Version Date	April 19, 2020
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Protocol Number	E25001
NCT	TBD
Protocol Title	A Clinical Performance Evaluation of the SARS-COV-2 Direct Antigen Rapid Test "DART"

Approvals:

Site	**Sponsor**
_____ PI Printed Name _____ Principal Investigator Date	_____ Irene Bosch, PhD Date CTO E25BIO, Inc Address: 501 Massachusetts Ave. Cambridge, MA 02139

Summary of Changes from Previous Version:

Version #	Version Date	Summary of Revisions Made
1	**03Apr2020**	
2	**19Apr2020**	

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STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements (United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812). Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

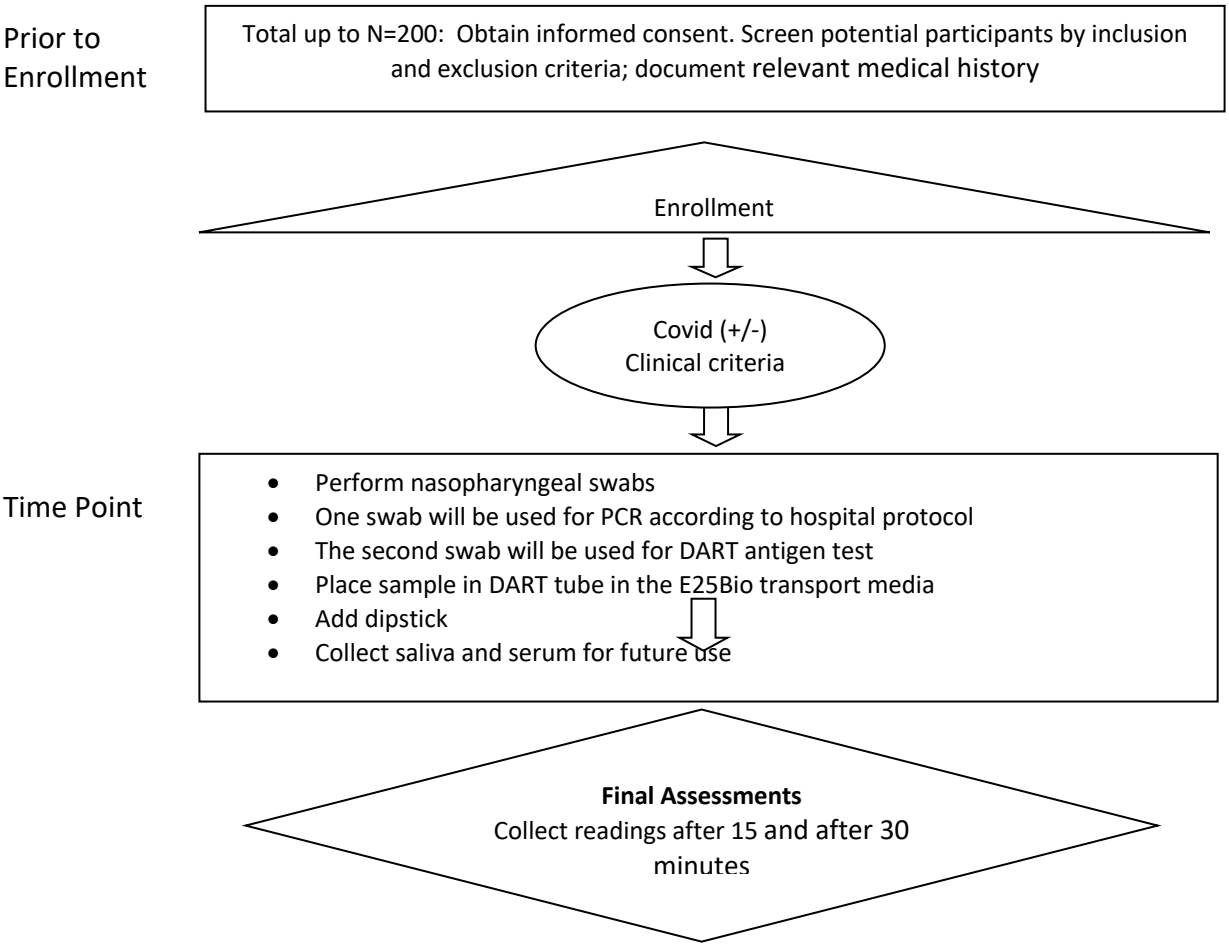
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Clinical Performance Evaluation of the SARS-COV-2 Direct Antigen Rapid Test "DART"
Study Description:	A rapid point of care bioassay for the detection of virus particles will be compared to the hospital validated RT-PCR detection standard. Nasopharyngeal and saliva samples will be collected along with hospital standard of care collection.
Intended Use	The SARS-CoV-2 DART is a bioassay intended for rapid point-of-care detection of the SARS-CoV-2 virus
Objective	**Primary**: To validate the performance of SARS-COV-2 DART in a clinical setting
Endpoints:	*Primary: Compared to Gold Standard PCR, DART with nasopharyngeal swab will provide agreement with respect to PCR*

