CLINICAL STUDY PROTOCOL
(Master study protocol)

Protocol Title

Evaluation of the performance of novel molecular point of care diagnostics for SARS-CoV-2

Short title

COVID-19 novel molecular point of care diagnostics evaluation

Protocol Version Number:

Version 1.0

Date:

25 October 2022

Disease Programme:

Pandemic Threats

FIND
Diagnosis for all

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Confidentiality Statement:

FIND

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*Terms of references and nature of agreements are available from FIND on request.

Signature Page (Sponsor)

We, the undersigned, have developed, reviewed and approved this protocol, including appendices. We will supervise and coordinate the clinical study according to the principles outlined in the Declaration of Helsinki and Good Clinical Practice and in compliance with applicable regulatory requirements.

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Statement of Principal Investigator

In signing this page, I, the undersigned, agree to conduct the study, *Evaluation of the performance of novel molecular point of care diagnostics for SARS-CoV-2*, according to the protocol and ICH-Good Clinical Practice (GCP) E6 (R2) guidelines and in compliance with applicable regulations.

I will ensure that the requirements relating to obtaining Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review and approval are met. I will promptly report to the IRB/IEC any and all changes in the research activities covered by this protocol.

I have sufficient time to properly conduct and complete the study within the agreed study period and I have adequate resources (staff and facilities) for the foreseen duration of the study.

I am responsible for supervising any individual or party to whom I delegate study related duties and functions conducted at the study site. Further, I will ensure this individual or party is qualified to perform those study-related duties and functions.

I certify that key individuals involved with the conduct of this study, including myself, have completed GCP training and, if applicable, Human Subjects Protection Training.

I also certify that I will be responsible for the integrity and quality of the data generated for this study.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No participant's names or personal identifying information may be disclosed. All participant data will be anonymized and identified by assigned numbers on all Case Report Forms, laboratory samples and other study related information (such as essential documents) forwarded to FIND. Essential documents (including the informed consent forms) required by ICH-GCP E6(R2) will be retained for a period of at least ten years. Monitoring and auditing by FIND, and inspection by the appropriate regulatory authority(ies), will be permitted.

I will maintain confidentiality of this protocol and all other related investigational materials. Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of FIND.

(Site specific) Name of Principal Investigator: _____
(Print)

Signature: _____ Date: _____
DD/MMM/YYYY

Site to add more site staff and signatures, if applicable/required by their Institute

Protocol History/Amendment Summary*

Version number	Release date	Comments
1.0	25 October 2022	Initial version

*Refer to Appendix 3 for Protocol Amendment History

List of Abbreviations and Acronyms

Abbreviation/acronym	Meaning
AE	Adverse Event
Ag RDT	Antigen Rapid Diagnostic Test
CONSORT	Consolidated Standards of Reporting Studies
CPHL	Central Public Health Laboratories
CRF	Case Report Form
Ct	Cycle threshold
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practice
GDoP	Good Documentation Practice
HUG	Hopitaux Universitaires de Genève
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Council on Harmonisation
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention-to-Test
LSTM	Liverpool School of Tropical Medicine
POC	Point-of-Care
PP	Per Protocol Population
PPE	Personal Protective Equipment
QC	Quality Control
RT-PCR	Real Time Reverse Transcription Polymerase Chain Reaction
SAP	Statistical Analysis Plan

SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUS	System Usability Scale
UTM	Universal Transport Medium
VTM	Viral Transport Medium
WHO	World Health Organisation

Protocol Synopsis

Title	Evaluation of the performance of novel molecular point of care diagnostics for SARS-CoV-2
Short title	Covid-19 molecular POC diagnostics evaluation
Protocol version and date	Version 1.0 – 25 October 2022 These parts may be adapted in site-specific protocol
Background and rationale	The aim of this study is to independently evaluate the performance of novel molecular point-of-care (POC) assays for the direct detection of SARS-CoV-2 nucleic acid (RNA) in comparison to the current reference standard, laboratory-based real-time reverse-transcription PCR (RT-PCR), for use to diagnose COVID-19, a serious and sometimes fatal respiratory infection caused by the coronavirus SARS-CoV-2. A total of 3 molecular POC devices, detecting SARS-CoV-2 and other viral pathogens, have been selected by FIND through open calls for expressions of interest. These are Covid/RSV/Flu Nudge Test (DnaNudge Ltd, Nudge test from hereon), Test Kit for SARS-CoV-2 RNA Detection in Biological Material Using PCR Method (Mirai Genomics, Mirai test from hereon) and GenomEra (Abacus Diagnostica Oy, GenomEra test from hereon). Other molecular POC devices currently in the late development stage may become available for assessment of clinical performance at later time, should these pass FIND's selection criteria. The COVID-19 pandemic has rapidly spread across the globe. As of 3 October 2022, there are approximately a total of 623 million confirmed cases reported worldwide, that resulted in a total of 6.55 million deaths. The current weekly incidence is on average 1 million new cases. However, the consensus among public health officials is that the number of infected individuals is far higher. Given the wide range of possible symptoms and the potential for transmission before individuals are aware that they are infected, exposure to SARS-CoV-2 is a particular hazard for health care providers. Though diagnostic capacity has greatly improved due to the introduction of novel antigen rapid diagnostic tests (Ag RDT), long turnaround times for results of the current reference standard for testing (RT-PCR) is still a major challenge. This impacts on the ability of public health officials to track and contain the disease. The lack of capacity, in turn, is due in part to the logistic challenges and global reagent shortages faced by laboratories attempting to implement new RT-PCR assays for SARS-CoV-2. Rapid sample-in-answer-out molecular POC devices, if shown to have sufficient accuracy to aid in clinical decision-making, could contribute substantially to control the disease spread globally. Molecular POC devices might provide a source of immediate diagnostic testing in low-and middle-income countries unable to implement RT-PCR due to lack of sample transport and storage facilities at local laboratories.
Primary objective	1.1 To evaluate the diagnostic accuracy of molecular POC devices in detecting SARS-CoV-2 on respiratory specimens, compared with reference standard RT-PCR (WHO EUL or FDA EUA approved), among COVID-19 symptomatic individuals.

