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Protocol for Randomized Controlled Trial of Artificial Intelligence Mobile Health Platform for Early Detection of COVID-19 in Quarantine Subjects using Wearable Physiology Biosensor

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Protocol for Randomized Controlled Trial of Artificial Intelligence Mobile Health Platform for Early Detection of COVID-19 in Quarantine Subjects using Wearable Physiology Biosensor

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ABSTRACT

Introduction: There is an outbreak of Coronavirus Disease 2019 (COVID-19) worldwide. To date, there is no specific therapy or vaccine, thereby rigorous implementation of traditional public health measures including isolation and quarantine remain the most effective tools to control the outbreak. Current quarantine approach for asymptomatic individuals with COVID-19 contacts requires temperature and symptom surveillance. The intermittent nature and high dependency on self-discipline of the approach undermine its practicality. Advances in multi-sensor technologies made it possible to continuously monitor physiological parameters using wearable biosensors with a variety of form-factors.

Objective: To explore the potential of continuous multi-parameter physiological monitoring using a wearable biosensor in detecting early clinical progression of COVID-19.

Method: This randomized controlled open-labelled trial will involve 200 to 1,000 asymptomatic subjects with close COVID-19 contact under mandatory quarantine at designated facilities in Hong Kong. Subjects will be randomized to receive a remote monitoring strategy (intervention group) or standard strategy (control group) in a 1:1 ratio during the 14 day-quarantine period. In addition to fever and symptom surveillance in the control, subjects in the intervention group will wear a wearable biosensor on their arm to continuously monitor skin temperature, respiratory rate, blood pressure, pulse rate, blood oxygen saturation and daily activities, which is transferred in real time via Bluetooth to a smartphone application called Biovitals® Sentinel. The data is then processed using a cloud-based multi-variate physiology analytics engine

called Biovitals® to detect subtle physiology changes which is displayed on a web-based dashboard for clinicians review. The primary outcome is the time to diagnosis of COVID-19.

Ethics and Dissemination: Applied for approval from institutional review board at the study sites. Results will be published in peer-reviewed journals.

Conclusion: The study will provide essential information about the potential of remote multi-sensor physiological monitoring using wearable biosensor in COVID-19 outbreak control.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Automatic physiological data collection by wearable biosensor that do not rely on self-discipline of quarantined subjects.
- Large number of physiological parameters monitored, including skin temperature, respiratory rate, blood pressure, pulse rate, blood oxygen saturation and daily activities, instead of relying solely on temperature measurement.
- Continuous data collection and analysis throughout the day.
- Limited by being single-center based and exploratory in nature.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) emerged in December 2019,(1-4) and in mere few months has spread to more than 104 countries, resulting in an outbreak of viral pneumonia worldwide. As of March 12, 2020, the virus has reportedly caused 127,863 infections and 4,718 deaths globally.(5) The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on January 30, 2020 and further characterized it as pandemic on March 11, 2020. As there has yet been specific therapeutic or vaccine for the condition, rigorous implementation of traditional public health measures including isolation, quarantine, social distancing, and community containment is the principle strategy to control the COVID-19 epidemic.(6) In addition to isolation of confirmed COVID-19 infected patients from non-infected population, it is equally if not more important to quarantine asymptomatic individuals with possible exposure to COVID-19 in order to reduce the viral spread. Indeed, quarantine measures have been initiated in many countries and regions, which restrict movements of asymptomatic individuals with COVID-19 exposure often with fever and symptom surveillance at home or designated facilities for the presumed incubation period (14 days). While conceptually attractive, the intermittency and high dependency of self-discipline for body temperature and symptom surveillance undermine the practicality and effectiveness of the approach. Furthermore, it has been reported that as many as 50% of COVID-19 infected patients had not had fever until the full-blown disease,(3, 7) thereby body temperature surveillance *per se* may not be sufficient to detect early disease progression.

In the past few decades, advances in sensor technology miniaturize electronic physiological sensors that could be incorporated into wearable devices allowing

continuous monitoring of physiological parameters such as skin temperature, heart rate, respiratory rate, oxygen saturation, perspiration and activity of ambulatory subjects in a 24/7 basis.(8, 9) Together with current telecommunication platform capable of instantaneous and multi-directional massive data transfer, it is possible to remotely monitor a large number of individual subjects' physiological parameters in a real-time manner, and relay to managing physicians for timely intervention. Nonetheless, such potentials have not been fully explored in the real-world disease management. The current study will assess the impact of remote continuous monitoring in asymptomatic subjects with COVID-19 exposure under mandatory quarantine at designated facilities in Hong Kong using Biovitals® Sentinel Platform. The platform consists of continuous real-time physiological monitoring using a clinical-grade wearable biosensor worn on the upper arm called Everion® (Biofourmis, Singapore) and an artificial intelligence-powered physiology analytical platform Biovitals® (Biofourmis, Singapore) to detect progression of disease. The research hypothesis is that the continuous physiological data collected using Biovitals® Sentinel and the patient reported outcomes will be processed through a cloud-based analytics platform, Biovitals® that will be able to detect physiology changes (and other clinically meaningful alerts) which would indicate early clinical progression in quarantined subjects with COVID-19 exposure.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).(10, 11) The underlying protocol follows the Consolidated Standards of Reporting Trials (CONSORT).(12, 13) Registration on clinicaltrials.gov has been submitted and pending approval.

Study Design and Participants

This is a prospective, randomized controlled, open-labeled study. Asymptomatic subjects with COVID-19 exposure at designated facilities under the compulsory quarantine measure introduced on February 8, 2020 in Hong Kong, fulfilling inclusion and exclusion criteria of the study will be invited to participate in this study. Table 1 summarizes the inclusion and exclusion criteria.

There will be 2 phases of the subject recruitment. The initial run-in phase is a single arm, open-label study design confirmation phase with approximately 100 subjects. All subjects will undergo remote physiological monitoring using Biovitals® Sentinel platform. The data collected from the platform and clinical data from health system will be used to validate the solution and the study design for the randomized phase. In the subsequent randomized phase, subjects will be randomized in a 1:1 ratio to (1) Continuous remote physiological monitoring using Biovitals® Sentinel platform (Intervention group) or (2) Usual care (Control group) during the 14 day-quarantine period. (Figure 1)

In addition to daily body temperature monitoring and symptom surveillance in the Control group, subjects randomized to the Intervention group will wear a multi-sensor-based wearable armband biosensor, Everion®, during the quarantine period. Everion® is a wearable vital sign monitor capable to track heart rate, heart rate variability, blood oxygen saturation, blood pulse wave, respiration rate under rest, skin blood perfusion, activity, steps, skin temperature, barometric pressure and electrodermal activity. The wearable monitors will be worn for 22-23 hours per day and be recharged while bathing or showering. In addition, patients will be instructed to

report their symptoms and record their cough sounds using the specially-designed smartphone application daily. The physiological parameters obtained will be automatically transferred in real time through a specially-designed smartphone application to secured cloud storage for processing using Biovitals® Analytics Engine and display the results on a web-based clinicians dashboard for review. (Figure 2 and Figure 3) Biovitals® Analytics Engine processed these multiple physiology parameters and detects subtle physiology changes precursor to critical events thereby enabling clinicians to review and intervene. As an additional safety measure specific alert thresholds for individual physiological parameters have also been set. Study investigators will remotely review individual subjects' physiological parameters every 4 hours, and order diagnostic tests for COVID-19 infection through instant communication (electronic communication and/or phone). In addition, after initial run-in phase together with adequate number of confirmed COVID-19, physiological data will be used to enhance Biovitals® prediction model for COVID-19 infection using machine learning technology.

Outcomes

The primary outcome measure is the time to detection of COVID-19 infection using nasopharyngeal sampling for COVID-19 RT-PCR.

The secondary outcomes include wearable device adherence, sensitivity and specificity of Biovitals® Sentinel in identifying COVID-19 subjects, viral load of COVID-19 using nasopharyngeal sampling for RT-PCR at diagnosis, cross-infection rate within family cluster, length of hospital stay, length of intensive care unit stay, non-invasive

and invasive ventilation use, National Early Warning Score 2, worsening of comorbidities and mortality.

Sample size and statistical analysis

Sample size for the randomization phase will be determined based on the result from the phase I run-in period involving approximately 100 subjects. Data normality of continuous variables will be assessed using skewness statistics. Baseline characteristics of the two study groups will be compared using ANOVA, chi-square or Fisher's exact tests, as appropriate. Analysis of the primary and secondary outcomes will conform to the intention-to-treat principle. Cox regression analysis will be performed to compare the time to diagnosis of COVID-19 infection between the study groups with adjustment for potential confounders. For other secondary outcomes, the generalized estimating equations model will be used to compare the differential changes in each of the outcomes across the 14-day time points between the two study arms, with adjustment for the potential confounders.

Randomization

Patients will be randomized to Intervention group or Control group using a computer-generated random number to derive allocation sequence prior to enrollment in the study. Study staff responsible for enrollment will be informed of randomization assignment after entering information of subjects to a designated computer system. For any subject found to be ineligible for the study after randomization, the original assignment will be re-assigned to the next eligible subject. Subjects and clinicians will not be blinded to the randomization assignment. Data staff responsible for data entry will be blinded from randomization assignment.

Data collection and management

After enrollment, each subject will be assigned a unique identifier to be used in database. Data will be entered by study staff and data accuracy will be verified by study principal investigator. Data quality control measures include queries to identify missing data, outliers and discrepancies. The database will be password protected and encrypted. Only study staff will have access to the database. Subjects who withdraw from the study will have continuous monitoring stopped, usual care continued and final outcome collected for analysis.

Data monitoring

Due to the minimal risk nature of the study, there is no external data and safety monitoring board. The principal investigator and study staff will monitor data internally and meet weekly in person or by phone to ensure the study is being proceeded as intended.

Patient and public involvement

We received input from quarantined individuals and healthcare providers which guided the design of the current study and choice of research questions. No quarantined individuals or the public were directly involved in the design of the study and choice of outcome measures. No quarantined individuals or the public will be involved in recruitment or conduct of the study. Results of the study will be disseminated to subjects, the public and the scientific community.

ETHICS AND DISSEMINATION

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol has been approved by the Institutional Review Board of The University of Hong Kong, and Hong Kong West Cluster, Hospital Authority, Hong Kong. Pending approval from the Institutional Review Board of the Department of Health, Hong Kong SAR Government, Hong Kong SAR, China. Written informed consents will be obtained from all study participants by study staff responsible for recruitment. Important protocol modifications will be conveyed to investigators, Institutional Review Board, trial registries, regulators, journals and trial participants. After enrollment, each subject will be assigned a unique identifier to be used in database. Personal identity of subjects will not be used for any public purpose, publication, or transmitted outside of the study team.

