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A prospective study to evaluate the real-world diagnostic accuracy and potential clinical impact of the Veros COVID-19 test in adults presenting to the Emergency Department with suspected COVID-19: ED-POC

Diagnostic Accuracy of a Novel COVID-19 Test

Chief Investigator: Professor Tristan W Clark

RESEARCH REFERENCE NUMBERS

IRAS Project ID:	**320705**
Sponsor's Number:	**RHM MED1913**
Research Ethics Committee Number:	**22/NE/0225**
CPMS ID:	**54620**
ISRCTN Number:	***-Pending-***

PROTOCOL VERSION NUMBER AND DATE

1.0 20th September 2022

SPONSOR

University Hospital Southampton NHS Foundation Trust

Title of Study

A prospective study to evaluate the real-world diagnostic accuracy and potential clinical impact of the Veros COVID-19 test in adults presenting to the Emergency Department with suspected COVID-19: ED-POC

Short Trial Title

Diagnostic Accuracy of a Novel COVID-19 test

PROTOCOL VERSION NUMBER AND DATE

Version	Date	Key Modifications	Author(s)
1.0	20th September 2022	N/A	Dr Mary Chapman Prof Tristan Clark

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted, and that the Chief Investigator (CI) agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's (and any other relevant) SOPs, Good Clinical Practice (GCP) guidelines, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I confirm that I will make the findings of the study publicly available through publication, or other dissemination tools, without any unnecessary delay, that an honest accurate and transparent account of the trial will be given and that any discrepancies from the study (as planned in this protocol) will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

Rachael Pulham 21/10/2022

Name (please print):

Rachael Pulham

Position:

.....

Chief Investigator:

Date:12/10/2022

Signature:

Name: Professor Tristan Clark

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Funder	Sense Biodetection Limited
Key Protocol Contributors	• Professor Tristan W Clark • Dr Mary E Chapman • Dr Nathan J Brendish

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ii. LIST OF ABBREVIATIONS

AMU	Acute Medical Unit
CES	School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton
CI	Chief Investigator
COVID-19	Coronavirus disease 2019
e-CRF	Electronic Case Report Form
ED	Emergency Department
EPR	Electronic Patient Record
GeneXpert	GeneXpert Xpress SARS-CoV-2/Flu/RSV assay
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
MHRA	Medicines and Healthcare products Regulatory Agency
mPOCT	Molecular Point-of-Care Test
NEWS2	National Early Warning Score 2
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health and Care
NPV	Negative Predictive Value
PPE	Personal Protective Equipment
PPV	Positive Predictive Value
PHE	Public Health England
PI	Principal Investigator
PIS	Participant Information Sheet
RAU	Respiratory Assessment Unit
REC	Research Ethics Committee
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TPP	Target Product Profile
UHS	University Hospital Southampton NHS Foundation Trust
VTM	Viral Transport Medium

iii. STUDY SUMMARY

Title	A prospective study to evaluate the real-world diagnostic accuracy and potential clinical impact of the Veros COVID-19 test in adults presenting to the Emergency Department with suspected COVID-19: ED-POC	
Short Title	Diagnostic accuracy of a novel COVID-19 test	
Design	Prospectively recruited diagnostic accuracy study	
Participants	Adults aged 18 years old, or over, presenting to hospital with suspected COVID-19 and/or an acute respiratory infection	
Planned Sample Size	400 (with the intention of recruiting 150 COVID-19 positive patients and 250 COVID-19 negative patients)	
Planned Recruitment Period	• Recruitment period – 1 year • Data Analysis – 5 years	
	Objectives	Outcome Measures
Primary	• To evaluate the diagnostic accuracy of the Veros COVID-19 test in a clinical setting.	• Sensitivity, specificity, positive predictive value, and negative predictive value of the results of the Veros COVID-19 test, compared to the reference standard (GeneXpert Xpress SARS-CoV-2 assay).
Secondary	• To evaluate the speed of the Veros COVID-19 test. • To evaluate the reliability/failure rate of the Veros COVID-19 test. • To evaluate the ease-of-use of the Veros COVID-19 test compared to the reference standard • To evaluate the infectiousness of samples with discordant results. • To evaluate the relationship between viral load (as determined by GeneXpert Cycle threshold (Ct) values) and the performance of the Veros COVID-19 test.	• Time to result for the Veros COVID-19 test compared to the reference standard. • Proportionate failure rate of the Veros COVD-19 test to provide a valid result. • Ease-of-use (derived from quantitative data from questionnaires provided to users of the Veros COVID-19 test and reference standard test). • The proportion of discordant results that are viral culture positive. • The performance of the Veros COVID-19 test results across high, medium, and low viral loads (as determined by Ct value bins).
Exploratory	• To evaluate the clinical significance of discordant results between the Veros COVID-19 test and the reference standard. • The potential reduction in time to patient transfer to definitive ward area, COVID-19 antiviral administration, and discharge from the Emergency Department (ED).	• Qualitative assessment of patient records. • Time from COVID-19 testing to arrival in a definitive ward area (COVID-19 positive or COVID-19 negative), time to COVID-19 antiviral administration and time to discharge from the ED.

