined baselines, and other machine learning approaches beside the random forest used within algorithm 1.0***	***12/20/21***	***$20,000***		***$20,000***
38	***-***	***Report #10***	***12/25/21***	***N/A***		***N/A***
39	***27***	***Split algorithm 2.0 by sex, age, significant confounding conditions (e.g. diabetes), and re-train to***	***1/25/21***	***$20,000***		***$20,000***

		quantify increased efficacy per demographic				
40	***28***	***Quantify demographic coverage gaps in support of future efforts to cover diversity appropriately for algorithms to be deployed across more diverse populations***	***2/25/22***	***$20,000***		***$20,000***
41	-	Final Business and Technical Report	2/28/22	N/A		N/A
		Total		***$5,156,561***		***$5,156,561***