Dataset used during the study will be available from the corresponding author on reasonable request. Collaboration with other investigators interested in optimizing quarantine strategies for COVID-19 will be welcomed. The results of the trial will be published in peer-reviewed journals and presented in conferences.

DISCUSSION

Emerging in December 2019, the COVID-19 has spread at a rate far outstripping the capacity of many medical systems.(14) Traditionally, public health measures including isolation and quarantine are the cornerstone to curb the spread of infectious diseases by interrupting person-to-person transmission, and are particularly important when no specific therapeutics or vaccines are available.(6) Indeed, early detection of infected individuals amongst those with viral exposure followed by isolation would effectively

reduce overt viral shedding in the community; nonetheless, early detection can be challenging.

Symptom and fever surveillance amongst individuals with COVID-19 exposure is a commonly used method to detect infected individuals in the absence of medical testing. However, symptom declaration and intermittent body temperature measurement *per se* may not be sufficient to detect early disease progression. Indeed, up to 50% COVID-19 infected patients were so called "asymptomatic" and did not have fever until the full-blown disease. (7) Conceivably, while fever is one of cardinal symptoms specific for active infection, many other physiological alterations such as heart rate, respiratory rate, oxygen saturation, perspiration and so on may likewise indicate active infection. However, practically speaking, they are more difficult to accurately measure without medical training.

The intervention arm of current study differs from the existing symptom and fever surveillance-based quarantine program in several important aspects. The incorporation of a wide-range of physiological parameters instead of a single physiological parameter, intermittent body temperature, from skin temperature, heart rate, respiratory rate, oxygen saturation, motion activity, and so on collected on a 24/7 basis will provide a more accurate assessment of the individuals' physiological changes and increase the chance for early detection of clinical progression. (9) At the same time, the use of contemporary mobile communication technology facilitates automatic collection and transfer of physiological data. This can enhance patient compliance with the monitoring system as well as greatly shorten the time between detection of an abnormality and consequent intervention. In the past decades, wearable technology has been

increasingly used for medical diagnosis notably arrhythmia detection.(15-21) Indeed, the wide array of physiological parameters and the massive continuous dynamic physiological data particularly when analyzed in an integrative approach using artificial intelligence technology, can in principle provide a much in-depth understanding of disease process, thereby enhancing management. Nonetheless, such potentials have not been fully explored in the real-world disease management. In short term, the results of the current study may provide insights of the disease progression of COVID-19 infection and possible ways to reduce the disease spread. In long term, the study may demonstrate an important example of how new technologies can be incorporated into existing medical service.

Author Contributions:

CWS, IFNH, CKW, RCFT and KSR contributed to the conception and design of the study. DTYH, ART, TKWT, MZ and MOYT contributed to the acquisition of data. Data analysis and interpretation will be conducted by CWS, IFNH, CKW, RCFT, KSR, GC, SCC and YML. CWS, IFNH and CKW wrote first draft of the protocol. ART, MZ and YML revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published.

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None.

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The Everion® wearable devices are donated by Biofourmis Singapore, and Harmony ltd. The mobile phone and cellular data are supported by PCCW ltd.

Declaration of interest:

None.

Legends:

Figure 1: Study flow.

Figure 2: (A) Wearable device and Home screen of the dedicated smartphone app; (B) App screen for symptom surveillance; and (C) App screen for cough sound recording.

Figure 3: Web-based dashboard for clinicians.

Table 1. Inclusion and exclusion criteria

Inclusion criteria • Age ≥ 18 years • Asymptomatic for COVID-19 pneumonia • With close COVID-19 contact under mandatory quarantine at destinated facilities in Hong Kong • Voluntarily agrees to participate by providing written informed consent
Exclusion criteria • Symptoms suggestive of COVID-19 infection including fever, upper respiratory symptoms, and/or gastrointestinal symptoms at recruitment. • Confirmed COVID-19 infection • Planned laboratory test for COVID-19 • Inability or refusal to provide inform consent • Lack of skills in operating simple electronic devices

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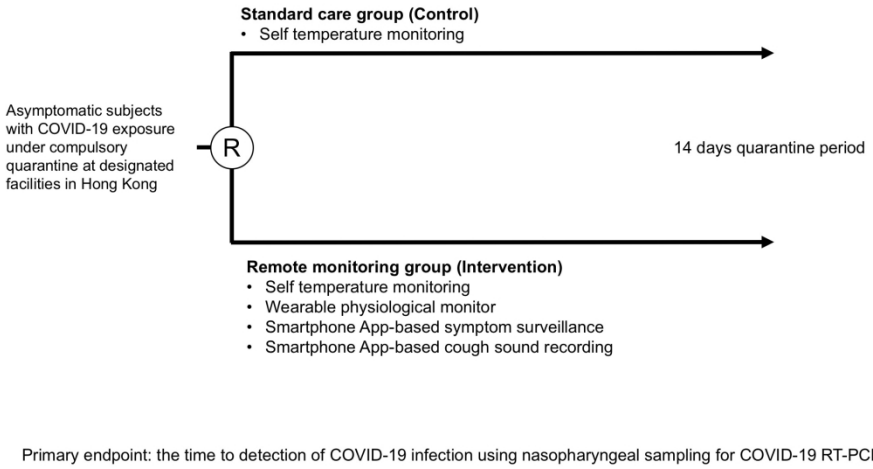

Figure 1

Figure 1: Study flow.

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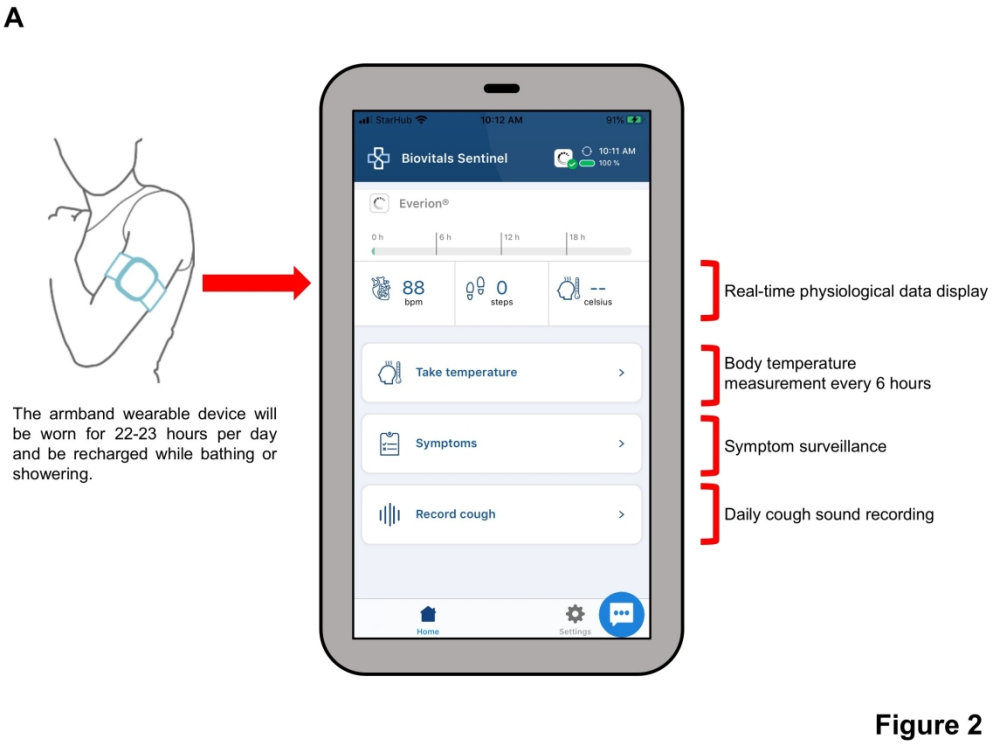

Figure 2

Figure 2: (A) Wearable device and Home screen of the dedicated smartphone app.

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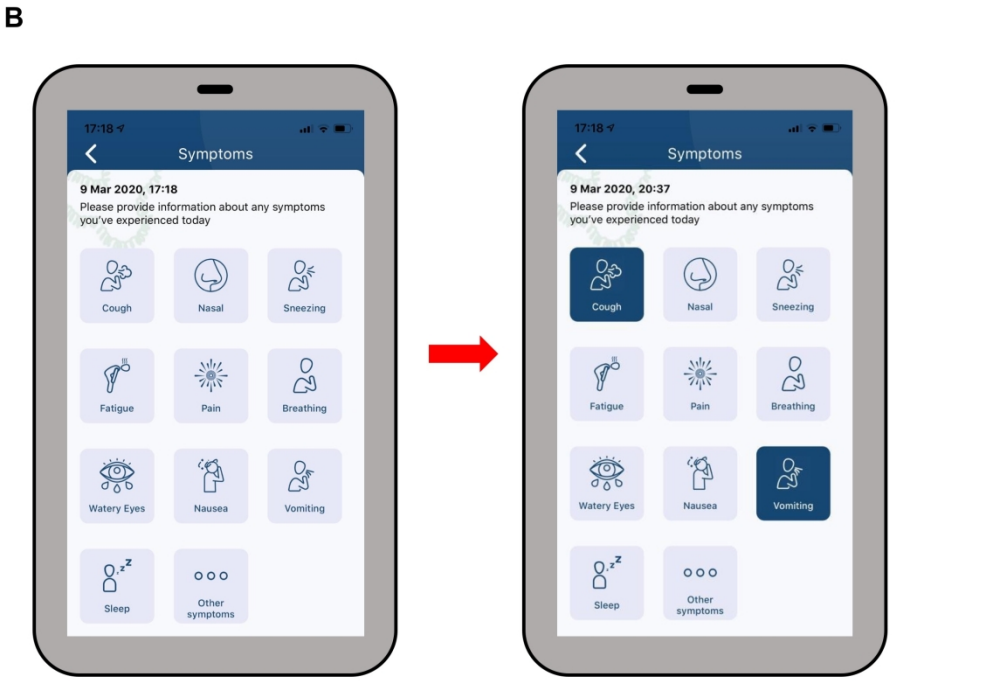

Figure 2

Figure 2: (B) App screen for symptom surveillance.