Study Population:	Samples will be collected in an Emergency Room setting from up to 200 subjects who entered the hospital over concerns about SARS-CoV-2. The goal is to collect a minimum of N=30 confirmed Covid-19 positive subjects and N=30 confirmed Covid-19 negative subjects of comparable ages, genders and races.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	*Beth Israel Deaconess Medical Center*
Study Duration:	The trial is expected to take 1 month
Participant Duration:	Individual participation only includes sample collection

1.2 SCHEMA


Prior to Enrollment
Total up to N=200: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; document relevant medical history
Enrollment
Covid (+/-)
Clinical criteria
Time Point
Perform nasopharyngeal swabs
One swab will be used for PCR according to hospital protocol
The second swab will be used for DART antigen test
Place sample in DART tube in the E25Bio transport media
Add dipstick
Collect saliva and serum for future use
Final Assessments
Collect readings after 15 and after 30 minutes

2 INTRODUCTION

2.1 STUDY RATIONALE

The current standard of care for diagnosis of SARS-CoV-2 infection involves sample collection to be prepared and measured via real time-polymerase chain reaction (RT-PCR). This process is often time consuming depending on the level of automation within the laboratory processing the samples. In many cases, sample turn-around times can take hours to several days. A rapid assay that does not require the sophisticated laboratory equipment and techniques could provide a significant advantage to the way practitioners screen and ultimately treat patients.

2.2 BACKGROUND

The SARS-CoV-2 Direct Antigen Rapid Test ("DART") is an immunoassay for point-of-care, qualitative detection of SARS-CoV-2 viral particles/secreted protein in nasopharyngeal swabs from suspected patients with COVID-19 infection. Dipsticks are printed with a monoclonal antibody that binds the signature SARS-CoV-2 viral particles/protein (Test line) and a control antibody (Control line) for quality control. A second monoclonal antibody is attached to gold nanoparticles (conjugate) and quencher buffer, and mixed with the patient samples, though in the near future the final format will contain the dry conjugate. The SARS-CoV-2 viral particles/Spike protein attach to both antibodies resulting in a visual line on the test strip within 15 minutes. Prior experience for detection virus and viral proteins via antibody binding using lateral flow are E25Bio portfolio platform for dengue, Zika and Chikungunya viruses among others.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

- Potential risk of False Positive results leading to unnecessary clinical care which may include medications and additional diagnostic tests.
- Potential risk of False Negatives which may delay potential therapeutic care, and in severe cases may delay critical lifesaving care
- Negative results cannot be proven negative

In both cases, the risks are mitigated by the Inclusion/Exclusion requirement that subjects test positive or negative for Covid-19 via the standard RT-PCR diagnostics.

2.3.2 KNOWN POTENTIAL BENEFITS

No potential benefits to the subject are expected as a result of participation in this trial. The benefits to future patients may include a more rapid point-of-care diagnostic test than currently available.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is to confirm performance and validation of the SARS-CoV-2 DART bioassay for rapid detection of infection when using nasopharyngeal swab	*Agreement with respect to PCR*	*Commonly accepted thresholds for antigen lateral flow bioassays*

4 STUDY DESIGN

4.1 OVERALL DESIGN

This trial is a clinical performance validation comparing DART to RT-PCR. The endpoints will be agreement with PCR. We know that the sensitivity of PCR will not reach 100%, but we will use PCR to define positive samples. In addition, routine pathogen screen will be in place for Influenza A and B, Adenovirus, RSV for the Hospital Clia Lab protocols.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Alternatives to genome detection are critical for front line point of care medical specialists when battling an active epidemic. Lateral flow bioassays are relatively inexpensive to manufacture, easy to store, and easy for front line medical

technicians to use. A test that is comparable and reproducible when compared to Gold Standard RT-PCR will meet these critical needs.