iv. FUNDING

FUNDERS	FINANCIAL AND NON-FINANCIAL SUPPORT
Sense Biodetection Limited	Financial support Non-financial support in the form of consumables free of charge (the Veros COVID-19 test kits and the Veros control materials)

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor is University Hospital Southampton NHS Foundation Trust (UHS), which is the organisation that is taking legal responsibility for the trial.

The funder and Sponsor of the study have had no role in the study conception and design, and will have no role in the study's conduct, data analysis, or manuscript preparation.

vi. PROTOCOL CONTRIBUTORS

Professor Tristan W Clark

Dr Mary E Chapman

Dr Nathan J Brendish

1 BACKGROUND

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a coronavirus first identified as a cause of human infection in November 2019. By March 2020, a pandemic was declared and, at the time of writing, has resulted in over 600 million confirmed cases and nearly 6.5 million deaths[1]. Over the course of the pandemic, infection rates and the number of related hospitalisations have fluctuated greatly in the United Kingdom, as public health strategies changed, and new viral variants presented. Each surge in case numbers has led to morbidity, mortality, and disruptions to the provision of healthcare services, with impact felt even in times of lower prevalence[2].

While the rapid roll-out of vaccines and changes to the virulence of viral strains have improved the morbidity and mortality associated with infection, COVID-19 will remain a defining feature of the coming years, dangerous to the general population (with the immunocompromised and unvaccinated likely to be at higher risk) and disruptive to healthcare services already under significant pressure. These problems could be compounded by the as yet unpredictable emergence of new variants[3].

The pathway of patients with symptoms suggestive of COVID-19 is typically that, on being triaged in Emergency Departments (ED), they are cohorted together in separate areas while awaiting COVID-19 test results. This has required the reworking of departmental layouts to meet varying prevalence, disruptions to downstream hospital flow and delayed definitive ward placements. The cohorting of symptomatic patients together, both those that will go on to test positive with those that will test negative, also increases the risk of hospital acquired COVID-19[4].

Diagnostic techniques and COVID-19 testing capacity have evolved rapidly during the pandemic, with testing initially run only through centralised laboratory-based RT-PCR and now superseded by molecular point of care testing (mPOCT) in ED settings. This has reduced time to results from, in one trial, a median of 21.3 hours to 1.7 hours[5] and introduced benefits such as reductions in nosocomial COVID-19 infections[6].

The development of single-use analyser-free COVID-19 tests heralds the next step forward in COVID-19 diagnostics. A range of devices are being investigated, reporting result concordances of 95-98% with reference standards [7,8]. Such devices have many features that meet the desirable criteria specified by the Medicines and Healthcare Products Regulatory Agency (MHRA)'s Target Product Profile (TPP)[9] for the development of novel COVID-19 POCTs.