Secondary objectives	2.1 To evaluate the diagnostic accuracy of such platforms in detecting SARS-CoV-2 on respiratory specimens, compared with reference standard RT-PCR in specific subgroups defined based on disease stage (days since symptoms onset), RT-PCR Ct values (as surrogate for viral load). Participant's vaccination status, previous SARS-CoV-2 infection(s) and SARS-CoV-2 genetic variant causing participant's infection, determined by sequencing of the viral genome, may also be considered as subgroups. 2.2 To assess the ease of use of the molecular POC devices being evaluated using a System Usability Scale (SUS) questionnaire administered to platform's operators (minimum 3, where possible).
Primary endpoint (outcome)	1.1 Point estimates of sensitivity and specificity of molecular POC platforms for SARS-CoV-2, with 95% confidence intervals, using RT-PCR as reference standard.
Secondary endpoints (outcomes)	2.1 Point estimates of sensitivity and specificity of molecular POC platforms for SARS-CoV-2 with 95% confidence intervals, using RT-PCR as reference standard. 2.2 Scores obtained from responses to a questionnaire for ease-of-use assessment administered to the operators of the devices.
Study design	This is a prospective, diagnostic accuracy study. The 3 devices selected will be evaluated in 3 different countries, Switzerland, Uganda and United Kingdom, with one device per country. Test results provided by these POC devices are for research use only and will not be reported for participant clinical management. Considering that the COVID-19 pandemic situation is constantly changing, and countries are moving from an acute pandemic response towards coexistence with the virus, supplementing approaches to meet the study objectives may be discussed with single study sites and adopted during the study, provided that specific go/no go criteria are met, and study validity and integrity can be preserved. Examples of supplementing approaches: 1. Enrichment strategies for enrolment in case of low prevalence of COVID-19 in the evaluation settings, e.g., including close symptomatic contacts of a confirmed COVID-19 case through contact tracing procedures, etc. 2. Use of frozen respiratory specimens from biobanks and/or same-day, fresh respiratory specimens left-overs available in the local diagnostic laboratory 3. Inclusion of additional study sites.
Study sites/setting	The study will initially include 3 evaluation sites, located in Switzerland (Hôpitaux Universitaires de Genève), Uganda (Central Public Health Laboratories), and United Kingdom (Liverpool School of Tropical Medicine). Each evaluation site may recruit study participants from one or more associated clinics. Additional sites may be considered should i) other POC devices pass FIND's screening for clinical performance evaluation and/or ii) COVID-19 pandemic situation change in the above-mentioned sites, making the study no longer feasible in such sites, hence triggering the need to find replacing sites.
Study population	Specimens to be tested for this study must originate from adult symptomatic individuals (≥ 18 years old) suspected to have COVID-19 (as per national or WHO case definitions).

Sample Size	Enrolment will target to reach 100 specimens with detectable SARS-CoV-2 RNA levels (by RT-PCR) and 100 specimens with no detectable SARS-CoV-2 RNA levels, as recommended by the WHO EUL "Instructions and requirements for Emergency Use Listing (EUL) Submission: In vitro diagnostics detecting SARS-CoV-2 nucleic acid or antigen". Based on the assumption that the sensitivity of the index tests will be at least 97%, 100 PCR positive will enable us to achieve an estimate with two-sided 95% confidence interval of 10%, with power of 80%. A total of 100 confirmed PCR negatives will enable us to achieve an estimate of a specificity of 99% with a two-sided 95% confidence interval width of 6% and a power of 80%. With an estimated disease prevalence of 5% and a prevalence power of 80%, recruiting 100 confirmed positives will be the limiting factor, and 2171 participants are needed to be screened to reach this number. Should the COVID-19 prevalence fall below 1% for more than continuous 2 weeks, enrolment may be paused and resumed when the epidemic situation changes. Should the epidemic situation not change, introduction of supplementing approaches will be considered.
Eligibility criteria	Participants/specimens are eligible to be included in the study only if all the following **Inclusion criteria** apply: • Adult individuals (≥18 years of age) with symptoms suggesting plausible COVID-19 infection (as per WHO or national clinical case definitions) • Individuals who have voluntarily given written consent to participate in this study or who have given their written consent for their specimen to be used for future research studies • Individuals able to provide the specimens required for the study Participants are not eligible to be included in the study if any of the following **Exclusion Criteria** apply: • Individuals on oxygen therapy • Individuals with recent history of excessive nose bleeds • Individuals with hemodynamic instability as determined by their treating physician • Individuals already enrolled in other clinical studies, where similar respiratory specimens are collected on the same day.
Study duration	The study will last approximately 6-9 months.
Time schedule	- Study preparation and IRB approvals: 3.5 months - Training and site activation: 0.5 month - Enrolment and data collection: 1-4 months - Data cleaning/data lock and final analysis: 1 month

Schedule of Activities / Sample Flow

Procedures	Day of Enrolment	Timepoint 2	Notes
Inclusion and exclusion criteria verification	X		
Informed consent and participant enrolment	X		
Participant clinical information collection	X		
Sample collection for reference and index test	X		
Index test performance (molecular POC)	X		Sample must be processed according to manufacturer's instructions (within 3h after collection)
Reference test performance (RT-PCR)	X	X	RT-PCR may be performed on another day or in batch (if not used for diagnosis), depending on site's workload/workflow
Ease-of-Use questionnaire completion	n/a	n/a	To be completed by Molecular POC device operators by the end of the study
Sequencing of RT-PCR positive samples		X	Samples may be batched and processed according to site-specific procedures and frequency
Completion of CRFs, including OpenClinica data entry	X	X	Some data may become available later (e.g., sequencing result)
ICFs, CRFs review and study data QC by Principal Investigator or designee	X	X	Data accuracy and quality should be verified at least on a weekly basis
Adverse Event (AE)/Serious Adverse Event (SAE) review	X	X	Limited scope, see Appendix 2

1 Introduction

1.1 Study Rationale

Corona-Virus-Disease-19 (COVID-19) is a serious respiratory infection caused by the coronavirus SARS-CoV-2. The COVID-19 outbreak has rapidly spread across the globe with approximately a total of 623 million cases and around 6.5 million deaths.

Prevention remains the mainstay of epidemic control in the shortage/absence of vaccines (or slow uptake) or effective treatment. The hallmark of effective prevention programs includes timely and accurate diagnosis. The need for specialized laboratories for RT-PCR confirmatory testing and point of care antigen and molecular diagnostics is of paramount importance in achieving timely diagnosis.

In this context, SARS-CoV-2 testing using rapid molecular POC tests holds great potential. A test that can reliably detect early infection at POC can facilitate rapid case identification and isolation, reduce the risks of transmission, and make decentralized SARS-CoV-2 testing data more readily available to inform prevention measures.

Hundreds of novel molecular POC tests detecting SARS-COV-2 RNA have been developed and are now commercialized. Following open calls for expressions of interest the Foundation for Innovative New Diagnostics (FIND) will conduct clinical performance evaluation studies in collaboration with multiple independent sites to determine the accuracy of such tests.

The purpose of this study is to provide independent evaluation data on several COVID-19 molecular POC tests to the global health community so that countries have objective evidence on the clinical performance of these assays. A total of 3 molecular POC devices, detecting SARS-CoV-2 and other viral respiratory pathogens, have been selected by FIND through such open calls. These are Covid/RSV/Flu Nudge Test (DnaNudge Ltd, Nudge test from hereon), Test Kit for SARS-CoV-2 RNA Detection in Biological Material Using PCR Method (Mirai Genomics, Mirai test from hereon) and GenomEra (Abacus Diagnostica Oy, GenomEra test from hereon). As part of this overarching study, each COVID-19 molecular POC tests will be assessed and compared against the reference standard RT-PCR validated at each study site involved (i.e., WHO EUL or FDA EUA approved). Each molecular POC device assessment is treated as a sub-study and complies with the current protocol. Other molecular POC devices currently in the late development stage may become available for assessment of clinical performance at later time, should these pass FIND's selection criteria.