4.3 END OF STUDY DEFINITION

Study Subjects are not expected to participate beyond consent and collection of the nasopharyngeal and saliva samples.

The end of the study is defined as completion of the last procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Up to 200 subjects will be screened, consented, and enrolled to obtain 60 eligible candidates. In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of verbal informed consent form
2. Subject is suspected case of COVID-19 by clinical criteria: a patient with acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath, fatigue, decreased appetite, myalgia) AND with no other etiology that fully explains the clinical presentation, with or without a history of close contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms.
3. Subject is an appropriate candidate for Nasopharyngeal sample collection
4. Subject is willing to provide nasopharyngeal swab and saliva samples

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Individuals who present to ER with 10 or greater days of COVID-19 Related Symptoms, (Fever, Cough, Fatigue, Decreased Appetite, Shortness of Breath, Myalgia) or post-defervescence and/or convalescence

6 CONVALESCENCE.PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY SAMPLE EVALUATION

Subjects may withdraw consent at any time and request that their samples not be processed.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY PROCEDURES

All reagents and DART viral transport media will be provided by the sponsor and shipped together. The dipsticks should be kept at Room Temperature until use.

1. Subjects will be approached by research staff to determine if they would be interested in participating in a study that requires an additional sample collection. If willing, then a qualified study team member will conduct the informed consent process with the subject, obtain verbal agreement by subject, document verbal consent of the participant, and provide a copy of the informed consent form information sheet to the participant.
2. Study staff will complete the necessary source document elements and case report forms collecting relevant subject demographic information, eligibility criteria, and medical history. Medical personnel will collect nasopharyngeal swabs (2X samples each), saliva, and serum.
3. One of the swabs will be utilized to conduct the traditional PCR method at the Hospital
4. The second nasopharyngeal swab collected in the 0.4ml viral E25Bio transport media
5. Mix vigorously and let stand until use within the next minutes
6. In a tube provided, apply the 100µl viral transport media
7. Insert dipstick for DART test into the tube.
8. The liquid should be moving up into the tests strip for minimum of 15 min and maximum of 30 minutes.
9. Visually read and interpret the final result as indicated below, two lines= positive. One line=negative and record on form.
10. A second DART swab may be administered if the results of the first swab are not interpretable.
11. Medical staff will collect saliva sample from participant for future use.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

7.2.3.3 EXPECTEDNESS

Nasopharyngeal swabs are taken on routine basis by trained medical staff. There are no known expected reactions beyond mild discomfort.

7.2.4 SERIOUS ADVERSE EVENT REPORTING

There is minimal to absent adverse events (AEs) for the current protocol as it constitutes a protocol for an external in vitro diagnostic device. The AE are not associated with the diagnostic device itself but are associated with the performance of the nasopharyngeal swab procedure.

Serious AEs occurring after a subject is consented through 30 minutes following sample retrieval must be reported as SAEs on the Innovations SAE Report Form and followed until resolution (with autopsy report if applicable). The Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, the SAE Report Form should be completed with the necessary information.
The SAE Report Form should be sent to the Innovations Safety Department via fax or e-mail using the following contact information (during both business and non-business hours):

Sarah Cannon Innovations Safety Department
Safety Dept. Fax #: 1-866-807-4325
Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Reporting UADEs:
The study investigator shall complete an Unanticipated Adverse Device Effect (UADE) Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8 STATISTICAL CONSIDERATIONS

Details of the statistical analysis are described in the FDA Guidance, 'Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests'.

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): The DART antigen test will be compared to Gold Standard RT-PCR for the detection of SARS-Cov-2. We will be reporting the agreement between these two techniques.
- From the laboratory at BEI (NIH) we obtained performances reaching 100 % sensitivity and 100% specificity from validated laboratory viral samples.
- Percent Positive Agreement = A/(A + C) or True Positives/(True Positives + False Negatives)
- Negative Percent Agreement = D/(B + D) or True Negatives/(True Negatives + False positives)

8.2 SAMPLE SIZE DETERMINATION

The sample size was based upon FDA guidance regarding EUA clinical validation procedures following EUA approval. N= 30 positive samples and N=30 negative samples should provide sufficient confidence that the DART bioassay is sensitive and specific for detection of SARS-Cov-2 early infection.