Among this new generation of COVID-19 diagnostics, the Veros COVID-19 test (by Sense Biodetection Limited) is single-use, handheld, analyser free, has no reliance on a power source, requires no dedicated user training, and uses nucleic acid amplification to provide a qualitative positive or negative result on an anterior nasal swab sample in approximately 15 minutes. Its characteristics satisfy most of the desirable criteria set forward by the MHRA TPP for novel COVID-19 POCTS, and initial data provided by Sense Biodetection Limited (based on 292 evaluable subjects in a prospective clinical study of symptomatic adults with suspected COVID-19) reported a PPA of 95.2%, an NPA of 99.5% and an overall percentage agreement (OPA) of 97.99% [10] when compared to a reference standard qRT-PCR test. This initial data also reports only a 6% return of invalid test results (the 6% of samples that initially returned an invalid result were subsequently run again on a new test kit and all then returned valid results).

While these initial results are promising, further evaluation is needed to gauge the test's potential in clinical settings. This study aims to evaluate the real-world diagnostic accuracy of the Veros COVID-19 test compared to a current reference standard (the Cepheid GeneXpert Xpress SARS-CoV-2 assay) [11] in adult patients presenting to secondary care with suspected COVID-19 and/or acute respiratory illness (ARI).

Time to result, ease-of-use and proportionate reliability can also be assessed. The cases of patients with discordance between the Veros COVID-19 test result and the reference standard can be further investigated using viral culture and GeneXpert Ct values to explore the possible significance of conflicting results between testing modalities.

Should the Veros COVID-19 test demonstrate acceptable diagnostic accuracy when compared to the current reference standard, it could offer scope to improve time to results, and both portability and accessibility of accurate COVID-19 testing.

Methods:

We will undertake a diagnostic accuracy study of the Veros COVID-19 test, in the form of a prospectively recruited study. Adult patients presenting to the ED with suspected COVID-19 and/or symptoms of an ARI will be recruited and tested at the point-of-care using the Veros COVID-19 test kit. A second swab will be taken and stored for potential further testing in form of viral culture. These patients will also be receiving COVID-19 testing from the clinical team in the ED as part of their routine clinical care, which will be run on the Cepheid GeneXpert Xpress SARS-CoV-2 assay (a component of the Cepheid GeneXpert Xpress SARS-CoV-2/Flu/RSV test).

The result of the GeneXpert SARS-CoV-2 assay, as part of their routine clinical care, is available to clinical staff to facilitate decision making for patients. Results of the Veros COVID-19 test will not be disclosed to clinical staff or participating patients. Active patient participation in the study will end after sample collection.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) (with 95% confidence intervals) of the Veros COVID-19 test can then be calculated using the GeneXpert SARS-CoV-2 result as the reference standard (from here on in this protocol, the GeneXpert SARS-CoV-2 component of the SARS-CoV-2/Flu/RSV test will be referred to as the reference standard). Additional data to be collected from the electronic patient record (EPR) will consist of anonymised baseline clinical data and outcome data. These will be analysed to evaluate secondary outcome measures.

2 RATIONALE

COVID-19 will remain a burden on healthcare services and their patients for years to come. Improvements in diagnostics have already led to quantifiable improvements in patient outcomes over

the course of the pandemic[6] and streamlined patient flow, reducing the time from arrival in hospital to definitive ward placements[5]. Diagnostics like the Veros COVID-19 test could be the next step towards faster diagnosis and appropriate treatment, while also minimising the impact of COVID-19 on patient flow by providing faster results (without reliance on analysers or dedicated staff training).

EDs, and other admitting departments, currently require cohorted areas for symptomatic patients while COVID-19 results are awaited and before downstream ward placements can be decided. Reducing time to results to just 15 minutes (at the time of writing, and to the best of the team's knowledge, the Veros COVID-19 test is the only analyser-free COVID-19 POCT with a time to result of ≤15 minutes) could improve patient flow, reduce the need for large cohorted areas in EDs, and rapidly identify those patients that could benefit from antiviral treatment. The removal of analysers and their maintenance needs could also potentially reduce the cost associated per COVID-19 test, while also removing reliance on complex analysers requiring specialist repair, maintenance, and user training.