1.2 Background

The COVID-19 pandemic has rapidly spread across the globe. As of 3 October 2022 there are approximately a total of 623 million confirmed cases reported worldwide, that resulted in a total of 6.55 million deaths (https://covid19.who.int/). The current weekly incidence is on average 1 million new cases. However, the consensus among public health officials is that the number of infected individuals is far higher due to massive undertesting and underreporting. Given the wide range of possible symptoms and the potential for transmission before individuals are aware that they are infected, exposure to SARS-CoV-2 is a particular hazard for the community. Though diagnostic capacity has greatly improved due to

introduction of novel Ag RDTs, long turnaround times for results of the current reference standard for testing (RT-PCR) is still a major challenge. This impacts on the ability of public health officials to track and contain the disease. The lack of capacity, in turn, is due in part to the logistic challenges and global reagent shortages faced by laboratories attempting to implement new RT-PCR assays for SARS-CoV-2.

Rapid sample-in-answer-out molecular point of care (POC) devices, if shown to have sufficient accuracy to aid in clinical decision-making, could contribute substantially to control the disease spread globally. Molecular POC devices might provide a source of immediate diagnostic testing in low-and middle-income countries unable to implement RT-PCR due to lack of transport and storage facilities at local laboratories.

1.3 Benefit/Risk Assessment

The *in vitro* diagnostics (IVDs) under investigation are considered low risk to prospectively enrolled study participants because collection of respiratory samples is a minimally invasive procedure and involves minimal participant discomfort. This procedure will be performed by healthcare professionals trained to collect the routine respiratory swab for the reference standard RT-PCR test. The probability of an adverse event (AE) or serious adverse event (SAE) occurring to a study participant to be associated with the investigational product is extremely low.

This is a diagnostic accuracy study that will not utilize test results for clinical decision making. All study participants and personnel will be made aware that the novel COVID-19 molecular POC platforms under study are for research purposes only and cannot be used to determine whether to initiate treatment, nor for any other clinical management decisions.

Post-test counselling and linkage to care will be provided at the study sites to enrolled participants with positive COVID-19 status by the RT-PCR reference test.

(SITE to add specific details regarding if needed)

Participants will not benefit directly from participation in the study, but the study will benefit to society through publication of study results and providing data to inform discussions on COVID-19 molecular POC testing policy. The development of COVID-19 molecular POC tests will improve diagnosis and treatment of COVID-19, facilitate studies to understand its prevalence and natural history, and ultimately lead to effective vaccination and therapeutic strategies. Knowledge gained from this study may benefit society by improving COVID-19 diagnosis in low- and middle-income countries in the future.

2 Study Objectives and Endpoints

The objectives and corresponding endpoints of this study are described in Table 1.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
1.1 To evaluate the diagnostic accuracy of molecular POC devices in detecting SARS-CoV-2 on respiratory specimens, compared with reference standard RT-PCR (WHO EUL or FDA EUA approved), among COVID-19 symptomatic individuals.	1.1 Point estimates of sensitivity and specificity of molecular POC platforms for SARS-CoV-2, with 95% confidence intervals, using RT-PCR as reference standard.
Secondary	
2.1 To evaluate the diagnostic accuracy of such platforms in detecting SARS-CoV-2 on respiratory specimens, compared with reference standard RT-PCR in specific subgroups defined based on disease stage (days since symptoms onset), RT-PCR Ct values (as surrogate for viral load). Participant's vaccination status, previous COVID-19 infection(s) and SARS-CoV-2 genetic variant causing participant's infection, determined by sequencing of the viral genome, may also be considered as subgroups. 2.2 To assess the ease of use of the molecular POC devices being evaluated using a System Usability Scale (SUS) questionnaire administered to platform's operators (minimum 3, where possible).	2.1 Point estimates of sensitivity and specificity of molecular POC platforms for SARS-CoV-2 with 95% confidence intervals, using RT-PCR as reference standard. 2.2 Scores obtained from responses to a questionnaire for ease-of-use assessment administered to the operators of the devices.

3 Study Design

3.1 General Design

This is a prospective, diagnostic accuracy study. The same study design will be applied to each COVID-19 molecular POC evaluation (sub-study) performed under this protocol. The 3 devices selected will be evaluated in 3 different countries, Switzerland, Uganda and United Kingdom, with **one device per country**. In detail, the sites coordinating the evaluation in each country will be: Hôpitaux Universitaires de Genève (HUG, Switzerland), Central Public Health Laboratories, (CPHL, Uganda) and Liverpool School of Tropical Medicine (LSTM, United Kingdom). Each evaluation site may recruit study participants from one or more associated clinics.
(SITE to add specific setting details, where needed)

Considering that the COVID-19 pandemic situation is constantly changing, and countries are moving from an acute pandemic response towards coexistence with the virus, supplementing approaches to meet the study objectives may be discussed with single study sites and adopted during the study, provided that specific go/no go criteria are met, and study validity and integrity can be preserved. Potential supplementing approaches considered:

1. Enrichment strategies for recruitment may be considered in case of low prevalence of COVID-19 in the evaluation settings, e.g., including close symptomatic contacts of a confirmed COVID-19 cases through contact tracing procedures.
2. Should the local COVID-19 epidemic situation and/or country-specific policies (e.g., COVID-19 related restrictions, testing centres and recommendations, etc) change in any of the selected countries, making difficult to continue with the prospective study design and to achieve study objectives, frozen respiratory specimens from FIND or local biobanks and/or same-day, fresh respiratory specimens left-overs available in the local diagnostic laboratory may be used. This is in accordance with WHO guidelines for conducting NAT test evaluations (PQDx_347 COVID-19 NAT and Ag RDTs version 6; 17 March 2022 (who.int))
3. Additional sites may be considered should the COVID-19 pandemic situation change in the above-mentioned sites, making the study no longer feasible.

Supplemental procedures will allow to achieve the primary objective of the study and, most likely, to assess the usability of the POC under evaluation. Data collected, though, may not be sufficient/available to perform the subgroups analyses of the secondary objectives.

Clinical performance of molecular POC devices for viral pathogens other than SARS-CoV-2 included in their detection panel will not be evaluated. Specificity, sensitivity of each index test will be evaluated against WHO/FDA EUL-approved RT-PCR test as a reference method, as recommended by the WHO guidelines.
All study specimens and relevant information will be collected from enrolled participants on the day of recruitment. There will be no follow-up visits. Only PCR results can be communicated to the participant.

Additional sites may be considered should other POC devices pass FIND's screening for clinical performance evaluation.

3.2 Scientific Rationale for study Design

A prospective design has important advantages over a retrospective design, including a participant sample that is better defined in terms of the participant's clinical characteristics, and standardized methods for performing the test(s) and reference standard procedure. In some circumstances a prospective design is the only possible approach due to the intended use of the test (e.g., at the point of care) or disease under investigation.