8.3 POPULATIONS FOR ANALYSES

Subjects testing positive or negative by PCR and having DART assessments

8.4 STATISTICAL ANALYSES

8.4.1 GENERAL APPROACH

The 2X2 binary method is industry standard when testing a new clinical diagnostic with the gold standard.
The positive and negative percent agreement between the candidate device results generated separately for each claimed matrix comparator method using 2 x 2 tables as follows:

	Clinical comparator method/Clinical truth (RT-PCR)		
E25Bio Test		**Positive**	**Negative**
	Positive	**A**	**B**
	Negative	**C**	**D**

Percent Positive Agreement = A/(A + C) or True Positives/(True Positives + False Negatives)

Negative Percent Agreement = D/(B + D) or True Negatives/(True Negatives + False positives)

8.4.2 SAFETY ANALYSES

Adverse events will be recorded and categorized according to toxicity and relationship to procedure.

Adverse events will be analyzed by a very common summary of AEs is by SOC (System Organ Class), Preferred Term, and Grade).

8.4.3 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be used to describe age, race, and gender of the sample population.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The human samples will be anonymized if consented for future investigations.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator and/or appropriate delegated medical personnel will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to

discuss the study with their family or surrogates or think about it prior to agreeing to participate. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Once the participant provides verbal consent, the PI or delegated team member will sign the informed consent document. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

9.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the sponsor facilities.

9.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at participating hospitals, central lab, or sponsor labs for up to 3 years. After the study is completed, the de-identified, archived data will be transmitted to and stored at the sponsor facilities, for use by other researchers including those outside of the study.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Hospital/Central facility and/or sponsor laboratories with the same goal as the sharing of data. These samples could be used to research the causes of COVID-19 and spread of SARS-CoV-2, its complications and other conditions for which individuals with SARS-CoV-2 infection are at increased risk, and to improve treatment.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the sponsor.

9.1.5 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

9.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.1.7 DATA HANDLING AND RECORD KEEPING

9.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the hospital electronic medical records, should be consistent with the data recorded on the source documents. A 21 CFR Part 11 compliant medical record will be electronically transferred to the sponsor per agreed upon terms and standards.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the approved databasea 21 CFR Part 11-compliant data capture system provided by the CRO. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

9.1.7.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to the sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.9 PUBLICATION AND DATA SHARING POLICY

It is expected that publications will result from these studies, and investigators/institutions are encouraged to generate manuscripts.

a. The results of the present study, in the event that they form part of a multi -center trial, may not be published until the overall results have been published.

b. The Sponsor shall not cite the investigators' names without their authorization, except in the case of references to works already published.

c. Any publication and/or disclosure in any form of the results of medical investigations carried out with the Sponsor's products must be agreed with the Sponsor prior to its publication and/or disclosure.

d. The sponsor allows the publication, with the mentions that are legally provided for, of the data obtained in this Trial in journals of recognised scientific prestige and its disclosure in seminars and conferences within the medical professional field, providing that the provisions established in sections a) and c) of this clause are respected.

e. Section c) above is understood to be applicable to information obtained in Trials that have not been completed or have been suspended before completion.

f. The research team shall not disclose the results of the investigation to third parties, with the exception of the procedure foreseen in this clause.

The publication of the clinical study will include key personnel, scientific personnel and medical key contributors. The source of funding will be stated, proper statement of commercial interest will be disclosed. The confidentiality agreement will include the details regarding data sharing policy.

9.1.10 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial

NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10 REFERENCES

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11 APPENDIX A – CASE REPORT FORM

.

Case Report Form (CRF)

E25001

FINAL_ Version 0.8, 19/APR/2020

Table of Contents

12 ADMINISTRATIVE

Template: VISIT-01 Version 12/3/2013

12.1 VISIT

Visit Name:	_____
Visit Date (DD/MON/YYYY):	☐☐/☐☐☐/☐☐☐☐

12.2 PATIENT INFORMATION

Patient Number	☐☐☐☐☐☐☐☐
Patient Caption	☐☐☐☐☐☐☐☐

13 SCREENING

Template: IE-01 Version

13.1 ELIGIBILITY

What was the date of informed consent? (DD/MON/YYYY): ☐☐/☐☐☐/☐☐☐☐

Protocol version used to confirm eligibility:

☐ Protocol Version 1 (Original)

☐ Protocol Version 2 (Amendment 1)

☐ Protocol Version 3 (Amendment 2)

Did the patient have symptoms consistent with a clinical assessment of COVID-19? ☐ Yes ☐ No

Did the patient meet all eligibility criteria? ☐ Yes ☐ No

If No, specify critera not met:

Type of Criterion Failed	**Failed Criterion Number**
☐ Inclusion ☐ Exclusion	☐☐☐

Did the patient enroll? ☐ Yes ☐ No

If No, specify reason: _____

13.2 DEMOGRAPHICS

Date of Birth (DD/MON/YYYY): ☐☐/☐☐☐/☐☐☐☐
Sex: ☐ Female
Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino
Race: ☐ American Indian or Alaskan Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander

General Note: Race option is check all that apply.