Realising these potential benefits requires further evaluation of the Veros COVID-19 test. Should its diagnostic accuracy be acceptable when compared to the reference standard and its reliability acceptable, the potential for portable, rapid, analyser-free COVID-19 testing could offer a range of benefits to secondary care.

Assessment and management of risk

No greater risk to patients enrolled in this study is anticipated than those present during routine clinical care. The harm associated with respiratory swabs is minimal and typically limited to mild and short-lived discomfort at the time the swabs are performed.

3 AIMS, OBJECTIVES AND OUTCOME MEASURES

Aim – To evaluate the real-world diagnostic accuracy of the Veros COVID-19 test, and its potential clinical impact in the emergency department.

3.1 Objectives

Primary objective:

- To evaluate the diagnostic accuracy of the Veros COVID-19 test in adults presenting to secondary care with symptoms of suspected COVID-19/ARI, compared to the reference standard.

Secondary objectives:

- To evaluate the time to result for the Veros COVID-19 test compared to the reference standard.
- To evaluate the reliability/failure rate of the Veros COVID-19 test.
- To evaluate the ease-of-use of the Veros COVID-19 test in a clinical setting, compared to the reference standard.
- To evaluate the infectiousness of samples with discordant test results.
- To evaluate the relationship between viral load (as determined by the reference standard's Cycle threshold (Ct) values and the performance of the Veros COVID-19 test).

Exploratory objectives:

- To evaluate the clinical relevance of discordant results between the Veros COVID-19 test and the reference standard.
- To investigate the potential clinical impact of reduced time to results in COVID-19 testing by investigating time to patient transfer to a definitive ward area, time to antiviral administration and time to discharge from the ED.

3.2 Outcome measures

Primary outcome measure:

- Diagnostic accuracy of the Veros COVID-19 test compared to the reference standard. Sensitivity, specificity, PPV, and NPV (with 95% confidence intervals) will be calculated to evaluate the level of accuracy.

Secondary outcome measures:

- Time to result for the Veros COVID-19 test compared to the reference standard.
- Proportionate failure rate of the Veros COVID-19 test (with the failure to provide a valid result after use of a test denoting a failed test).
- Ease-of-use (derived from quantitative data from questionnaires provided to users – See *Appendix 1*).
- The proportion of discordant results that are viral culture positive (See *Appendix 2* for the laboratory protocol for SARS-CoV-2 cell culture).
- The performance of the Veros COVID-19 test across high, medium and low viral loads as determined by Ct value bins (with a Ct value of <25 indicating high levels of virus, Ct>25<30 medium levels of virus and Ct>30 low levels of virus[12]).

Exploratory outcome measures:

- Qualitative clinical assessment of the significance of discordant results between the Veros COVID-19 test and the reference standard. This will be informed by a review of the patient's clinical data along with the results of the viral culture and Ct values, allowing an assessment of the likely clinical significance of discordant results.
- Time from COVID-19 testing to arrival in a definitive ward area, to COVID-19 antiviral administration and to discharge from the ED.

4 Study Process

This is a prospectively recruited diagnostic accuracy study, investigating the Veros COVID-19 test.

Adult patients presenting to the ED with symptoms of COVID-19 and/or ARI will be eligible to participate. They will be approached and consented for the taking of two samples in addition to those taken as part of routine clinical care (which includes a combined nose and throat viral swab which will be tested for COVID-19 on the reference standard assay by ED staff, as is currently routine care for new presentations of possible COVID-19 infection in the ED). The two samples required by the study

will be *Number 1*: an anterior nasal swab, to be run in department on the Veros COVID-19 test kits by research team staff, and *Number 2:* a combined nose and throat swab for storage, in case later required for viral culture and other testing.

Patient care will not be altered from routine clinical care as clinical staff and participants will not be informed of the results of the Veros COVID-19 tests. This is because the Veros COVID-19 test is not yet used during routine clinical care and has not undergone local validation or verification. Participants will have received routine COVID-19 testing from the clinical team, in the form of the combined nose and throat swab run on the reference standard assay.