On the other hand, COVID-19 pandemic situation is constantly changing, and countries are moving from an acute pandemic response towards a sustained management approach, learning coexistence with the virus. With vaccination campaigns rolling out, each country is free to calibrate public health and social measures according to their local epidemiological and economic context. This coexistence phase can translate in testing centres closure, testing costs being transferred to the patient, social or travel restriction measures being lifted or lightened with Covid-19 testing no longer mandatory, making a prospective design extremely difficult to implement. In such circumstances, the only possibility to perform this study is through supplementing specimens

collected prospectively with specimens available in FIND or local biobanks and/or in local diagnostic laboratories associated with the study sites.

3.3 End of Study Definition

The end of the study is defined as the date the minimum required number of COVID-19 RT-PCR positive and negative specimens will be reached.

A participant is considered to have completed the study after the respiratory specimens needed to perform the reference standard RT-PCR test and the index test under evaluation have been collected, alongside the relevant clinical study information.

3.4 Study Population and Eligibility

The study will focus on adults with symptoms compatible with COVID-19 (and/or specimens collected from them) attending healthcare facilities in Switzerland, Uganda and United Kingdom.

(SITE to add specific setting details, if needed)

If a participant is screened and enrolled but is not able to provide the specimens required for the study, this participant will be withdrawn.

A participant can only be enrolled once in the study. Co-enrolment in multiple studies on the same day is not allowed (i.e., where the subject is asked to provide similar respiratory specimens in parallel).

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

3.5 Inclusion Criteria

Participants/specimens are eligible to be included in the study only if all the following inclusion criteria apply:

- Adult individuals (≥18 years of age) with symptoms suggesting plausible COVID-19 infection (as per WHO or national clinical case definitions)
- Individuals who have voluntarily given written consent to participate in this study or who have given their written consent for their specimen to be used for future research studies
- Individuals providing the specimens required for the study.

3.6 Exclusion Criteria

Participants are not eligible to be included in the study if any of the following exclusion criteria apply:

- Individuals on oxygen therapy
- Individuals with recent history of excessive nose bleeds
- Individuals with hemodynamic instability as determined by their treating physician
- Individuals already enrolled in other clinical studies, where similar respiratory specimens are collected on the same day.

3.7 Screen Failures

Screen failures are defined as participants who verbally consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Studies (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, screen failure reasons, and any serious adverse event (SAE). Individuals who do not meet the criteria for participation in the study (screen failure) may not be rescreened. Screen failures should not have an assigned participant study ID but should be recorded on the screening log.

4 Study Intervention

Study Intervention is defined as any investigational intervention(s), marketed product(s), or medical device(s) intended to be used with a study participant according to the study protocol.

4.1 Investigational Product

Novel molecular POC tests results will not be used for clinical decision making.
A total of 3 molecular POC devices, detecting SARS-CoV-2 and other viral pathogens, have been selected by FIND through open calls for expressions of interest. These are Nudge test, Mirai test and GenomEra test. These will be evaluated at LSTM (Nudge test), HUG (Mirai test) and CPHL (GenomEra test). The novel molecular POC devices under evaluation within this protocol are also listed in Appendix 1. Other tests, currently in late development stage, may be considered as they become available for clinical performance evaluation and vetted through discussions with FIND and the WHO Collaborating Centre for COVID diagnostic test evaluation.

Instructions for use of the investigational products will be provided by each manufacturer and shared with sites.
Medical device incidents, including those resulting from malfunctions of the device (or IVD), must be detected, documented and reported by the Investigator at each site throughout the study (see Appendix 2).

4.2 Preparation/Handling/Storage/Accountability

Acquisition

Procurement of the investigational products (devices and test kits) will be done through FIND, who coordinates shipments from the manufacturer or FIND warehouse in Geneva, Switzerland, to study site. It is the responsibility of each study site to maintain an updated inventory of the study materials and inform FIND immediately if additional materials are required.

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit to the testing sites. In turn, testing sites will maintain an updated inventory of the investigational product received. Any discrepancies must be reported to FIND and resolved before its use.

Installation and Storage

Procedures for devices installation and test kits storage and disposal will be described in the corresponding Instructions for Use (IFU) and manuals. Device installation will strictly adhere to manufacturers instruction, meeting all manufacturer and site-specific requirements as well for new equipment installation.

The investigational products (devices and test kits) will be installed and stored in a secure, environmentally controlled, and monitored area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

Test Handling and Performance

Testing using the investigational products will be performed according to the manufacturer's instructions. Only respiratory samples, as per index test manufacturer's claim, from participants enrolled in the study or from biobanks will be processed with the investigational product for the main aims and only authorized site staff will be responsible for processing.

Accountability

The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Investigational product accountability logs filled at each site will ensure the proper follow-up of the devices and used, failed and remaining test kits.

Export and Import Permits

The Investigator at study site is responsible for making import permit applications in a timely manner. FIND logistics team will support providing documentation required from the Sponsor, usually including commercial invoice, packaging list and FIND donation letter. (SITE to amend accordingly where necessary.)

Quality Check for Incoming Shipments

Upon arrival of each new shipment of devices and assays, the sites will conduct an incoming quality check (visual inspection of integrity of device, check expiry date of device-associated kits, visual inspection of integrity of kit components). New lots may only be used after this quality check is successfully passed.

Local procurement

Sites are responsible for assessing their needs and procuring any supplies, reagents and kits needed for the study that are locally available and to include these costs in the study budget prior to the study initiation.

4.3 Minimisation of Error and Bias

Participant/specimen selection

Spectrum bias will be avoided by enrolling a consecutive series of study participants, and by using a prospective study design. Enrolment will be based on clearly defined eligibility criteria. To ensure the validity and generalizability of study results, descriptive statistics on participant characteristics (days since symptom onset and RT-PCR Ct values, as surrogate for viral load) will be reported.

If frozen or same-day fresh left-over specimens will be used, spectrum bias will be avoided by:

- Randomly selecting specimens from biobanks, considering only inclusion criteria and previous RT-PCR qualitative result (positive or negative)
- Testing consecutive fresh left-over specimens from the diagnostic laboratory, considering only the inclusion criteria.

Index test

There will be no risk of index test results review bias as result interpretation is performed directly by the device and the personnel operating the device will only need to record the results as they are.
To avoid the risk of sample degradation and to comply with the intended use of the device as POC, the operator will run the test within maximum 3 hours after sample collection or as per instructions agreed with the specific device manufacturer.
Ideally, the molecular POC device will be placed in the same room where specimen collection takes place; in case this will not be possible, the device will be placed in dedicated laboratory facilities close (next door) to participants recruitment/sampling location.

Should the test fail, no repetition will be performed. The result will be recorded as reported by the device (e.g., failed, invalid). This will prevent that molecular POC devices allowing test repetition from left-over material without the need of collecting a new specimen may be favoured compared to POC requiring a new specimen for test repetition, like Nudge test.

Standardization of device operation by different users, part of the study team, will be ensured with proper training at the beginning of the study. Proficiency and/or competency assessments will be conducted before initiating and/or during the study at discretion of FIND study team. (SITE-specific

procedures may be added.) As part of the training, molecular POC operators will be instructed to perform the test after all relevant samples will be collected and the study participant will have left the sample collection/testing area. Additionally, the molecular POC testing will be done in the absence of the treating clinician to avoid that the results of the molecular POC are mistakenly used or influence the clinical decision-making process.