13.3 COVID-19 RELATED SYMPTOMS

Has the patient experienced any past and/or concomitant diseases related to COVID19? ☐ Yes ☐ No

MH Number	Medical History Term	Number of Days Since Onset of Symptoms	Ongoing
1	Fever	☐☐	☐ Yes ☐ No
2	Cough	☐☐	☐ Yes ☐ No
3	Fatigue	☐☐	☐ Yes ☐ No
4	Decreased appetite	☐☐	☐ Yes ☐ No
5	Shortness of breath	☐☐	☐ Yes

			☐ No
6	Chills	☐☐	☐ Yes ☐ No
7	Muscle Aches	☐☐	☐ Yes ☐ No
8	Sore Throat	☐☐	☐ Yes ☐ No
9	Loss of smell	☐☐	☐ Yes ☐ No
10	Loss of taste	☐☐	☐ Yes ☐ No
11	Nausea	☐☐	☐ Yes ☐ No

Template: CUSTOM

13.4 MEDICAL HISTORY

Did the patient provide additional medical history information? ☐ Yes ☐ No

MH Number	Medical History Term	Check all that apply	Ongoing
1	Addiction	☐	☐ Yes ☐ No
2	Anemia	☐	☐ Yes ☐ No
3	Anxiety	☐	☐ Yes ☐ No
4	Arthritis	☐	☐ Yes ☐ No
5	Asthma	☐	☐ Yes

			☐ No
6	Bipolar disorder	☐	☐ Yes ☐ No
7	Congestive Heart Failure	☐	☐ Yes ☐ No
8	COPD	☐	☐ Yes ☐ No
9	Dementia	☐	☐ Yes ☐ No
10	Depression	☐	☐ Yes ☐ No
11	Diabetes Mellitus	☐	☐ Yes ☐ No
12	GERD	☐	☐ Yes ☐ No
13	Hepatitis	☐	☐ Yes

			☐ No
14	Hyperlipdemia	☐	☐ Yes ☐ No
15	Hypertension	☐	☐ Yes ☐ No
16	Irritable Bowel Syndrome	☐	☐ Yes ☐ No
17	Migraine	☐	☐ Yes ☐ No
18	Osteoporosis	☐	☐ Yes ☐ No
19	Pulmonary Embolism	☐	☐ Yes ☐ No
20	Seizures	☐	☐ Yes ☐ No

14 ASSESSMENTS

Template: PC-01

14.1 SAMPLE COLLECTION

Were any samples collected? ☐ Yes ☐ No

Check if Not Done	Sample	Collection Date (DD/MON/YYYY)	Collection Time (HH:MM)	If Not Done, indicate reason
☐	PCR Nasopharyngeal Swab. Sent to Laboratory	☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Informed consent withdrawn ☐ Adverse Event ☐ Other _____
☐	DART Nasopharyngeal Swab	☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Informed consent withdrawn ☐ Adverse Event ☐ Other _____
☐	Saliva. Sent to Laboratory	☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Informed consent withdrawn ☐ Adverse Event ☐ Other _____

☐	Serum. Sent to Laboratory	☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Informed consent withdrawn ☐ Adverse Event ☐ Other _____

General Note: *Per page 2 of protocol version 1, saliva is to be collected.*

Template: Custom

14.2 DART DIPSTICK VISUAL ASSESSMENT

Date of Dipstick Assessment (DD/MON/YYYY): ☐☐/☐☐☐/☐☐☐☐

Check if not done	Protocol Timepoint	Time of Dipstick Assessment (HH:MM):	Result	If the assessment was not done, what was the reason?
☐	15 Minutes	☐☐:☐☐	☐ Positive for COVID-19 (Two lines on dipstick) ☐ Negative for COVID-19 (One line on dipstick) ☐ Inconclusive ☐ No result assessment done	_____
☐	30 Minutes	☐☐:☐☐	☐ Positive for COVID-19 (Two lines on dipstick) ☐ Negative for COVID-19 (One line on dipstick) ☐ Inconclusive ☐ No result assessment done	_____