The results of the Veros COVID-19 test and the reference standard can be compared to assess diagnostic accuracy, while time to results can also be recorded and compared.

Questionnaires will be given to research staff using the Veros COVID-19 test, and to users of the GeneXpert analyser, to evaluate the tests' ease-of-use. The questionnaire is adapted from an ease-of-use scoring system developed for a randomised controlled trial that evaluated the ease-of-use of 10 different diagnostic modalities. *Nicholson et al* based their scoring system upon the US Clinical Laboratory Improvement Amendments (CLIA) categorisation criteria that grade aspects of a test system by its level of complexity across a range of criteria[13]. This ease-of-use questionnaire has undergone minor adaptations for this study to reflect improvements made to the turnaround time of test results since the scoring system was developed (See *Appendix 1* for the adapted questionnaire).

Research team members will carry out the Veros COVID-19 tests, and results will be recorded manually in the ED (as the tests do not interface with NHS systems) while the reference standard test result will be reviewed on the participant's EPR.

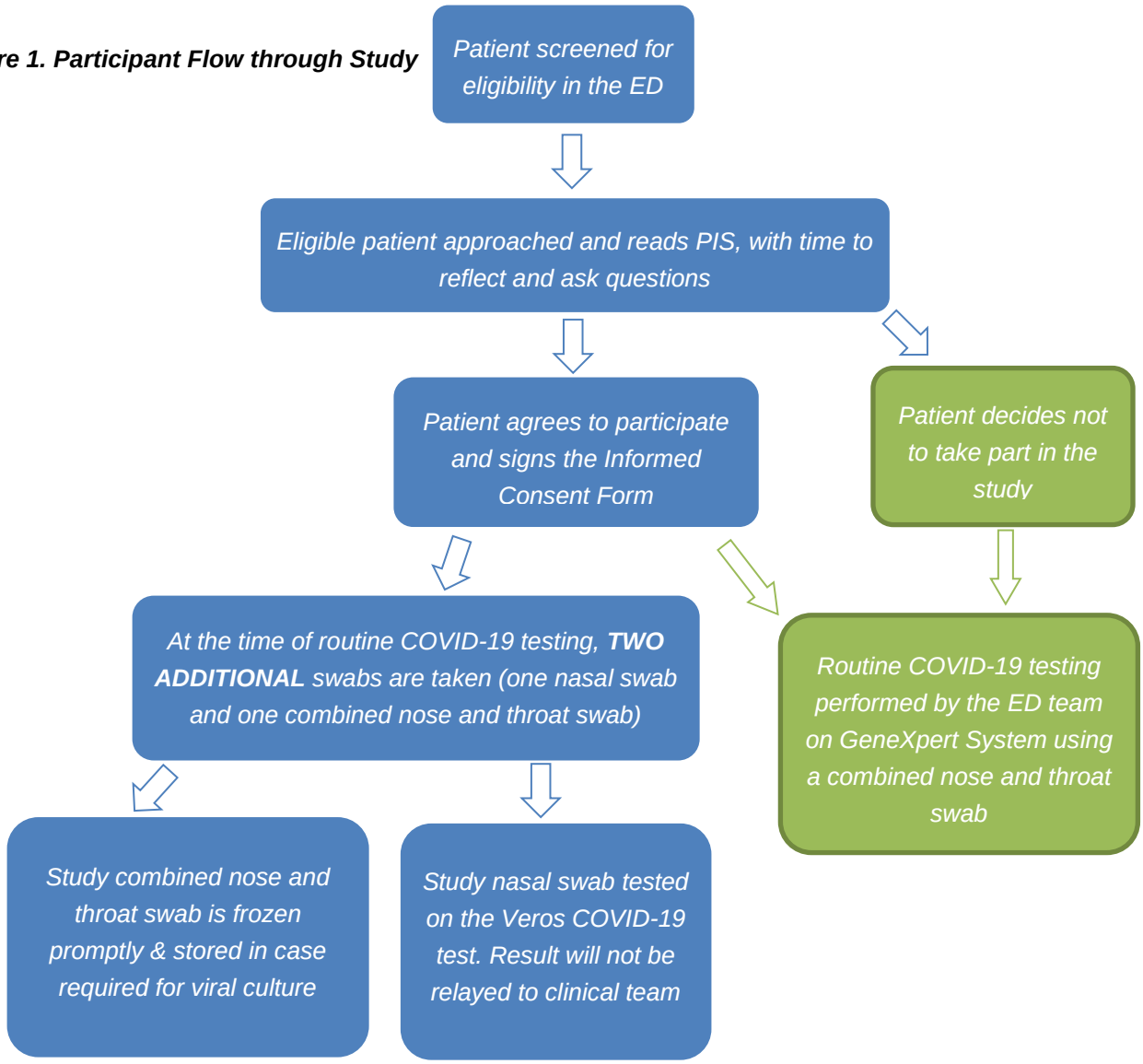
Participant involvement in the study is considered to have ended once their last physical interaction with the research team has been completed, although some retrospectively collected outcome measures will be extracted from the EPR after this time. For all patients, it is intended that the final physical interaction with the research team be on the same day as enrolment, at the taking of samples.