Reference test

The reference standard RT-PCR (WHO EUL or FDA EUA approved), where possible, will be performed at an accredited/certified reference laboratory under routine quality control (see section 6 for procedures details). In case of a first indeterminate result, the test may be repeated a second time from the stored left-over sample as per local procedure. (SITE to adapt if necessary)

Flow and timing

With a prospective design, the sample for the index test will be collected in parallel to the sample that will be used for the reference test, so disease progression bias is not a concern. Samples for RT-PCR reference test will be transported from the collection sites to the reference/testing laboratory. Therefore, control measures will be implemented to ensure the quality of specimens during transport. (SITE to adapt if necessary)

If frozen specimens will be used, where possible, to avoid tempering with the integrity of biobanks by continuous freezing and thawing, frozen specimens will be retrieved from the freezers once and batch tested immediately after thawing.

Independence of the investigators from manufacturers

All aspects of the study, including specimen collection, testing, data entry, and data analysis, will be performed independently of the manufacturer of the molecular POC being evaluated. All de-identified clinical and laboratory data will be analysed by FIND and the study team. Both organizations do not have any financial ties/commercial interests or personal conflicts of interest related to any participating test manufacturers.

Handling of discordant results

Discordant results between standard RT-PCR test and index test will not be investigated, as PCR is considered the reference test.

If frozen specimens will be used, discordant results between initial RT-PCR (before freezing and biobanking) and repeated RT-PCR (on thawed specimen selected for the study) may be further investigated.

4.4 Randomisation

Not applicable for this study.

4.5 Blinding Procedure

Blinding is not required for this study.

5 Participant Discontinuation/Withdrawal

5.1 Participant Discontinuation/Withdrawal from the Study

A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons.

Depending on site-specific informed consent:

- If a participant withdraws consent for disclosure of future information, FIND may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any data collected for the study, and the Investigator must document this in the site study records.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- If a participant withdraws from the study, he/she may request destruction of any residual samples stored, and the Investigator must document this in the site study records.

(SITE to adapt and clarify what happens to samples and data after participant's withdrawal in agreement with ICF)

5.2 Lost to Follow Up

Not applicable for this study.

6 Study Procedures

Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants/specimens meet eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Detailed study procedures will be described in the Study Manual.

6.1 Specimen Collection, Handling, Transport and Storage

Participants will be recruited at the study sites (SITE to add specific details where participants will be recruited). Participants who meet all inclusion and none of the exclusion criteria and showing interest in participating in the study, will be informed by an authorized study site team member. All elements of the consent form will be carefully, patiently, and clearly explained to the prospective subject, providing him/her sufficient time to ask questions and to make his/her decision. If he/she decides to participate, the participant and the authorized study site team member, responsible for conducting the informed consent process, will sign the consent form. Participants will only be enrolled to the study after signing the informed consent.

Selected sites have established procedures for respiratory sample collection for SARS-CoV-2 diagnostic testing. Health care workers collecting samples are already trained specifically in respiratory sample collection and handling techniques and will be wearing appropriate personal protective equipment (PPE) at the time of sample collection. A respiratory sample for reference testing will be collected for routine testing on the day of enrolment as per clinical routine. A study-specific respiratory sample (e.g., nasal swab or as per index test manufacturer's claim) will be collected as well on the same day, unless the index test can be performed on the same sample as the reference test, and used to perform molecular POC testing immediately after collection (Table 2). Site-specific instructions on temporal sequence for specimens' collection for reference and index tests will be followed.

The novel molecular POC assay will be performed within designated SARS-CoV-2 isolation zones directly at recruitment/sampling location or in dedicated laboratory facilities close (next door) to participants recruitment/sampling location, ensuring safety for everyone in that area and timely processing of the index test, as per IFU. (SITE to add specific details on molecular POC location). Operators running the index test and lab personnel will be wearing appropriate PPE per clinical routine, and the testing will not add any new biosafety hazard to routine clinical practices.

Participants will be diagnosed based on RT-PCR results performed on the routine diagnostic sample (nasopharyngeal swab) and clinical signs and symptoms by their treating physician; results of novel molecular POC devices tests will not be used for clinical management.

Table 2: Sample types and testing

Sample Type	Testing	Additional Notes
Routine RT-PCR Nasopharyngeal Swab (x1)	• Molecular reference testing for COVID-19 (RT-PCR) as per standard of care (usually placed in standard VTM/UTM). • Mirai device testing for study purposes (processed as recommended by test manufacturer in the IFU).	Transported at 2-8°C to reference/testing laboratory after collection. Leftover sample after RT-PCR testing will be kept at -70°C or lower until the study ends or longer depending on the site-specific informed consent. Leftover samples may be used for repeating RT-PCR testing and/or genomic sequencing following positive RT-PCR results. SITE to clarify whether the remaining specimen may be stored in biobank for future studies.
Molecular POC devices specific respiratory sample: • Nasal Swab for Nudge and GenomEra (x1 as per assay IFU); • Nasopharyngeal Swab for Mirai (the same sample for reference test can be used)	Nudge, Mirai and GenomEra devices testing for study purposes (processed as recommended by test manufacturer in the IFU).	Processed immediately (within 3h max from collection or as per instructions agreed with the specific device manufacturer) at the collection site or at dedicated laboratory facility close (next door).

If frozen or same-day fresh left-over specimens will be used, specimen type and collection/storage medium must be validated by FIND for evaluation with the specific molecular POC. Device manufacturer will be consulted to this purpose (Table 3). Where possible, to avoid tempering with the integrity of biobanks by continuous freezing and thawing, frozen specimens will be retrieved from the freezers once and batch tested.

Table 3. Specimen types and volumes required for molecular POC devices

Type of specimen	Specimen type required for POC test			Volume of specimen required per test		
	DnaNudge	Mirai	GenomEra	DnaNudge	Mirai	GenomEra
Frozen specimen (from biobank)	Specimen in UTM/VTM	Specimen in UTM/VTM	Specimen in Copan eNAT	Pipette 200-250ul VTM/UTM to swab chamber.	Mix 200 ul of a UTM with sample and add 800ul of the GenPad SSB	50ul of specimen collected in Copan eNAT
Same-day fresh specimen (left-over from diagnostic laboratory)	Nasal swab	Nasopharyngeal swab	Nasal swab	200-250ul VTM/UTM	200ul	50ul

6.2 Reference Standard Test and Index Test Procedures

The **reference test** will be one of the FDA/WHO EUA/EUL approved assays detecting SARS-CoV-2 RNA, as recommended by WHO EUL guideline "Instructions and requirements for Emergency Use Listing (EUL) Submission: In vitro diagnostics detecting SARS-CoV-2 nucleic acid or antigen", unless importation or supply chain issues prevent the use of any of such tests in specific settings selected for the evaluation. In this case, other comparable RT-PCRs might be implemented throughout the study provided they are considered equivalent in respect to the study, as long as it is a country-approved method. (SITE to add specific details on their reference RT-PCR test).
The respiratory sample for the reference test will be processed by trained personnel according to the specific Standard Operating Procedure (SOP) in place (the same day of collection or the next day, depending on site workflow). The result will be recorded in the corresponding Case Report Form (CRF).
If possible, the same site-specific RT-PCR protocol will be used for the entire POC evaluation, to ensure consistency throughout the study.