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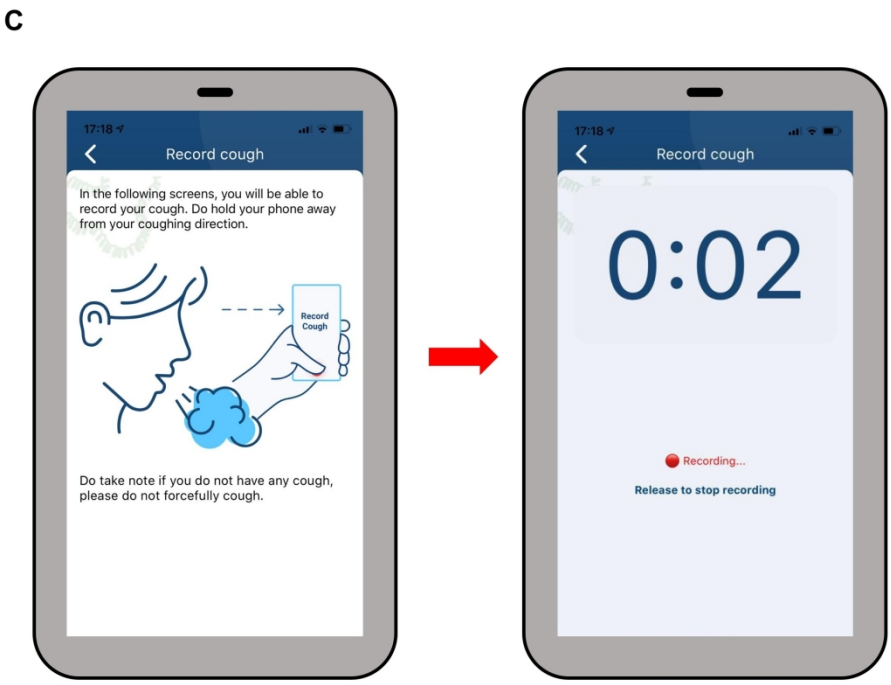

Figure 2

Figure 2: (C) App screen for cough sound recording.

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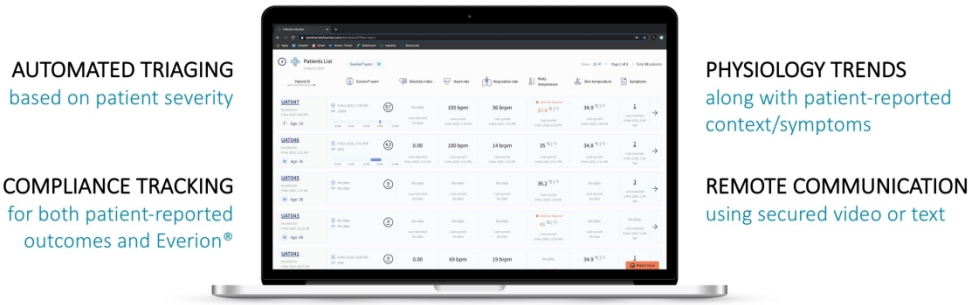

Figure 3

Figure 3: Web-based dashboard for clinicians.

254x190mm (240 x 240 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
	2b	All items from the World Health Organization Trial Registration Data Set	Uploaded to BMJ Open server
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	15

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 11, 15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-9

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set

1. Primary Registry and Trial Identifying Number	Clinicaltrial.gov Registration submitted, pending approval
2. Date of Registration in Primary Registry	Clinicaltrial.gov Registration submitted, pending approval
3. Secondary Identifying Numbers	None
4. Source(s) of Monetary or Material Support	The Everion® wearable devices are donated by Biofourmis Singapore, and Harmony ltd. The mobile phone and cellular data are supported by PCCW ltd.
5. Primary Sponsor	None
6. Secondary Sponsor(s)	None
7. Contact for Public Queries	Professor Ivan FN Hung MD Division of Infectious Diseases, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China. Tel: (852) 2255 4049 Fax: (852) 2818 6304

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9. Public Title	Using Biovitals® Sentinel to Monitor Disease Progression in Subjects Quarantined for Suspected COVID-19
10. Scientific Title	Using Biovitals® Sentinel to Monitor Disease Progression in Subjects Quarantined for Suspected COVID-19
11. Countries of Recruitment	Hong Kong, China
12. Health Condition(s) or Problem(s) Studied	Coronavirus Disease 2019 (COVID-19)
13. Intervention	Intervention Arm: Continuous physiological monitoring using Biovitals platform including (1) Armband with multiple physiological sensor, (2) Remote monitoring, and (3) Analytic platform. The armband will be worn for 23 hours a day and off for 1 hour during showering for recharging the battery.

	Control Arm: Standard Care
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: Age ≥ 18 years Asymptomatic for COVID-19 pneumonia With close COVID-19 contact under mandatory quarantine at destinated facilities in Hong Kong Voluntarily agrees to participate by providing written informed consent Exclusion criteria: Symptoms suggestive of COVID-19 infection including fever, upper respiratory symptoms, and/or gastrointestinal symptoms at recruitment. Confirmed COVID-19 infection Planned laboratory test for COVID-19 Inability or refusal to provide inform consent Lack of skills in operating simple electronic devices
15. Study Type	Study Type: Interventional Participants Allocation: Randomized (details in protocol manuscript) Intervention Model: Parallel Assignment

	Masking: None (Open Label) Primary Purpose: Diagnostic
16. Date of First Enrollment	March 16, 2020
17. Target Sample Size	200 – 1000
18. Recruitment Status	Pending
19. Primary Outcome(s)	Time to diagnosis of COVID-19 by RT-PCR in subjects Metric: Time from quarantine to diagnosis of COVID-19 Time Frame: within 14 days
20. Key Secondary Outcome(s)	1. Compliance to complete the study Metric: Percentage of device usage time Time Frame: within 14 days Sensitivity and specificity of Biovitals® Sentinel to identify COVID-19 positive subjects Metric: Sensitivity and specificity of Biovitals® Sentinel to identify COVID-19 positibe subjects Time Frame: within 14 days Viral load of COVID-19 positive subjects Metric: COVID-19 viral load by RT-PCR Time Frame: On day of COVID-19 diagnosis

	Cross infection rate within the family cluster Metric: Percentage of family members infected Time Frame: within 14 days Length of hospital stay of positive subjects Metric: Length of hospital stay Time Frame: 1 year at study completion Length of ICU stay of positive patients Metric: Length of ICU stay Time Frame: 1 year at study completion Non-invasive and invasive ventilatory support Metric: Percentage of COVID-19 positive patients requiring non-invasive and invasive ventilatory support Time Frame: 1 year at study completion National Early Warning Score 2 rating of COVID-19 positive patients Metric: National Early Warning Score 2 rating Time Frame: On day of COVID-19 diagnosis

	Worsening of comorbidities Metric: Worsening of comorbidities Time Frame: 1 year at study completion Mortality Metric: Mortality Time Frame: 1 year at study completion

BMJ Open

Protocol for Randomized Controlled Trial of Artificial Intelligence Mobile Health Platform for Early Detection of COVID-19 in Quarantine Subjects using Wearable Physiology Biosensor

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Protocol for Randomized Controlled Trial of Artificial Intelligence Mobile Health Platform for Early Detection of COVID-19 in Quarantine Subjects using Wearable Physiology Biosensor

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ABSTRACT

Introduction: There is an outbreak of Coronavirus Disease 2019 (COVID-19) worldwide. To date, there is no specific therapy or vaccine, thereby rigorous implementation of traditional public health measures including isolation and quarantine remain the most effective tools to control the outbreak. Current quarantine approach for asymptomatic individuals with COVID-19 contacts requires temperature and symptom surveillance. The intermittent nature and high dependency on self-discipline of the approach undermine its practicality. Advances in multi-sensor technologies made it possible to continuously monitor physiological parameters using wearable biosensors with a variety of form-factors.

Objective: To explore the potential of continuous multi-parameter physiological monitoring using a wearable biosensor in detecting early clinical progression of COVID-19.

Method: This randomized controlled open-labelled trial will involve 200 to 1,000 asymptomatic subjects with close COVID-19 contact under mandatory quarantine at designated facilities in Hong Kong. Subjects will be randomized to receive a remote monitoring strategy (intervention group) or standard strategy (control group) in a 1:1 ratio during the 14 day-quarantine period. In addition to fever and symptom surveillance in the control, subjects in the intervention group will wear a wearable biosensor on their arm to continuously monitor skin temperature, respiratory rate, blood pressure, pulse rate, blood oxygen saturation and daily activities, which is transferred in real time via Bluetooth to a smartphone application called Biovitals® Sentinel. The data is then processed using a cloud-based multi-variate physiology analytics engine

called Biovitals® to detect subtle physiology changes which is displayed on a web-based dashboard for clinicians review. The primary outcome is the time to diagnosis of COVID-19.

Ethics and Dissemination: Applied for approval from institutional review board at the study sites. Results will be published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Automatic physiological data collection by wearable biosensor that do not rely on self-discipline of quarantined subjects.
- Large number of physiological parameters monitored, including skin temperature, respiratory rate, blood pressure, pulse rate, blood oxygen saturation and daily activities, instead of relying solely on temperature measurement.
- Continuous data collection and analysis throughout the day.
- Limited by being single-center based and exploratory in nature.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) emerged in December 2019,(1-4) and in mere few months has spread to more than 104 countries, resulting in an outbreak of viral pneumonia worldwide. As of March 12, 2020, the virus has reportedly caused 127,863 infections and 4,718 deaths globally.(5) The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on January 30, 2020 and further characterized it as pandemic on March 11, 2020. As there has yet been specific therapeutic or vaccine for the condition, rigorous implementation of traditional public health measures including isolation, quarantine, social distancing, and community containment is the principle strategy to control the COVID-19 epidemic.(6) In addition to isolation of confirmed COVID-19 infected patients from non-infected population, it is equally if not more important to quarantine asymptomatic individuals with possible exposure to COVID-19 in order to reduce the viral spread. Indeed, quarantine measures have been initiated in many countries and regions, which restrict movement of asymptomatic individuals with COVID-19 exposure often with fever and symptom surveillance at home or designated facilities for the presumed incubation period (14 days). While conceptually attractive, the intermittent nature and high dependency of self-discipline for body temperature and symptom surveillance undermine the practicality and effectiveness of the approach. Furthermore, it has been reported that as many as 50% of COVID-19 infected patients had no fever until developing full-blown disease,(3, 7) thereby body temperature surveillance *per se* may not be sufficient to detect early disease progression.