The time to result for the Veros COVID-19 test will be established by the research team member recording time from sampling to the return of a result on the test device, while time to result for the reference standard will be recorded from sampling to the time that a result is released to the EPR.

The combined nose and throat swab sample, taken for possible further testing (viral culture to allow the evaluation of discordant COVID-19 results from the Veros COVID-19 test and reference standard) will be frozen at -80°C (+/- 10°C) until sent for culture. This will allow an assessment of the infectiousness of samples.

Patient flow through the study is shown in *Figure 1*.

Figure 1. Participant Flow through Study



5 TRIAL SETTING

- Single centre diagnostic accuracy study
- Emergency Department (also to include any direct medical admissions to the Acute Medical Unit (AMU) at Southampton General Hospital, UHS)

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Is a patient in the ED or AMU at Southampton General Hospital, UHS
- Aged ≥ 18 years old
- Can be recruited promptly into the study on arrival to hospital at the time of/prior to routine point-of-care testing for COVID-19

And

- Has an acute respiratory illness (ARI)

OR

- Does not have an ARI but is a suspected case of COVID-19 according to the current PHE case definition

And

- Has the capacity to consent to the study

Note – an episode of ARI is defined as an acute upper or lower respiratory illness (including rhinitis, rhinosinusitis, pharyngitis, pneumonia, bronchitis, and influenza like illness) or an acute exacerbation of a chronic respiratory illness (including an exacerbation of COPD, asthma, or bronchiectasis). For the study, ARI as a provisional, working, differential or confirmed diagnosis must be made by the clinical team/ED triage team.

6.2 Exclusion criteria

- Not fulfilling all inclusion criteria
- Declines nasal/pharyngeal swabbing

Concurrent, prior, or subsequent enrolment in another study is unlikely to be an exclusion criterion. Co-recruitment requires local, valid, R&D approval that is prospectively applied for and agreed between principal investigators (documented by a "12-week exemption form" or similar).

The inclusion of pregnant women is permitted in the study. No additional risk is perceived to pregnant women or their offspring by any of the study procedures. No additional data collection or monitoring is therefore anticipated in this group.

7 TRIAL PROCEDURES

7.1 Recruitment, Participant Identification & Screening

As part of routine clinical care, patients with symptoms of an ARI or suspected COVID-19 will be streamed into a cohorted area (such as the Respiratory Assessment Unit in the ED) by the clinical teams. They will then receive routine COVID-19 testing, and remain there while awaiting COVID-19 test results and onward movement from ED. In these cohorted areas, patients will be identified as potentially eligible participants and approached by members of the clinical team. Eligibility will then be confirmed by members of the research team and informed consent sought prior to/at the time of the taking of routine nose and throat swabs for COVID-19 testing. If consent is obtained, the additional two swabs (the anterior nasal swab for testing on the Veros COVID-19 test, and the combined nose and throat swab for storage for future testing) for the study can then be taken. Several baseline data points will also be collected at this stage. Sampling and collection of baseline data will comprise the final physical interaction of the research team with the participating patient.