CASE DEFINITIONS for COVID-19:

Confirmed COVID-19 case: A participant will be considered COVID-19-positive if he/she has a valid positive result on a country-approved RT-PCR test.

No COVID-19: Participants will be considered COVID-19-negative if they have a valid negative RT-PCR result.

The respiratory sample for the **index test** (molecular POC) will be processed by personnel trained by the test manufacturer directly, or FIND team trained by the manufacturer, following the specific IFU provided by the manufacturer. The result will be recorded in the corresponding CRF. After assay completion, the test report generated by the device will be exported and uploaded in Open Clinica and a copy filed in the Investigator Site File (ISF) either paper or electronic. In case the test report cannot be exported from the device, a screenshot/picture of the test screen will be uploaded

in OpenClinica as source document for this study and a copy filed in the Investigator Site File (ISF) either paper or electronic. The molecular POC device will be operated, cleaned and maintained only by trained staff and according to manufacturer's instructions, ensuring device technical and health checks will be performed, where necessary.

Enrolled participants can be diagnosed based on RT-PCR results and clinical signs and symptoms by their treating physician; *the results of the molecular POC tests will not be used for clinical management.*

6.3 Other Tests: COVID-19 Genome Sequencing

Leftover aliquot of nasopharyngeal swabs tested positive in the reference assay will undergo sequencing for surveillance of SARS-CoV-2 variants for study purposes. Sequencing will be performed following the procedure established in the sequencing laboratory/facility routinely utilized by the selected study sites. (SITE to add specific details on their sequencing facility and procedure).

6.4 Safety Assessments

The study will comply with all biosafety precautions appropriate to the study procedures, including respiratory specimen collection, handling, processing, and disposal, to protect study participants and personnel. The index test will be performed within designated SARS-CoV-2 isolation zones. The reference test will be performed in laboratories designated for safe handling of these specimen types and following laboratory's safety protocols. All testing will be performed by appropriately trained personnel wearing all required PPE. The probability of (serious) adverse events (AE, SAE) occurring to a study participant while collecting the respiratory sample is deemed to be extremely low, as this procedure is considered to be very low risk. Nevertheless, should such event occur, this will be managed following the procedures described in section 7.

6.5 Other Study Procedures

The operators of the molecular POC device will be asked to complete an Ease-of-Use questionnaire to assess the perceived usability of index test. The answers provided by the operators will be converted into a score using a System Usability Scale.

7 Safety and Incident Reporting

Given that this is a diagnostic accuracy study that is not utilizing test results for patient care in clinical decision making and given that additional procedures for the study, i.e., respiratory swabs collection are extremely low risk, the probability of an AE or SAE occurring to a study participant to be associated with the investigational products is extremely low. There are no known expected

participant's reactions beyond mild discomfort. Nevertheless, safety and incident reporting are described in specific sections below. Warnings, precautions, and safety recommendations described in each device IFU provided by the manufacturer will be carefully read and observed. Country-specific safety reporting requirements to IEC/IRB and Regulatory Authorities will be followed.

This study does not have predefined termination criteria being an accuracy study.

SITE to add details on specific safety reporting requirements by the IEC/IRB

7.1 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and Serious Adverse Event (SAE) can be found in Appendix 2.

Given the nature of this study AE reporting is limited in scope to:

- SAEs that may be associated with respiratory sample collection.
- SAEs that occur at the testing sites using the investigational product (see section 7.1.3 Medical device incidents).
- Any other serious events that affect the rights safety or welfare of subjects.

There is minimal to absent likelihood of AEs for the current protocol evaluating an external *in vitro* medical diagnostic device for both study participants and devices users. For study participant, the AE will not be associated with the diagnostic device itself but could be associated with the performance of the respiratory sample collection procedure (procedure-related AE).

7.1.1 Time Period for Collecting SAE Information

Information will be collected during specimen collection and testing of the investigational product. SAEs will be recorded and reported to the sponsor or designee within 24 hours of the Investigator aware of the event.

All participant-related SAEs will be collected from the signing of the informed consent form (ICF) until completion of the procedures to collect the respiratory specimens and participant discharged from the study.

All device operator-related SAEs will be collected during all steps required for running the assay and during cleaning/maintenance procedures performance, during all periods of the study in which the device is used.

The Investigator will submit any updated SAE data to the sponsor within 24 hours of being made aware of the event.

Investigators are not obligated to actively seek SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study participation, the Investigator must promptly notify FIND.

7.1.2 Reporting and follow up of SAEs

All SAEs will be followed until resolution, stabilization, or the event is otherwise explained.
Prompt notification by the Investigator to FIND study team (Clinical Study Manager and/or Clinical Research Associate, Scientist and Project Manager) of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and operators are met.
Each site will also be provided with AE log and SAE report form. SAEs will be reported to the sponsor or designee within 24 hours of the Investigator aware of the event.
FIND will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
An Investigator who receives a safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from FIND will review and then file it in the Investigator Site File (ISF) and will notify the IRB/IEC, if appropriate, according to local requirements.

7.1.3 Medical Device Incidents (including Malfunctions)

Medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.
An incident is any event/malfunction/deterioration in characteristics and/or performance of a device that causes, or has the potential to cause, unexpected or unwanted effects involving the health and safety of participants, users, or other persons. This study focuses on molecular POC devices tests where the medical device itself does not come in contact with the study participant; if any, incident could only be associated with the performance of the respiratory sample collection procedure (procedure-related incident).
All the molecular POC devices investigated are instruments, whose installation will be executed ensuring strict adherence to instructions provided by the manufactures, meeting all requirements as per device manual and site-specific for installing new equipment, and including appropriate safety checks (e.g., electricity). Each device will be operated, cleaned and maintained only by trained staff and according to manufacturer's instructions. This is not an interventional study; therefore, device malfunctions are of limited concern for this study. Nevertheless, should any incident/malfunction arise due to the device itself, inadequate IFU, inappropriate user practice or inappropriate environment in which the device is used or stored, this will be reported by the Investigator to FIND using a dedicated issue/incident log. FIND will inform the manufacturer in case of device malfunction.
NOTE: Incidents fulfilling the definition of an SAE will also follow the processes outlined above.

7.1.4 Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the Investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify FIND.
Any medical device incident occurring to participant during the study will be documented in accordance with the Investigator's normal clinical practice and on the issue/incident log.
Any medical device incident/malfunction occurring to/detected by user during the study will be documented in accordance with the Investigator's normal practice and on the issue/incident log.

7.1.5 Follow-up of Medical Device Incidents

All medical device incidents involving an SAE will be followed and reported in the same manner as other SAEs (see Section 7.1.2). This applies to all participants and device users.
The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator. It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by FIND) and describes any corrective or remedial actions taken to prevent recurrence of the incident. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

7.1.6 Reporting of Medical Device Incidents to FIND

Medical device incidents will be reported to FIND study team (Clinical Study Manager, Clinical Research Associate, Scientist and Project Manager) within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident via phone or by email. Where applicable, FIND will promptly inform the manufacturer.