In the past few decades, advances in sensor technology miniaturize electronic physiological sensors that could be incorporated into wearable devices allowing

continuous monitoring of physiological parameters such as skin temperature, heart rate, respiratory rate, oxygen saturation, perspiration and activity of ambulatory subjects in a 24/7 basis.(8, 9) Together with current telecommunication platform capable of instantaneous and multi-directional massive data transfer, it is possible to remotely monitor a large number of individual subjects' physiological parameters in a real-time manner, and relay to managing physicians for timely intervention. Nonetheless, such potentials have not been fully explored in the real-world disease management. The current study will assess the impact of remote continuous monitoring in asymptomatic subjects with COVID-19 exposure under mandatory quarantine at designated facilities in Hong Kong using Biovitals® Sentinel Platform. The platform consists of continuous real-time physiological monitoring using a clinical-grade wearable biosensor worn on the upper arm called Everion® (Biofourmis, Singapore) and an artificial intelligence-powered physiology analytical platform Biovitals® (Biofourmis, Singapore) to detect progression of disease. The research hypothesis is that continuous physiological data collected using Biovitals® Sentinel and patient reported outcomes processed through a cloud-based analytics platform, Biovitals®, will allow detection of physiology changes (and other clinically meaningful alerts) that would indicate early clinical progression in quarantined subjects with COVID-19 exposure.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).(10, 11) The underlying protocol follows the Consolidated Standards of Reporting Trials (CONSORT).(12, 13) Registration on clinicaltrials.gov has been submitted and pending approval.

Study Design and Participants

This is a prospective, randomized controlled, open-labeled study. Asymptomatic subjects with COVID-19 exposure at designated facilities under the compulsory quarantine measure introduced on February 8, 2020 in Hong Kong, fulfilling inclusion and exclusion criteria of the study will be invited to participate in this study. Table 1 summarizes the inclusion and exclusion criteria.

There will be 2 phases of the subject recruitment. The initial run-in phase is a single arm, open-label study design confirmation phase with approximately 100 subjects. All subjects will undergo remote physiological monitoring using Biovitals® Sentinel platform. The data collected from the platform and clinical data from health system will be used to validate the solution and the study design for the randomized phase. In the subsequent randomized phase, subjects will be randomized in a 1:1 ratio to (1) Continuous remote physiological monitoring using Biovitals® Sentinel platform (Intervention group) or (2) Usual care (Control group) during the 14 day-quarantine period. (Figure 1)

In addition to daily body temperature monitoring and symptom surveillance in the Control group, subjects randomized to the Intervention group will wear a multi-sensor-based wearable armband biosensor, Everion®, during the quarantine period. Everion® is a wearable vital sign monitor capable to track heart rate, heart rate variability, blood oxygen saturation, blood pulse wave, respiration rate under rest, skin blood perfusion, activity, steps, skin temperature, barometric pressure and electrodermal activity. The wearable monitors will be worn for 22-23 hours per day and be recharged while bathing or showering. In addition, patients will be instructed to

report their symptoms and record their cough sounds using the specially-designed smartphone application daily. The physiological parameters obtained will be automatically transferred in real time through a specially-designed smartphone application to secured cloud storage for processing using Biovitals® Analytics Engine and display the results on a web-based clinicians dashboard for review. (Figure 2, Figure 3, Figure 4 and Figure 5) Biovitals® Analytics Engine processed these multiple physiology parameters and detects subtle physiology changes precursor to critical events thereby enabling clinicians to review and intervene. As an additional safety measure specific alert thresholds for individual physiological parameters have also been set. Study investigators will remotely review individual subjects' physiological parameters every 4 hours, and order diagnostic tests for COVID-19 infection through instant communication (electronic communication and/or phone). In addition, after initial run-in phase together with adequate number of confirmed COVID-19, physiological data will be used to enhance Biovitals® prediction model for COVID-19 infection using machine learning technology.

Outcomes

The primary outcome measure is the time to detection of COVID-19 infection using nasopharyngeal sampling for COVID-19 RT-PCR.

The secondary outcomes include wearable device adherence, sensitivity, specificity, positive predictive value, negative predictive value and the area under the receiver operating characteristic (ROC) curve of Biovitals® Sentinel in identifying COVID-19 subjects, viral load of COVID-19 using nasopharyngeal sampling for RT-PCR at diagnosis, cross-infection rate within family cluster, length of hospital stay, length of

intensive care unit stay, non-invasive and invasive ventilation use, National Early Warning Score 2, worsening of comorbidities and mortality.

Sample size and statistical analysis

Sample size for the randomization phase will be determined based on the result from the phase I run-in period involving approximately 100 subjects. Sample size of run-in period was determined by convenience sampling due to the lack of previous study with the research theme. To explore and estimate effect of longitudinally measured clinical and physiological data on time-to-event of primary and secondary outcome, joint modelling of longitudinal and time-to-event data analysis, and other statistical and/or machine learning-based methods will be utilized. Data normality of continuous variables will be assessed using skewness statistics. Baseline characteristics of the two study groups will be compared using ANOVA, chi-square or Fisher's exact tests, as appropriate. Analysis of the primary and secondary outcomes will conform to the intention-to-treat principle. Cox regression analysis will be performed to compare the time to diagnosis of COVID-19 infection between the study groups with adjustment for potential confounders. For other secondary outcomes, the generalized estimating equations model will be used to compare the differential changes in each of the outcomes across the 14-day time points between the two study arms, with adjustment for the potential confounders.

Randomization

Patients will be randomized to Intervention group or Control group using a computer-generated random number to derive allocation sequence prior to enrollment in the study. Study staff responsible for enrollment will be informed of randomization assignment

after entering information of subjects to a designated computer system. For any subject found to be ineligible for the study after randomization, the original assignment will be re-assigned to the next eligible subject. Subjects and clinicians will not be blinded to the randomization assignment. Data staff responsible for data entry will be blinded from randomization assignment.

Data collection and management

After enrollment, each subject will be assigned a unique identifier to be used in database. Data will be entered by study staff and data accuracy will be verified by study principal investigator. Data quality control measures include queries to identify missing data, outliers and discrepancies. The database will be password protected and encrypted. Only study staff will have access to the database. Subjects who withdraw from the study will have continuous monitoring stopped, usual care continued and final outcome collected for analysis.

Data monitoring

Due to the minimal risk nature of the study, there is no external data and safety monitoring board. The principal investigator and study staff will monitor data internally and meet weekly in person or by phone to ensure the study is being proceeded as intended.

Patient and public involvement

We received input from quarantined individuals and healthcare providers which guided the design of the current study and choice of research questions. No quarantined individuals or the public were directly involved in the design of the study and choice of

outcome measures. No quarantined individuals or the public will be involved in recruitment or conduct of the study. Results of the study will be disseminated to subjects, the public and the scientific community.

ETHICS AND DISSEMINATION

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol has been approved by the Institutional Review Board of The University of Hong Kong, and Hong Kong West Cluster, Hospital Authority, Hong Kong. The study protocol for run-in phase has been approved by the Institutional Review Board of the Department of Health, Hong Kong SAR Government, Hong Kong SAR, China. Approval for the study protocol for the randomization phase is still pending from the Institutional Review Board of the Department of Health, Hong Kong SAR Government, Hong Kong SAR, China. Written informed consents will be obtained from all study participants by study staff responsible for recruitment (Supplementary Files 1 and 2). Important protocol modifications will be conveyed to investigators, Institutional Review Board, trial registries, regulators, journals and trial participants. After enrollment, each subject will be assigned a unique identifier to be used in database. Personal identity of subjects will not be used for any public purpose, publication, or transmitted outside of the study team.

Dataset used during the study will be available from the corresponding author on reasonable request. Collaboration with other investigators interested in optimizing quarantine strategies for COVID-19 will be welcomed. The results of the trial will be published in peer-reviewed journals and presented in conferences.

DISCUSSION

Emerging in December 2019, the COVID-19 has spread at a rate far outstripping the capacity of many medical systems.(14) Traditionally, public health measures including isolation and quarantine are the cornerstone to curb the spread of infectious diseases by interrupting person-to-person transmission, and are particularly important when no specific therapeutics or vaccines are available.(6) Indeed, early detection of infected individuals amongst those with viral exposure followed by isolation would effectively reduce overt viral shedding in the community; nonetheless, early detection can be challenging.

Symptom and fever surveillance amongst individuals with COVID-19 exposure is a commonly used method to detect infected individuals in the absence of medical testing. However, symptom declaration and intermittent body temperature measurement *per se* may not be sufficient to detect early disease progression. Indeed, up to 50% COVID-19 infected patients were so called "asymptomatic" and did not have fever until the full-blown disease. (7) Conceivably, while fever is one of cardinal symptoms specific for active infection, many other physiological alterations such as heart rate, respiratory rate, oxygen saturation, perspiration and so on may likewise indicate active infection. However, practically speaking, they are more difficult to accurately measure without medical training.

The intervention arm of current study differs from the existing symptom and fever surveillance-based quarantine program in several important aspects. The incorporation of a wide-range of physiological parameters instead of a single physiological parameter, intermittent body temperature, from skin temperature, heart rate, respiratory rate,

oxygen saturation, motion activity, and so on collected on a 24/7 basis will provide a more accurate assessment of the individuals' physiological changes and increase the chance for early detection of clinical progression. (9) At the same time, the use of contemporary mobile communication technology facilitates automatic collection and transfer of physiological data. This can enhance patient compliance with the monitoring system as well as greatly shorten the time between detection of an abnormality and consequent intervention. In the past decades, wearable technology has been increasingly used for medical diagnosis notably arrhythmia detection.(15-21) Indeed, the wide array of physiological parameters and the massive continuous dynamic physiological data particularly when analyzed in an integrative approach using artificial intelligence technology, can in principle provide a much in-depth understanding of disease process, thereby enhancing management. Nonetheless, such potentials have not been fully explored in the real-world disease management. In short term, the results of the current study may provide insights of the disease progression of COVID-19 infection and possible ways to reduce the disease spread. In long term, the study may demonstrate an important example of how new technologies can be incorporated into existing medical service.

Author Contributions:

CWS, IFNH, CKW, RCFT and KSR contributed to the conception and design of the study. DTYH, ART, MZ and MOYT contributed to the acquisition of data. Data analysis and interpretation will be conducted by CWS, IFNH, CKW, RCFT, KSR, GC, SCC and YML. CWS, IFNH and CKW wrote first draft of the protocol. ART, MZ and YML revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published.

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The Everion® wearable devices are donated by Biofourmis Singapore, and Harmony ltd. The mobile phone and cellular data are supported by PCCW ltd.

Declaration of interest:

RCFT is employed by Harmony Medical Inc., which donated Everion® wearable devices. GC and SSC are employed by Biofourmis, which donated Everion® wearable devices.

Legends:

Figure 1: Study flow.

Figure 2: Wearable device and Home screen of the dedicated smartphone app.

Figure 3: Smartphone application screen for symptom surveillance.

Figure 4: Smartphone application screen for cough sound recording.

Figure 5: Web-based dashboard for clinicians.