The routine COVID-19 combined nose and throat swab will be processed by clinical staff using the reference standard assay, and the study's anterior nasal swab will be processed by the research team using the Veros COVID-19 test. The study's combined nose and throat swab sample (for viral culture) will be stored, frozen at -80°C (+/- 10°C), pending possible further testing.

7.2 Consent

Discussion of the study will be undertaken with the patient by a research team member and a Participant Information Sheet (PIS) provided to the patient. There will be opportunity for the participant to ask questions.

If the patient is willing to participate in the study and fulfils the eligibility criteria, the research team will obtain written informed consent using the Informed Consent Form (ICF). In view of the need for the rapid return of test results to facilitate onward patient care, and the need for routine and study swabs to be taken at comparable time points, the usual 24-hour consideration period for a participant cannot apply in this study. Given the low-risk nature of this respiratory tract sampling, that no changes to routine clinical care are planned for any participating patients and the brevity of the patient's physical involvement with the study, the research team feels that a shorter time to consider involvement is reasonable.

If the patient is willing to be involved in the study and is able to sign and date the ICF to indicate consent, they will do so. If the patient can provide informed consent but has difficulty writing or otherwise filling in the ICF, informed consent from the patient will be verified by an independent witness (this will usually be a clinical member of staff), and the independent witness would then fill in, sign and date the ICF on the patient's behalf. Both the person taking consent and either the patient or independent witness must personally sign and date the ICF. Copies of the ICF will be given to the patient (and witness if applicable) for their records and put into the patient's notes. The original ICF is stored securely by the study team in the Investigator Site File (ISF).

Each patient will be assumed to have capacity unless it is established that they lack capacity. As this study does not offer any direct benefit to the participants, patients lacking capacity and unable to consent for themselves will not be eligible for this study.

In the unlikely event, given the brevity of the patient's participation in the study, that a patient, who had capacity at the outset of the study, loses capacity before their active participation in the study is complete, they will be withdrawn from the study and any samples or data so far obtained will be

destroyed (although signed ICFs, minimal personal identifiable information to record the patient's initial involvement and subsequent withdrawal, and any completed point-of-care test result, will be retained).

Any members of the research team obtaining consent will have been trained to do so in accordance with the protocol, principles of Good Clinical Practice and the Declaration of Helsinki and will be competent in the assessment of mental capacity.

7.3 Data Collection

After documentation of the patient's identifiable data in the enrolment log, anonymised study data will be collected using ALEA e-Case Report Forms (eCRF).

Baseline anonymised data will be collected for all patients on their enrolment in the study. This will include:

- Date of birth
- Age
- Sex
- Ethnicity
- Vaccination status
- Comorbidities
- Admission observations and National Early Warning Score 2 (NEWS2)

The result of the Veros COVID-19 test will be documented when a result is returned at the point-of-care. The time to result for the Veros COVID-19 test will also be documented when this result is returned. This data, in an anonymised form, will be inputted directly to the Electronic Case Report Form (e-CRF).

Further data will be collected retrospectively, after the participant's last physical interaction with the research team. This will be collected from the EPR, from questionnaires given to test users and from return of anonymised results of samples sent for viral culture. This will consist of:

- The duration of illness prior to testing

- Clinical presentation at the time of testing
- Proportionate reliability of the Veros COVID-19 test
- The result of the GeneXpert Xpress SARS-CoV-2/Flu/RSV test
- Time to result for the GeneXpert Xpress SARS-CoV-2/Flu/RSV test
- Viral load/Ct values from GeneXpert analysis (where applicable)
- Results of viral cultures (where applicable)
- Time to arrival in definitive ward area
- Time to antiviral administration in COVID-19 positive patients (if appropriate)
- Time to discharge from the ED
- Ease-of-use scores for the Veros COVID-19 test and the reference standard test

7.4 Trial processes

Once enrolled, participants will be assigned a unique participant identification number/code. All study samples, their results and further data collection after enrolment will be identified by this unique participant identification number/code.