7.1.7 Regulatory Reporting Requirements for Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for FIND to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8 Statistical Considerations

8.1 Sample Size Determination

The sample size was developed in order to be able to obtain an estimate of the expected sensitivity and specificity of the index test based on the analytical data reported by the manufacturers:

- Sensitivity: 97% (Nudge), 98% (GenomEra), 98% (Mirai)
- Specificity: 99%
- Prevalence of COVID-19: 5%

Based on the WHO recommendations, 100 PCR positive will enable us to achieve a power of 80%, with a 95% confidence interval width of 10% under the assumption of a sensitivity value of 97%. A total of 100 confirmed PCR negatives will enable us to achieve an estimate of a specificity of 99% with a two-sided 95% confidence interval width of 6% and a power of 80%. With an estimated disease prevalence of 5% and a prevalence power of 80%, recruiting 100 confirmed positives will be the limiting factor, and 2171 participants are needed to be screened to reach this number.

8.2 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 4:

Table 4: Populations for Analysis

Population	Description
Enrolled/Intention-to-test (ITT)	All subjects successfully enrolled in the study (having signed the ICF)
Evaluable/Per Protocol Population (PP)	All subjects in ITT who have samples and valid results available for the index test evaluated at the specific site and the reference test.

8.3 Statistical Analysis Plan

The statistical analysis plan (SAP) for this study will be developed as a separate document and will describe in detail the procedures to analyse each endpoint, inclusion and exclusion of data, handling of missing data, definition of subgroups and any other relevant topic. This section is a brief summary of the planned statistical analyses of the primary and secondary endpoints.

General Methodology

Point estimates of sensitivity and specificity, with 95% confidence intervals based on Wilson's score method, will be calculated following the definitions below:

Table 5: Case predictions

	Reference standard classification			
Case prediction		Positive	Negative	Total
	Predicted positive	a	b	(a + b)
	Predicted negative	c	d	(c + d)
	Total	(a + c)	(b + d)	(a + b + c + d)

Table 6: Sensitivity and Specificity

a = True Positives b = False Positives c = False Negatives d = True Negatives	Sensitivity = a / (a + c) Specificity = d / (b + d)

The analyses of accuracy will be performed on the PP population for the analysis of the Endpoint 1.1, and will be stratified by the subgroups specified below for the analysis of the Endpoint 2.1:

- Sex (Men/Women)
- Days after symptom onset (1-3 days, 4-7 days, >7 days)
- Reference PCR Ct value (Ct < 18, 18 < Ct <= 25, 25 < Ct <= 33, Ct > 33)
- By COVID-19 vaccination status (no vaccination, one dose vaccination, multi-dose vaccination) as per information collected from participants
- By presence of previous SARS-CoV-2 infection(s) as per information collected from participants
- By SARS-CoV-2 genetic variant causing infection

The sum of usability scores will be calculated for the analysis of the Endpoint 2.2
Further details of each analyss will be described in the SAP.

8.3.1 Data Monitoring Committee (DMC)

A Data Monitoring Committee is not applicable for this study, as it is a low-risk study.

9 Regulatory and Ethical Considerations

9.1 Regulatory and Ethics Approvals

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
- Applicable Good Clinical Practice Guidelines: ICH GCP E6 (R2)
- Applicable laws and regulations (SITE to amend accordingly)

The protocol, protocol amendments, ICF and other relevant documents (e.g., advertisements) must be submitted to IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. A copy of the IRB/IEC approval letter should be filed at the investigator site. (SITE to amend accordingly)
FIND-approved versions of an amended study protocol should be signed by the Investigator(s). Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocol amendments restricted to clerical edits only will be provided to the study sites and submitted to the IRB/IEC for informational purposes.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, the WHO Good Clinical Laboratory Practice (GCLP), the Good Documentation Practice, and with applicable national regulations.

(SITE to amend accordingly)

9.2 Financial Disclosure

Investigators and sub-investigators will provide FIND with sufficient, accurate financial information as requested to allow FIND to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities, donors, entities funding the study.

9.3 Informed Consent Process

Eligible potential subjects will be recruited and documented written informed consent will be obtained by local clinical personnel/study staff trained in human subject's protections. Recruitment will occur at the time that the participant is approached for respiratory sample collection for COVID-19 testing per clinical routine. A written consent form describing confidentiality regulations and a participant information sheet describing the study purpose and procedures will be given to each subject.

The investigator or his/her representative will explain the nature of the study to the participant in a language understandable to him/her and will answer all questions about the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of ICH-GCP guidelines, and the IRB/IEC or study centre (SITE to amend accordingly, where necessary).

There must be evidence that written informed consent was obtained before the participant was enrolled in the study, and ample time was given to participant to consent. The date the written consent was obtained (as well as the time, ideally) must be recorded. The authorised person obtaining the informed consent must also sign and date the ICF.

Illiterate participants must provide a thumbprint on the ICF and the ICF signed and dated by an impartial witness.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study when new information, which might affect the participants decision about whether to continue in the research, becomes available and when study procedures involving participants are added, significantly modified or removed from the study. In case of non-substantive changes/minor changes, re-consent will not be necessary, as this will not increase risk or decrease benefit for participant.

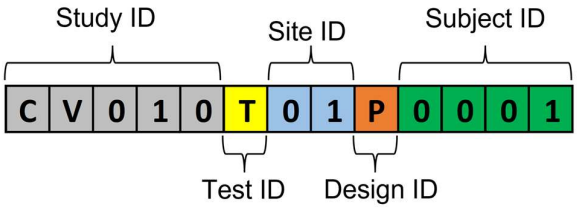
Participant will be explained that they are free to refuse to participate and may withdraw their consent at any time. Clinical personnel/study staff must explain that in this case the same patient care will be provided. The written consent form will be signed and dated by the participant and/or their legally authorized witness for illiterate participants. A signed original of this informed consent will be provided to the participant and a second original (complete and signed) will be attached to the subject's study record.

Should the reference test specimen be stored in authorized biobanks for future research studies, the ICF will contain a separate section that addresses the storage of the remaining specimen beyond the duration of the study and the use for future research studies. Participants will be told that they are free to agree or not to allow further use of samples and data stored beyond the end of the study for future research and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow sample and data further use for future research.

There will be no payment for participation in this research study, although participants may be reimbursed for time and transport a fee of 5-10USD max (SITE to amend accordingly, where necessary). There will be no costs to the subject for participating in this research study.

9.4 Data Protection

Participants/specimens will be assigned a unique identifier (see below a proposal example). Any participant/specimen records or datasets that will be transferred to FIND contain the identifier only; participant/subject names or any information which would make the participant/subject identifiable will not transferred.