Supplementary Files:

Supplementary File 1: Consent form of the run-in phase in English

Supplementary File 2: Consent form of the randomization phase in English

Table 1. Inclusion and exclusion criteria

Inclusion criteria • Age ≥ 18 years • Asymptomatic for COVID-19 pneumonia • With close COVID-19 contact under mandatory quarantine at destinated facilities in Hong Kong • Voluntarily agrees to participate by providing written informed consent
Exclusion criteria • Symptoms suggestive of COVID-19 infection including fever, upper respiratory symptoms, and/or gastrointestinal symptoms at recruitment. • Confirmed COVID-19 infection • Planned laboratory test for COVID-19 • Inability or refusal to provide inform consent • Lack of skills in operating simple electronic devices

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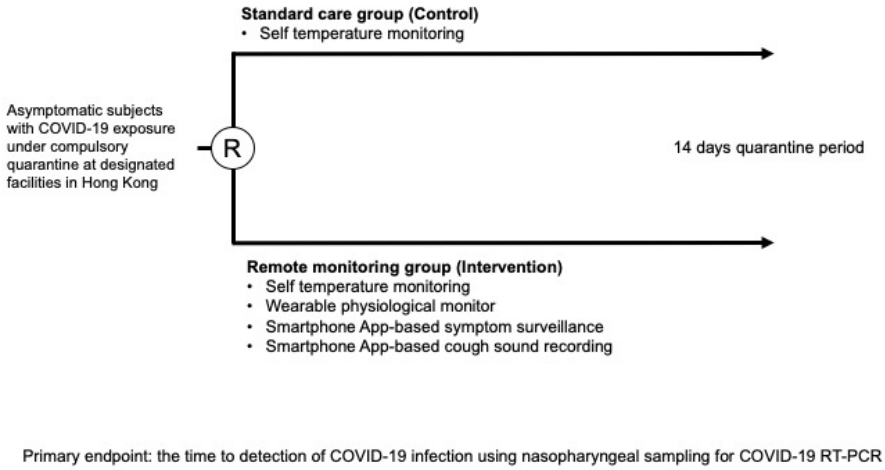

Figure 1

Figure 1: Study flow.

254x190mm (72 x 72 DPI)

Figure 2

Figure 2: Wearable device and Home screen of the dedicated smartphone app.

254x190mm (72 x 72 DPI)

Figure 3

Figure 3: Smartphone application screen for symptom surveillance.

254x190mm (72 x 72 DPI)

Figure 4

Figure 4: Smartphone application screen for cough sound recording.

254x190mm (72 x 72 DPI)

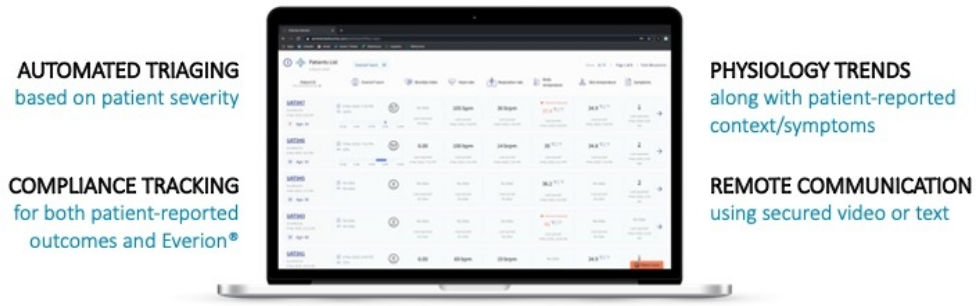

Figure 5

Figure 5: Web-based dashboard for clinicians.

254x190mm (72 x 72 DPI)

CONSENT FORM
(Run-in Phase)

Study Name:	Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19
Version No.:	COVID19_Biovitals_Consent_2_run_in_en (17/03/2020)
Protocol No:	COVID19_Biovitals_Protocol_1
Study Site:	Hospitals of the Hospital Authority, and Quarantine Sites of Hong Kong SAR Government
Study Doctors:	Prof HUNG Fan Ngai Ivan and Prof. SIU Chung Wah David

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You are being invited to take part in a research study. Before you decide, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask the study doctor or research staff any questions you may have before signing the attached consent form.

About This Study

The purpose of our study is to explore the potential of state-of-the-art wearable technology for remote monitoring of patients with suspected COVID-19 infection in order to achieve early diagnosis of the infection and prompt identification of complication to allow timely management.

Why have I been chosen?

You are considered high risk from having COVID-19, a condition associated with significant morbidity and mortality. Early diagnosis of the infection and prompt identification of complication would allow delivery of timely management, therefore you are invited into our study to undergo remote monitoring with wearable technology. We plan to recruit a total of 100 patients.

What will happen to me if I take part?

You will receive a Bioviotion® armband with multiple sensors for telemonitoring of your health status.

What are the benefits of participating?

Taking part in this study may or may not make your health better. Information from this study will help doctors learn more about the value of using remote monitoring with

wearable technology. This information will help patients in the future.

What if something goes wrong?

In the unlikely event of harm resulting directly from your participation in this study, medical treatment will be available. There are no special compensation arrangements provided to you. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you. If you have any queries related to the insurance coverage from your own insurer(s) for your participation in the study, please discuss with your insurance consultant.

What are the alternatives for treatment?

Your participation in this study is voluntary. You may choose not to participate in this study. You may decline to participate by simply telling your doctor. If you decide not to participate in this study, your follow-up appointments will be scheduled and conducted as directed by your physician. Your decision will not in any way affect your medical care or treatment.

What if new information becomes available?

During the course of the study, if any new information becomes available that may relate to your willingness to continue to participate in this study, your research doctor will tell you about it and discuss with you. You also have the rights of access to personal data and known study results, if and when needed.

Will my participation in this study be kept confidential?

As a subject in this research study, all your information will be kept confidential. Your name or your personal identity will not be used for any public purpose, publication, or transmitted outside of the medical centre.

Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance, Cap 486, you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. By

consenting to participate in this study, you expressly authorize the access to, the use of, and the retention of your personal data by the Investigator and members of his research team, and HKU/HA HKW IRB for the purposes and in the manner described in this informed consent process.

For any query, you should consult the Privacy Commissioner for Privacy Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

Who should I contact if have questions?

If you have any questions regarding this study, you may contact Prof. SIU Chung Wah David or Prof FUNG Fan Ngai Ivan at XXXXXXXX. If you have any queries regarding your rights in the study, you may contact the Secretary of Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster at 2255 4086.

By signing below, I agree that:

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

Title of the Project: Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19

Patient Identification Number for this trial: _____

Participant's Signature: _____
Participant's Name: _____
Date: _____

Investigator's Signature: _____
Investigator's Name: _____
Date: _____

Witness's Signature: _____
Witness's Name: _____
Date: _____

CONSENT FORM
(Randomization Phase)

Study Name:	Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19
Version No.:	COVID19_Biovitals_Consent_2_randomization_en (17/03/2020)
Protocol No:	COVID19_Biovitals_Protocol_1
Study Site:	Hospitals of the Hospital Authority, and Quarantine Sites of Hong Kong SAR Government
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The purpose of our study is to explore the potential of state-of-the-art wearable technology for remote monitoring of patients with suspected COVID-19 infection in order to achieve early diagnosis of the infection and prompt identification of complication to allow timely management.

Why have I been chosen?

You are considered high risk from having COVID-19, a condition associated with significant morbidity and mortality. Early diagnosis of the infection and prompt identification of complication would allow delivery of timely management, therefore you are invited into our study to undergo remote monitoring with wearable technology. We plan to recruit a total of 200 patients.

What will happen to me if I take part?

You will be randomized to receive standard of care or addition of Bioviotion® armband with multiple sensors for telemonitoring of your health status. If clinicians detected abnormality from your measured parameters, further medical investigation or intervention might be arranged.

What are the benefits of participating?

Taking part in this study may or may not make your health better. Information from this study will help doctors learn more about the value of using remote monitoring with wearable technology. This information will help patients in the future.

What if something goes wrong?

In the unlikely event of harm resulting directly from your participation in this study, medical treatment will be available. There are no special compensation arrangements provided to you. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you. If you have any queries related to the insurance coverage from your own insurer(s) for your participation in the study, please discuss with your insurance consultant.

What are the alternatives for treatment?

Your participation in this study is voluntary. You may choose not to participate in this study. You may decline to participate by simply telling your doctor. If you decide not to participate in this study, your follow-up appointments will be scheduled and conducted as directed by your physician. Your decision will not in any way affect your medical care or treatment.

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Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance, Cap 486, you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the

collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. By consenting to participate in this study, you expressly authorize the access to, the use of, and the retention of your personal data by the Investigator and members of his research team, and HKU/HA HKW IRB for the purposes and in the manner described in this informed consent process.

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2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

Title of the Project: Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19

Patient Identification Number for this trial: _____

Participant's Signature: _____
Participant's Name: _____
Date: _____

Investigator's Signature: _____
Investigator's Name: _____
Date: _____

Witness's Signature: _____
Witness's Name: _____
Date: _____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
	2b	All items from the World Health Organization Trial Registration Data Set	Uploaded to BMJ Open server
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	15

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 11, 15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-9

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Files 1, 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set

1. Primary Registry and Trial Identifying Number	Clinicaltrial.gov Registration submitted, pending approval
2. Date of Registration in Primary Registry	Clinicaltrial.gov Registration submitted, pending approval
3. Secondary Identifying Numbers	None
4. Source(s) of Monetary or Material Support	The Everion® wearable devices are donated by Biofourmis Singapore, and Harmony ltd. The mobile phone and cellular data are supported by PCCW ltd.
5. Primary Sponsor	None
6. Secondary Sponsor(s)	None
7. Contact for Public Queries	Professor Ivan FN Hung MD Division of Infectious Diseases, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China. Tel: (852) 2255 4049 Fax: (852) 2818 6304

	E-mail: ivanhung@hku.hk
8. Contact for Scientific Queries	Professor Ivan FN Hung MD Division of Infectious Diseases, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China. Tel: (852) 2255 4049 Fax: (852) 2818 6304 E-mail: ivanhung@hku.hk
9. Public Title	Using Biovitals® Sentinel to Monitor Disease Progression in Subjects Quarantined for Suspected COVID-19
10. Scientific Title	Using Biovitals® Sentinel to Monitor Disease Progression in Subjects Quarantined for Suspected COVID-19
11. Countries of Recruitment	Hong Kong, China
12. Health Condition(s) or Problem(s) Studied	Coronavirus Disease 2019 (COVID-19)
13. Intervention	Intervention Arm: Continuous physiological monitoring using Biovitals platform including (1) Armband with multiple physiological sensor, (2) Remote monitoring, and (3) Analytic platform. The armband will be worn for 23 hours a day and off for 1 hour during showering for recharging the battery.