If the assessment was inconclusive, was another sample collected? ☐ Yes ☐ No

Check if not done	Protocol Timepoint	Time of Dipstick Assessment (HH:MM):	Result	If the assessment was not done, what was the reason?
☐	15 Minutes	☐☐:☐☐	☐ Positive for COVID-19 (Two lines on dipstick) ☐ Negative for COVID-19 (One line on dipstick) ☐ Inconclusive ☐ No result assessment done	_____
☐	30 Minutes	☐☐:☐☐	☐ Positive for COVID-19 (Two lines on dipstick) ☐ Negative for COVID-19 (One line on dipstick) ☐ Inconclusive ☐ No result assessment done	_____

CP Note: *This form will not be displayed if the Sample Collection CRF indicates that no DART Nasopharyngeal Swab was collected.*

14.3 PCR RESULT

Date of PCR Result (DD/MON/YYYY): ☐☐/☐☐☐/☐☐☐☐Time of PCR Result (HH:MM): ☐☐:☐☐

Which PCR Platform was used for analysis?

- ☐ Abbott m2000 System
- ☐ Other, Specify: _____

What was the PCR test result?

- ☐ Positive for COVID-19
- ☐ Presumptive Positive for COVID-19
- ☐ Negative for COVID-19
- ☐ Invalid
- ☐ Other, Specify: _____

Ct Value: ☐☐

If the assessment was not done, what was the reason? _____

***CP Note**: This form will not be displayed if the Sample Collection CRF indicates that no PCR Nasopharyngeal Swab was collected.*

15 ADVERSE EVENTS

Template: AE-02

15.1 ADVERSE EVENTS

Were any adverse events experienced between informed consent and 30 minutes post sample collection? ☐ Yes ☐ No

AE Number: ☐☐☐

Adverse Event _____

Start Date (DD/MON/YYYY)	Start Time (HH:MM)	Outcome Post Swab	Toxicity Grade	Relationship to Study Intervention	Action Taken with Sample Collection	Serious	If SAE, criteria met for IRB submission?
☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Fatal ☐ Not Recovered or Not Resolved ☐ Recovered or Resolved ☐ Recovered or Resolved with Sequelae ☐ Recovering or Resolving ☐ Unknown	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5	☐ Related ☐ Possibly Related ☐ Not Related	☐ No Action ☐ Collection Interrupted ☐ Collection Discontinued	☐ Yes ☐ No	☐ Yes ☐ No

☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Fatal ☐ Not Recovered or Not Resolved ☐ Recovered or Resolved ☐ Recovered or Resolved with Sequelae ☐ Recovering or Resolving ☐ Unknown	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5	☐ Related ☐ Possibly Related ☐ Not Related	☐ No Action ☐ Collection Interrupted ☐ Collection Discontinued	☐ Yes ☐ No	☐ Yes ☐ No	
☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Fatal ☐ Not Recovered or Not Resolved ☐ Recovered or Resolved ☐ Recovered or Resolved with Sequelae ☐ Recovering or Resolving ☐ Unknown	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5	☐ Related ☐ Possibly Related ☐ Not Related	☐ No Action ☐ Collection Interrupted ☐ Collection Discontinued	☐ Yes ☐ No	☐ Yes ☐ No	
☐☐/☐☐☐/☐☐☐☐	☐☐:☐☐	☐ Fatal ☐ Not Recovered or Not Resolved ☐ Recovered or Resolved ☐ Recovered or Resolved with Sequelae ☐ Recovering or Resolving ☐ Unknown	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5	☐ Related ☐ Possibly Related ☐ Not Related	☐ No Action ☐ Collection Interrupted ☐ Collection Discontinued	☐ Yes ☐ No	☐ Yes ☐ No	

General Notes:

One CRF page should be used per unique (contiguous) AE

One row should be added each time the grade or seriousness changes

Only Adverse Events that occur between informed consent and 30 mins post sample collection will will be collected.

16 SUBJECT STATUS

Template: EOS-01

16.1 END OF STUDY

What was the date of study discontinuation (DD/MON/YYYY)? ☐☐/☐☐☐/☐☐☐☐

What was the patient's reason for study discontinuation?

- ☐ Completed
- ☐ Study Terminated by Sponsor
- ☐ Informed Consent Withdrawn
- ☐ Other, Specify:_____