The participant will be informed that his/her personal study-related data will be used by FIND in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant will be informed that his/her medical records may be examined by quality assurance auditors or other authorized personnel appointed by FIND, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10 Data Handling and Record Keeping

FIND is responsible for the data management of this study including quality control checks of the data and assessment of overall protocol compliance. All participant/specimen data relating to the study can be recorded in paper CRF by study site staff and entered from the paper CRF into FIND's online clinical study platform (OpenClinica Enterprise Edition version 4) or entered directly in OpenClinica, following Good Documentation Practice (GDoP). The Investigator or delegated designee is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 10 years after study completion unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of FIND. No records may be transferred to another location or party without written notification to FIND.

10.1 Source Data and Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (source data). The Investigator may need to request previous medical records or reports (if available), depending on the study. Source documents will be filed at the Investigator's site.

Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary.

The definition of what constitutes source data can be found in Table 7. To support the evaluation of assay performance, we will collect demographic and clinical data for each participant, where possible. Laboratory results of the novel molecular POC tests will be obtained directly from the device, including test failure or error and recorded on the corresponding CRF. Possibly, also the ambient temperature and humidity in the testing location will be recorded directly at the testing site on the CRF. Results of the routine RT-PCR tests, including Ct values, and of COVID-19 genome sequencing (for PCR positive samples) will also be obtained from reference/testing laboratories. We will also collect operator feedback on the ease of test operation and results reading using a standardized questionnaire.

Paper CRFs, which mirror the design of the electronic CRFs, may be used for ease of data entry by site study staff. The paper CRF will consist of some data that has been entered directly (e.g.: source data like information collected from participant clinical interview) and some data that has been transcribed from other sources, such as the PCR/sequencing/device report. Refer to the table below.

Table 7: Source data definition and record.

** As source documents, these must be maintained throughout the duration of the study and retained for 10 years after study completion.*

Type of source data	Original place of entry*
Eligibility and Informed Consent information	Paper CRFs or eCRFs (for direct data entry) and Informed Consent Form
Participants demographics	Paper CRFs or eCRFs (for direct data entry) or Site-specific Laboratory/Clinical Information Form
Participants medical history and clinical information (e.g. comorbidities, previous Covid 19 vaccinations and/or infections, symptoms, etc)	Paper CRFs or eCRFs (for direct data entry) or Site-specific Laboratory/Clinical Information Form
RT-PCR sample collection and processing information (e.g. kit name)	Paper CRFs or eCRFs (for direct data entry) or Site-specific Laboratory Form
RT-PCR sample results, including Ct values for sample and controls	Laboratory PCR form/report (electronic, paper or machine printout/screenshot/picture)
Molecular POC sample collection and processing information	Paper CRFs or eCRFs (for direct data entry) and/or device report/study worksheet
Molecular POC sample and control (internal, quality) results	Device report (electronic, paper or machine printout/screenshot/picture)

Positive RT-PCR sample sequencing information	Paper CRFs or eCRFs (for direct data entry) or Site-specific Laboratory Form
Positive RT-PCR sample sequencing results	CRF or Laboratory sequencing report (electronic, paper or machine printout/screenshot/picture)
Molecular POC ease of use questionnaire	Questionnaire

Other unidentified source data will be described in the Site Initiation/Monitoring Visit Report.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to participant medical records and source documents used for this study.

10.2 Data Management

Data Management procedures at FIND, including the setup of the database, programming edit and range checks and querying, are described in the Data Management Plan.

Results for testing each sample will be collected first on data collection form, and then recorded in OpenClinica, or recorded directly in OpenClinica. Results will be qualitative, according to manufacturer's instructions. After assay completion, the report of the results exported from the device will be uploaded in OpenClinica and a copy filed in the Investigator Site File (ISF) either paper or electronic. In case the device report cannot be exported, a screenshot/picture of the device screen report will be taken and uploaded as source documents for this study.

Data from each paper form will be entered in a timely manner into OpenClinica to allow remote monitoring. An electronic, site-specific database on OpenClinica platform will be used to capture all clinical information associated with each sample. Regular data quality control will be performed by the Investigator and/or study/site coordinator. Study results (reference and index test, sequencing) will be recorded with the specimen/participant unique identifier (ID) in paper CRF and then entered to OpenClinica database, or directly in OpenClinica.

Site staff will be responsible for entering data into OpenClinica where direct capture into EDC is not possible. Data will be cleaned of errors by FIND throughout the study as it is captured electronically.

The Investigator or delegated designee is responsible for verifying that data entries are accurate and correct. Data entered in the OpenClinica database must be consistent with the source documents or the discrepancies must be explained.

The site will be provided with individual password-protected accounts to access OpenClinica, following a training session given by FIND. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of FIND.

OpenClinica provides an audit trail system recording all data entries/changes and queries between FIND and the site. Data entry training will be provided by FIND, either on site or remotely sharing screen through Teams, Zoom or any other similar system.

11 Quality Management

Quality Management for this study consists of Quality Control activities, training and capacity building provided by FIND (or designee) to the investigational sites and laboratories, as well as the use of Standard Operating Procedures, Work Instructions, Tools and Templates.

Training on the protocol and the use of the IVDs and laboratory tests will be provided by FIND. Training on the EDC system will be provided by FIND Data Management prior to first participant enrolment or prior to database activation (release to production mode).

11.1 Quality Control (monitoring)

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The investigational site is responsible for performing regular Quality Control checks on the data they generate.

FIND will perform risk-based monitoring of this study and associated Quality Control checks. Where possible, study monitors will perform source data review and source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.2 Quality Assurance (auditing)

As part of routine Quality Assurance, FIND or designee may conduct an audit of the investigational site.

11.3 Study and Site Closure

FIND reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Investigational sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected.

The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for early closure of a study site by FIND are described in the contractual agreement.

12 Publication Policy

Data obtained from participation in this study are considered confidential. The investigators must adhere to the non-disclosure requirements set forth in the contractual agreement.

Participants of the study have the opportunity to be informed about the general outcome of the study. To do so, they are asked to contact an investigator. Furthermore, the study will be registered on clinicaltrials.gov and/or country-specific national public registries.

The Investigator is obligated to provide FIND or its designee with complete test results and all data obtained in this study. The information obtained during this study can be made available to other investigators and third parties, including regulatory agencies, only with written permission from FIND.

Authorship for scientific publication of the study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements, as described in the publication policy section of the contractual agreement.

13 Appendices

Appendix 1: Investigational products evaluated under this study protocol

Test manufacturer	Test name
DnaNudge (UK)	Covid/RSV/Flu Nudge Test
Mirai Genomics (Japan)	Test Kit for SARS-CoV-2 RNA Detection in Biological Material Using PCR Method
Abacus Diagnostica Oy (Finland).	GenomEra SARS-CoV-2, Flu A/B + RSV 2.0 Assay Kit

Appendix 2: Safety Definitions and Reporting

Adverse Event (AE) Definition
• An AE is any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) Definition:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAE Reporting to FIND
• The SAE Report must be sent to the FIND Head of Program and Study Manager via e-mail, marked High Priority, with a follow up call to ensure receipt. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames. • Contacts for SAE reporting can be found on the front of the protocol.

Appendix 3: Protocol Amendment Summary Table

Not applicable