	Control Arm: Standard Care
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: Age ≥ 18 years Asymptomatic for COVID-19 pneumonia With close COVID-19 contact under mandatory quarantine at destinated facilities in Hong Kong Voluntarily agrees to participate by providing written informed consent Exclusion criteria: Symptoms suggestive of COVID-19 infection including fever, upper respiratory symptoms, and/or gastrointestinal symptoms at recruitment. Confirmed COVID-19 infection Planned laboratory test for COVID-19 Inability or refusal to provide inform consent Lack of skills in operating simple electronic devices
15. Study Type	Study Type: Interventional Participants Allocation: Randomized (details in protocol manuscript) Intervention Model: Parallel Assignment

	Masking: None (Open Label) Primary Purpose: Diagnostic
16. Date of First Enrollment	March 16, 2020
17. Target Sample Size	200 – 1000
18. Recruitment Status	Pending
19. Primary Outcome(s)	Time to diagnosis of COVID-19 by RT-PCR in subjects Metric: Time from quarantine to diagnosis of COVID-19 Time Frame: within 14 days
20. Key Secondary Outcome(s)	1. Compliance to complete the study Metric: Percentage of device usage time Time Frame: within 14 days Sensitivity and specificity of Biovitals® Sentinel to identify COVID-19 positive subjects Metric: Sensitivity and specificity of Biovitals® Sentinel to identify COVID-19 positibe subjects Time Frame: within 14 days Viral load of COVID-19 positive subjects Metric: COVID-19 viral load by RT-PCR Time Frame: On day of COVID-19 diagnosis

	Cross infection rate within the family cluster Metric: Percentage of family members infected Time Frame: within 14 days Length of hospital stay of positive subjects Metric: Length of hospital stay Time Frame: 1 year at study completion Length of ICU stay of positive patients Metric: Length of ICU stay Time Frame: 1 year at study completion Non-invasive and invasive ventilatory support Metric: Percentage of COVID-19 positive patients requiring non-invasive and invasive ventilatory support Time Frame: 1 year at study completion National Early Warning Score 2 rating of COVID-19 positive patients Metric: National Early Warning Score 2 rating Time Frame: On day of COVID-19 diagnosis

	Worsening of comorbidities Metric: Worsening of comorbidities Time Frame: 1 year at study completion Mortality Metric: Mortality Time Frame: 1 year at study completion

BMJ Open

Protocol for a Randomized Controlled Trial of an Artificial Intelligence Mobile Health Platform for Early Detection of COVID-19 in Quarantine Subjects using a Wearable Biosensor

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Manuscript ID	bmjopen-2020-038555.R2
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Complete List of Authors:	Wong, Chun Ka; University of Hong Kong, Division of Cardiology, Department of Medicine Ho, Deborah Tip-Yin ; University of Hong Kong, Division of Infectious Diseases, Department of Medicine Tam, Anthony Raymond; University of Hong Kong, Division of Infectious Diseases, Department of Medicine zhou, Mi; University of Hong Kong, Division of Cardiology, Department of Medicine LAU, Yuk-Ming; University of Hong Kong, Division of Cardiology, Department of Medicine Tang, Milky Oi-Yan; University of Hong Kong, Division of Infectious Diseases, Department of Medicine Tong, Raymond Cheuk-Fung; Harmony Medical Inc. Rajput, Kuldeep Singh ; Biofourmis Chen, Gengbo; Biofourmis, Research and Development Chan, Soon-Chee; Biofourmis, Research and Development SIU, Chung-Wah; University of Hong Kong, Division of Cardiology, Department of Medicine Hung, Ivan Fan-Ngai; University of Hong Kong, Division of Infectious Diseases, Department of Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health
Keywords:	Infection control < INFECTIOUS DISEASES, VIROLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

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Protocol for a Randomized Controlled Trial of an Artificial Intelligence Mobile Health Platform for Early Detection of COVID-19 in Quarantine Subjects using a Wearable Biosensor

[1]Chun-Ka Wong, MBBS; [2] Deborah Tip-Yin HO, MMedSc; [2]Anthony Raymond TAM, MBBS; [1]Mi ZHOU, MBBS; [1]Yuk-Ming LAU, MBBS; [2]Milky Oi-Yan TANG, MSc; [3]Raymond Cheuk-Fung TONG, MD, PhD; [4]Kuldeep Singh Rajput; [5]Gengbo Chen, PhD; [5]Soon-Chee Chan; [1]Chung-Wah SIU, MD; and [2]Ivan Fan-Ngai HUNG, MD.

Affiliations: [1]Division of Cardiology, Department of Medicine, the University of Hong Kong, Hong Kong SAR, China; [2]Division of Infectious Diseases, Department of Medicine, the University of Hong Kong, Hong Kong SAR, China; [3]Harmony Medical Inc., Hong Kong SAR, China; [4]Biofourmis, Singapore; [5]Research and Development, Biofourmis, Singapore.

Protocol Version: COVID19_Wearable_1
Protocol Date: March 13, 2020
Keywords: COVID-19, Quarantine, Wearable Device, Remote Monitoring
Wordcount: 2617

Address for Correspondence:

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E-mail: ivanhung@hku.hk

ABSTRACT

Introduction: There is an outbreak of Coronavirus Disease 2019 (COVID-19) worldwide. As there is no effective therapy or vaccine yet, rigorous implementation of traditional public health measures such as isolation and quarantine remains the most effective tool to control the outbreak. When an asymptomatic individual with COVID-19 exposure is being quarantined, it is necessary to perform temperature and symptom surveillance. As such surveillance is intermittent in nature and highly dependent on self-discipline, it has limited effectiveness. Advances in biosensor technologies made it possible to continuously monitor physiological parameters using wearable biosensors with a variety of form-factors.

Objective: To explore the potential of using wearable biosensors to continuously monitor multi-dimensional physiological parameters for early detection of COVID-19 clinical progression.

Method: This randomized controlled open-labelled trial will involve 200 to 1,000 asymptomatic subjects with close COVID-19 contact under mandatory quarantine at designated facilities in Hong Kong. Subjects will be randomized to receive a remote monitoring strategy (intervention group) or standard strategy (control group) in a 1:1 ratio during the 14 day-quarantine period. In addition to fever and symptom surveillance in the control, subjects in the intervention group will wear wearable biosensors on their arms to continuously monitor skin temperature, respiratory rate, blood pressure, pulse rate, blood oxygen saturation and daily activities. These physiological parameters will be transferred in real time to a smartphone application called Biovitals® Sentinel. These data will then be processed using a cloud-based

multi-variate physiology analytics engine called Biovitals® to detect subtle physiological changes. The results will be displayed on a web-based dashboard for clinicians' review. The primary outcome is the time to diagnosis of COVID-19.

Ethics and Dissemination: Ethical approval obtained from institutional review board at the study sites. Results will be published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Automatic physiological data collection by wearable biosensor that do not rely on self-discipline of quarantined subjects.
- Large number of physiological parameters monitored, including skin temperature, respiratory rate, blood pressure, pulse rate, blood oxygen saturation and daily activities, instead of relying solely on temperature measurement.
- Continuous data collection and analysis throughout the day.
- Limited by being single-center based and exploratory in nature.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) emerged in December 2019,(1-4) and in mere few months has spread to more than 104 countries, resulting in an outbreak of viral pneumonia worldwide. As of March 12, 2020, the virus has reportedly caused 127,863 infections and 4,718 deaths globally.(5) The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on January 30, 2020 and further characterized it as pandemic on March 11, 2020. As there is no effective therapeutic or vaccine for the condition yet, rigorous implementation of traditional public health measures such as isolation, quarantine, social distancing, and community containment is the principle strategy used to control the COVID-19 epidemic.(6) In addition to isolating patients with confirmed COVID-19 infection from the non-infected population, it is equally if not more important to quarantine asymptomatic individuals with COVID-19 exposure in order to reduce viral spread in the community. Indeed, quarantine measures have been initiated in many countries and regions to restrict movement of asymptomatic individuals with COVID-19 exposure in the community. These individuals are required to stay at home or designated quarantine facilities. In addition, they are also asked to perform fever and symptom surveillance during the presumed incubation period (14 days). However, as such surveillance is intermittent in nature and highly dependent on self-discipline, it has limited effectiveness Furthermore, it has been reported that as many as 50% of COVID-19 infected patients had no fever until developing full-blown disease,(3, 7) thereby body temperature surveillance *per se* may not be sufficient to detect early disease progression.

In the past few decades, advances in technology allows progressive miniaturization of electronic biosensors such that they can be incorporated into wearable devices to allow

continuous monitoring of physiological parameters such as skin temperature, heart rate, respiratory rate, oxygen saturation, perspiration and activity of ambulatory subjects in a 24/7 basis.(8, 9) Together with state-of-the-art telecommunication technologies that allow instantaneous and multi-directional massive data transfer, it is now possible to remotely monitor physiological parameters of a large number of subjects in real-time. These data can subsequently be relayed to physicians to allow timely intervention. Nonetheless, the potentials of utilizing wearable biosensors to improve disease management have not been fully explored in the real-world settings. The current study aim to assess the impact of performing continuous remote monitoring of asymptomatic subjects with COVID-19 exposure under mandatory quarantine at designated facilities in Hong Kong using Biovitals® Sentinel Platform. The platform consists of a clinical-grade wearable biosensor worn on the upper arm called Everion® (Biofourmis, Singapore) which allows continuous multi-dimensional physiological parameters monitoring and an artificial intelligence-powered physiology analytical platform Biovitals® (Biofourmis, Singapore) for detecting disease progression. The research hypothesis is that by collecting continuous physiological data using Biovitals® Sentinel and patient reported outcomes, and processing them with a cloud-based analytics platform, Biovitals®, it will be possible to identify physiology changes and detect other clinically meaningful alerts that will indicate early clinical progression in quarantined subjects with COVID-19 exposure.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).(10, 11) The underlying protocol follows the

Consolidated Standards of Reporting Trials (CONSORT).(12, 13) The clinical trial was registered on clinicaltrials.gov (NCT04343794).

Study Design and Participants

This is a prospective, randomized controlled, open-labeled study. Asymptomatic subjects with COVID-19 exposure at designated facilities under the compulsory quarantine measure introduced on February 8, 2020 in Hong Kong, fulfilling inclusion and exclusion criteria of the study will be invited to participate in this study. Table 1 summarizes the inclusion and exclusion criteria.

There will be 2 phases of the subject recruitment. The initial run-in phase is a single arm, open-label study design confirmation phase with approximately 100 subjects. All subjects will undergo remote physiological monitoring using Biovitals® Sentinel platform. The data collected from the platform and clinical data from health system will be used to validate the solution and the study design for the randomized phase. In the subsequent randomized phase, subjects will be randomized in a 1:1 ratio to (1) Continuous remote physiological monitoring using Biovitals® Sentinel platform (Intervention group) or (2) Usual care (Control group) during the 14 day-quarantine period. (Figure 1)

In addition to daily body temperature monitoring and symptom surveillance in the Control group, subjects randomized to the Intervention group will wear a multi-sensor-based wearable armband biosensor, Everion®, during the quarantine period. Everion® is a wearable vital sign monitor capable of tracking heart rate, heart rate variability, blood oxygen saturation, blood pulse wave, respiration rate at rest, skin

blood perfusion, activity, steps, skin temperature, barometric pressure and electrodermal activity. The wearable biosensors will be worn for 22-23 hours per day and be recharged while bathing or showering. In addition, patients will be instructed to report their symptoms and record their cough sounds using the specially-designed smartphone application daily. The physiological parameters obtained will be automatically transferred in real-time through a specially-designed smartphone application to a secured cloud storage for processing using Biovitals® Analytics Engine. The results will be displayed on a web-based clinicians dashboard for review. (Figure 2, Figure 3, Figure 4 and Figure 5) Biovitals® Analytics Engine will process these multi-dimensional physiology parameters to detect subtle physiological changes preceding critical events, thereby enabling clinicians to promptly review and intervene. As an additional safety measure, specific alert thresholds for individual physiological parameters have also been set. Study investigators will remotely review individual subject's physiological parameters every 4 hours, and order diagnostic tests for COVID-19 infection through instant communication (electronic communication and/or phone). In addition, after the initial run-in phase and having recruited adequate number of subjects with subsequently confirmed COVID-19, the collected physiological data will be used to enhance Biovitals® prediction model for COVID-19 infection using machine learning technology.

Outcomes

The primary outcome measure is the time to detection of COVID-19 infection using nasopharyngeal sampling for COVID-19 RT-PCR.

The secondary outcomes include wearable device adherence, sensitivity, specificity, positive predictive value, negative predictive value and the area under the receiver operating characteristic (ROC) curve of Biovitals® Sentinel in identifying COVID-19 subjects, viral load of COVID-19 using nasopharyngeal sampling for RT-PCR at diagnosis, cross-infection rate within family cluster, length of hospital stay, length of intensive care unit stay, non-invasive and invasive ventilation use, National Early Warning Score 2, worsening of comorbidities and mortality.

Sample size and statistical analysis

Sample size for the randomization phase will be determined based on the result from the phase I run-in period involving approximately 100 subjects. Sample size of run-in period was determined by convenience sampling due to the lack of previous study with the research theme. To explore and estimate effect of longitudinally measured clinical and physiological data on time-to-event of primary and secondary outcome, joint modelling of longitudinal and time-to-event data analysis, and other statistical and/or machine learning-based methods will be utilized. Data normality of continuous variables will be assessed using skewness statistics. Baseline characteristics of the two study groups will be compared using ANOVA, chi-square or Fisher's exact tests, as appropriate. Analysis of the primary and secondary outcomes will conform to the intention-to-treat principle. Cox regression analysis will be performed to compare the time to diagnosis of COVID-19 infection between the study groups with adjustment for potential confounders. For other secondary outcomes, the generalized estimating equations model will be used to compare the differential changes in each of the outcomes across the 14-day time points between the two study arms, with adjustment for the potential confounders.

Randomization

Patients will be randomized to Intervention group or Control group using a computer-generated random number to derive allocation sequence prior to enrollment in the study. Study staff responsible for enrollment will be informed of the randomization assignment after entering information of the subjects to a designated computer system. If a subject is found to be ineligible for the study after randomization, the original assignment will be re-assigned to the next eligible subject. Subjects and clinicians will not be blinded to the randomization assignment. Data staff responsible for data entry will be blinded from randomization assignment.

Data collection and management

After enrollment, each subject will be assigned a unique identifier to be used in database. Data will be entered by study staff and data accuracy will be verified by study principal investigator. Data quality control measures include queries to identify missing data, outliers and discrepancies. The database will be password protected and encrypted. Only study staff will have access to the database. Subjects who withdraw from the study will have continuous monitoring stopped, usual care continued and final outcome collected for analysis.

Data monitoring

Due to the minimal risk nature of the study, there is no external data and safety monitoring board. The principal investigator and study staff will monitor data internally and meet weekly in person or by phone to ensure the study is being proceeded as intended.

Patient and public involvement

We received input from quarantined individuals and healthcare providers which guided the design of the current study and choice of research questions. No quarantined individuals or the public were directly involved in the design of the study and choice of outcome measures. No quarantined individuals or the public will be involved in recruitment or conduct of the study. Results of the study will be disseminated to subjects, the public and the scientific community.

ETHICS AND DISSEMINATION

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol has been approved by the Institutional Review Board of The University of Hong Kong, and Hong Kong West Cluster, Hospital Authority, Hong Kong. Written informed consents will be obtained from all study participants by study staff responsible for recruitment (Supplementary Files 1 and 2). Important protocol modifications will be conveyed to investigators, Institutional Review Board, trial registries, regulators, journals and trial participants. After enrollment, each subject will be assigned a unique identifier to be used in database. Personal identity of subjects will not be used for any public purpose, publication, or transmitted outside of the study team.

Dataset used during the study will be available from the corresponding author on reasonable request. Collaboration with other investigators interested in optimizing quarantine strategies for COVID-19 will be welcomed. The results of the trial will be published in peer-reviewed journals and presented in conferences.

DISCUSSION

Emerging in December 2019, the COVID-19 has spread at a rate far outstripping the capacity of many medical systems.(14) Traditionally, public health measures including isolation and quarantine are the cornerstone to curb the spread of infectious diseases by interrupting person-to-person transmission, and are particularly important when no specific therapeutics or vaccines are available.(6) Indeed, early detection of infected individuals amongst those with viral exposure followed by isolation would effectively reduce overt viral shedding in the community; nonetheless, early detection can be challenging.

Symptom and fever surveillance amongst individuals with COVID-19 exposure is a commonly used method to detect infected individuals in the absence of medical testing. However, symptom declaration and intermittent body temperature measurement *per se* may not be sufficient to detect early disease progression. Indeed, up to 50% COVID-19 infected patients were so called "asymptomatic" and did not have fever until the full-blown disease. (7) Conceivably, while fever is one of cardinal symptoms specific for active infection, many other physiological alterations such as heart rate, respiratory rate, oxygen saturation, perspiration and so on may likewise indicate active infection. However, practically speaking, they are more difficult to accurately measure without medical training.

The intervention arm of current study differs from the existing symptom and fever surveillance-based quarantine program in several important aspects. By incorporating a wide-range of continuously collected physiological parameters instead of solely

relying on intermittent body temperature, it is possible to more accurately assess individual's physiological changes for detecting early disease progression. (9) At the same time, the use of contemporary mobile communication technology facilitates automatic collection and transfer of physiological data. These measures can enhance patient compliance with the monitoring system as well as greatly shorten the time between detection of an abnormality and subsequent intervention. In the past decades, wearable technology has been increasingly used for medical diagnosis, most notably in arrhythmia detection.(15-21) Indeed, by continuously collecting multi-dimensional physiological parameters and analyzing them with machine learning techniques, it is possible to acquire a much more in-depth understanding of different disease processes, which potentially allows us to improve clinical management. Nonetheless, such potentials have not been fully explored in the real-world disease management. In short term, the results of the current study may provide insights regarding detecting disease progression of COVID-19 infection through physiological data monitoring and possible ways to reduce the disease spread. In long term, the study may demonstrate an important example of how wearable technologies and machine learning techniques can be incorporated into existing medical services.

The clinical trial is limited by its single-centered characteristic and being exploratory in nature.

Author Contributions:

CWS, IFNH, CKW, RCFT and KSR contributed to the conception and design of the study. DTYH, ART, MZ and MOYT contributed to the acquisition of data. Data analysis and interpretation will be conducted by CWS, IFNH, CKW, RCFT, KSR, GC, SCC and YML. CWS, IFNH and CKW wrote first draft of the protocol. ART, MZ and YML revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published.

Funding statement:

None.

Acknowledgement:

The Everion® wearable devices are donated by Biofourmis Singapore, and Harmony ltd. The mobile phone and cellular data are supported by PCCW ltd.

Declaration of interest:

RCFT is employed by Harmony Medical Inc., which donated Everion® wearable devices. GC and SSC are employed by Biofourmis, which donated Everion® wearable devices.

Legends:

Figure 1: Study flow.

Figure 2: Wearable device and Home screen of the dedicated smartphone app.

Figure 3: Smartphone application screen for symptom surveillance.

Figure 4: Smartphone application screen for cough sound recording.

Figure 5: Web-based dashboard for clinicians.

Supplementary Files:

Supplementary File 1: Consent form of the run-in phase in English

Supplementary File 2: Consent form of the randomization phase in English

Table 1. Inclusion and exclusion criteria

Inclusion criteria • Age ≥ 18 years • Asymptomatic for COVID-19 pneumonia • With close COVID-19 contact under mandatory quarantine at destinated facilities in Hong Kong • Voluntarily agrees to participate by providing written informed consent
Exclusion criteria • Symptoms suggestive of COVID-19 infection including fever, upper respiratory symptoms, and/or gastrointestinal symptoms at recruitment. • Confirmed COVID-19 infection • Planned laboratory test for COVID-19 • Inability or refusal to provide inform consent • Lack of skills in operating simple electronic devices

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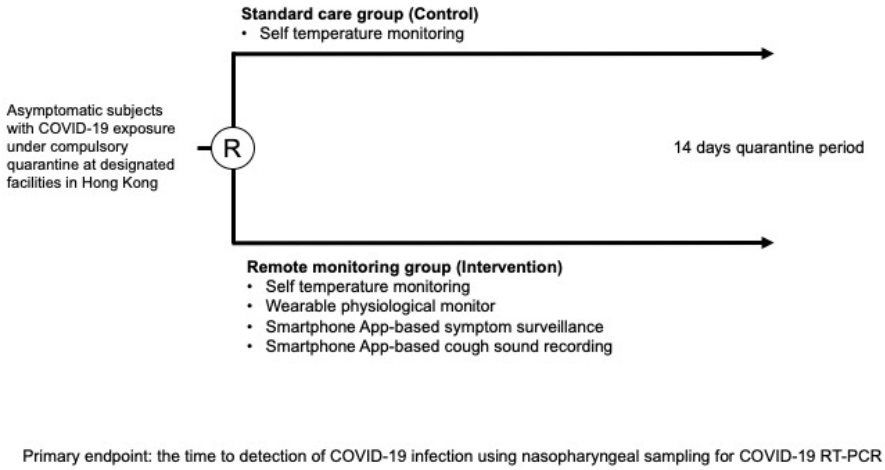

Figure 1

Figure 1: Study flow.

254x190mm (72 x 72 DPI)

Figure 2

Figure 2: Wearable device and Home screen of the dedicated smartphone app.

254x190mm (72 x 72 DPI)

Figure 3

Figure 3: Smartphone application screen for symptom surveillance.

254x190mm (72 x 72 DPI)

Figure 4

Figure 4: Smartphone application screen for cough sound recording.

254x190mm (72 x 72 DPI)

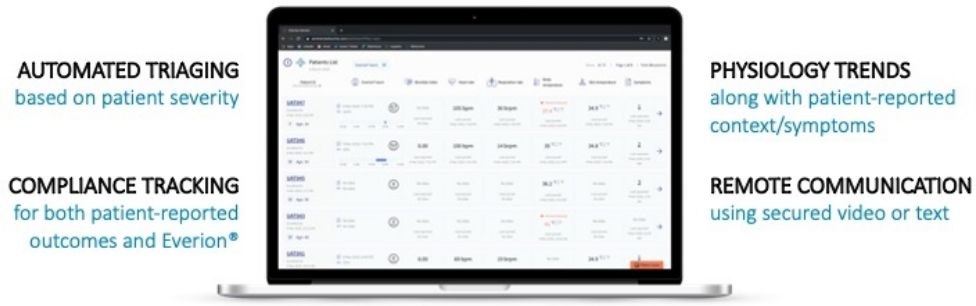

Figure 5

Figure 5: Web-based dashboard for clinicians.

254x190mm (72 x 72 DPI)

CONSENT FORM
(Run-in Phase)

Study Name:	Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19
Version No.:	COVID19_Biovitals_Consent_2_run_in_en (17/03/2020)
Protocol No:	COVID19_Biovitals_Protocol_1
Study Site:	Hospitals of the Hospital Authority, and Quarantine Sites of Hong Kong SAR Government
Study Doctors:	Prof HUNG Fan Ngai Ivan and Prof. SIU Chung Wah David

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You are being invited to take part in a research study. Before you decide, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask the study doctor or research staff any questions you may have before signing the attached consent form.

About This Study

The purpose of our study is to explore the potential of state-of-the-art wearable technology for remote monitoring of patients with suspected COVID-19 infection in order to achieve early diagnosis of the infection and prompt identification of complication to allow timely management.

Why have I been chosen?

You are considered high risk from having COVID-19, a condition associated with significant morbidity and mortality. Early diagnosis of the infection and prompt identification of complication would allow delivery of timely management, therefore you are invited into our study to undergo remote monitoring with wearable technology. We plan to recruit a total of 100 patients.

What will happen to me if I take part?

You will receive a Bioviotion® armband with multiple sensors for telemonitoring of your health status.

What are the benefits of participating?

Taking part in this study may or may not make your health better. Information from this study will help doctors learn more about the value of using remote monitoring with

wearable technology. This information will help patients in the future.

What if something goes wrong?

In the unlikely event of harm resulting directly from your participation in this study, medical treatment will be available. There are no special compensation arrangements provided to you. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you. If you have any queries related to the insurance coverage from your own insurer(s) for your participation in the study, please discuss with your insurance consultant.

What are the alternatives for treatment?

Your participation in this study is voluntary. You may choose not to participate in this study. You may decline to participate by simply telling your doctor. If you decide not to participate in this study, your follow-up appointments will be scheduled and conducted as directed by your physician. Your decision will not in any way affect your medical care or treatment.

What if new information becomes available?

During the course of the study, if any new information becomes available that may relate to your willingness to continue to participate in this study, your research doctor will tell you about it and discuss with you. You also have the rights of access to personal data and known study results, if and when needed.

Will my participation in this study be kept confidential?

As a subject in this research study, all your information will be kept confidential. Your name or your personal identity will not be used for any public purpose, publication, or transmitted outside of the medical centre.

Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance, Cap 486, you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. By

consenting to participate in this study, you expressly authorize the access to, the use of, and the retention of your personal data by the Investigator and members of his research team, and HKU/HA HKW IRB for the purposes and in the manner described in this informed consent process.

For any query, you should consult the Privacy Commissioner for Privacy Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

Who should I contact if have questions?

If you have any questions regarding this study, you may contact Prof. SIU Chung Wah David or Prof FUNG Fan Ngai Ivan at XXXXXXXX. If you have any queries regarding your rights in the study, you may contact the Secretary of Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster at 2255 4086.

By signing below, I agree that:

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

Title of the Project: Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19

Patient Identification Number for this trial: _____

Participant's Signature: _____
Participant's Name: _____
Date: _____

Investigator's Signature: _____
Investigator's Name: _____
Date: _____

Witness's Signature: _____
Witness's Name: _____
Date: _____

CONSENT FORM
(Randomization Phase)

Study Name:	Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19
Version No.:	COVID19_Biovitals_Consent_2_randomization_en (17/03/2020)
Protocol No:	COVID19_Biovitals_Protocol_1
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Why have I been chosen?

You are considered high risk from having COVID-19, a condition associated with significant morbidity and mortality. Early diagnosis of the infection and prompt identification of complication would allow delivery of timely management, therefore you are invited into our study to undergo remote monitoring with wearable technology. We plan to recruit a total of 200 patients.

What will happen to me if I take part?

You will be randomized to receive standard of care or addition of Bioviotion® armband with multiple sensors for telemonitoring of your health status. If clinicians detected abnormality from your measured parameters, further medical investigation or intervention might be arranged.

What are the benefits of participating?

Taking part in this study may or may not make your health better. Information from this study will help doctors learn more about the value of using remote monitoring with wearable technology. This information will help patients in the future.

What if something goes wrong?

In the unlikely event of harm resulting directly from your participation in this study, medical treatment will be available. There are no special compensation arrangements provided to you. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you. If you have any queries related to the insurance coverage from your own insurer(s) for your participation in the study, please discuss with your insurance consultant.

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collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. By consenting to participate in this study, you expressly authorize the access to, the use of, and the retention of your personal data by the Investigator and members of his research team, and HKU/HA HKW IRB for the purposes and in the manner described in this informed consent process.

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2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

Title of the Project: Using Biovitals® in Early Detection of Progression of Disease in Patients Suspected with COVID-19

Patient Identification Number for this trial: _____

Participant's Signature: _____
Participant's Name: _____
Date: _____

Investigator's Signature: _____
Investigator's Name: _____
Date: _____

Witness's Signature: _____
Witness's Name: _____
Date: _____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
	2b	All items from the World Health Organization Trial Registration Data Set	Uploaded to BMJ Open server
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	15

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 11, 15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-9

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Files 1, 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set

1. Primary Registry and Trial Identifying Number	Clinicaltrial.gov Registration submitted, pending approval
2. Date of Registration in Primary Registry	Clinicaltrial.gov Registration submitted, pending approval
3. Secondary Identifying Numbers	None
4. Source(s) of Monetary or Material Support	The Everion® wearable devices are donated by Biofourmis Singapore, and Harmony ltd. The mobile phone and cellular data are supported by PCCW ltd.
5. Primary Sponsor	None
6. Secondary Sponsor(s)	None
7. Contact for Public Queries	Professor Ivan FN Hung MD Division of Infectious Diseases, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China. Tel: (852) 2255 4049 Fax: (852) 2818 6304

	E-mail: ivanhung@hku.hk
8. Contact for Scientific Queries	Professor Ivan FN Hung MD Division of Infectious Diseases, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China. Tel: (852) 2255 4049 Fax: (852) 2818 6304 E-mail: ivanhung@hku.hk
9. Public Title	Using Biovitals® Sentinel to Monitor Disease Progression in Subjects Quarantined for Suspected COVID-19
10. Scientific Title	Using Biovitals® Sentinel to Monitor Disease Progression in Subjects Quarantined for Suspected COVID-19
11. Countries of Recruitment	Hong Kong, China
12. Health Condition(s) or Problem(s) Studied	Coronavirus Disease 2019 (COVID-19)
13. Intervention	Intervention Arm: Continuous physiological monitoring using Biovitals platform including (1) Armband with multiple physiological sensor, (2) Remote monitoring, and (3) Analytic platform. The armband will be worn for 23 hours a day and off for 1 hour during showering for recharging the battery.

	Control Arm: Standard Care
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: Age ≥ 18 years Asymptomatic for COVID-19 pneumonia With close COVID-19 contact under mandatory quarantine at destinated facilities in Hong Kong Voluntarily agrees to participate by providing written informed consent Exclusion criteria: Symptoms suggestive of COVID-19 infection including fever, upper respiratory symptoms, and/or gastrointestinal symptoms at recruitment. Confirmed COVID-19 infection Planned laboratory test for COVID-19 Inability or refusal to provide inform consent Lack of skills in operating simple electronic devices
15. Study Type	Study Type: Interventional Participants Allocation: Randomized (details in protocol manuscript) Intervention Model: Parallel Assignment

	Masking: None (Open Label) Primary Purpose: Diagnostic
16. Date of First Enrollment	March 16, 2020
17. Target Sample Size	200 – 1000
18. Recruitment Status	Pending
19. Primary Outcome(s)	Time to diagnosis of COVID-19 by RT-PCR in subjects Metric: Time from quarantine to diagnosis of COVID-19 Time Frame: within 14 days
20. Key Secondary Outcome(s)	1. Compliance to complete the study Metric: Percentage of device usage time Time Frame: within 14 days Sensitivity and specificity of Biovitals® Sentinel to identify COVID-19 positive subjects Metric: Sensitivity and specificity of Biovitals® Sentinel to identify COVID-19 positibe subjects Time Frame: within 14 days Viral load of COVID-19 positive subjects Metric: COVID-19 viral load by RT-PCR Time Frame: On day of COVID-19 diagnosis

	Cross infection rate within the family cluster Metric: Percentage of family members infected Time Frame: within 14 days Length of hospital stay of positive subjects Metric: Length of hospital stay Time Frame: 1 year at study completion Length of ICU stay of positive patients Metric: Length of ICU stay Time Frame: 1 year at study completion Non-invasive and invasive ventilatory support Metric: Percentage of COVID-19 positive patients requiring non-invasive and invasive ventilatory support Time Frame: 1 year at study completion National Early Warning Score 2 rating of COVID-19 positive patients Metric: National Early Warning Score 2 rating Time Frame: On day of COVID-19 diagnosis

	Worsening of comorbidities Metric: Worsening of comorbidities Time Frame: 1 year at study completion Mortality Metric: Mortality Time Frame: 1 year at study completion