Respiratory samples will be collected from participants by a trained member of the research team, wearing PPE in accordance with the latest UHS infection prevention and control policy. These samples will be taken alongside the routine combined nose and throat swab which will be tested for SARS-CoV-2 on the reference standard test by clinical staff.

The required study samples will be:

1. An anterior nasal swab, from the Veros COVID-19 test kit, to be run on the Veros COVID-19 test.
2. A combined nose and throat swab which will be frozen and stored in case required for viral culture (to allow evaluation of the infectiousness of samples, and assessment of samples with discordance between the reference standard and the Veros COVID-19 test results).

The Veros COVID-19 test's anterior nasal swab will be placed immediately into the Veros COVID-19 test kit's sample buffer tube. The kit's transfer pipette will be used to transfer the sample over the sample chamber of the test device. Keeping the device level, the lid of the test device is slid forward until there is a click when the lid is half closed. The user pauses at this point, for several seconds, to allow the sample to flow into the test device before continuing to slide the lid forward to its end position. When the lid is fully forward, pressure applied down onto the lid seals the sample chamber. A green light indicates that the test is running, with results available approximately 15 minutes later. When the test is complete, a solid blue light appears on the device. Lines at the positive control mark indicate a valid test result and the concurrent presence of any line in the COVID-19 position indicates a positive test result. Absence of a line in the control position, or a red light instead of blue, indicates an invalid test result [10]. Results from the Veros COVID-19 test devices can be read at the point-of-care by research team members. Should an invalid result be returned, providing the sample has spent <1 hour at room temperature (15-30°C), the sample may be re-run using a new test device. Once a valid test result has been returned, the remaining sample will be stored, frozen at -80°C (+/- 10°C).

The study's combined nose and throat swab will be placed into 1ml of sterile Viral Transport Media (VTM) and will be promptly frozen at -80°C (+/- 10°C). This will allow samples to be sent for viral culture, if required, to evaluate their infectiousness. The laboratory protocol for SARS-CoV-2 cell culture is detailed in *Appendix 2*.

The reference standard result and Ct values can be read retrospectively from the EPR and UHS IT systems.

Users of the Veros COVID-19 test kits will be asked to complete questionnaires (See *Appendix 1*) after they have had experience of using the kits, with no dedicated prior training and with access only to the Veros COVID-19 test *Instructions for Use* document[10].

7.5 Withdrawal criteria

A participant may decide to withdraw from the study at any time, without giving a reason, and with no detriment to their medical care or legal rights.

The CI may withdraw a patient from the study in the interests of participant safety or the integrity of the research study, or on the advice of the Sponsor's representative (Research & Development (R&D) department).

Any patient who is withdrawing from the study has the options of withdrawing and having any data and/or samples collected so far retained or withdrawing and having their data and/or samples destroyed (but signed ICFs, minimal personal identifiable information to record the withdrawal, and any completed point-of-care test result will be retained). A note to file would normally be sufficient to record any withdrawal.

As previously described, although unlikely given the brevity of active participation in the study, should a patient lose capacity during active participation in the study processes having initially consented, they will be withdrawn from the study and any samples or data so far obtained will be destroyed (although signed ICFs, minimal personal identifiable information to record the patient's initial involvement and subsequent withdrawal, and any completed point-of-care test result will be retained).

7.6 Storage and analysis of clinical samples

Two samples will be taken from each participating patient for this study.

Sample 1:

- Is an anterior nasal swab, placed into the sample buffer tube (swab and buffer tube from the Veros COVID-19 test kit), and run on the Veros COVID-19 test.
- If an invalid result is returned, the same sample will be used to run a second test (the sample must have spent no more than an hour at temperatures between 15-30°C).
- Once the Veros COVID-19 test has returned a valid result, the remaining sample, identifiable only by the participant's unique participant identification number, will be retained and stored at -80°C (+/- 10°C).

Sample 2:

- Is a combined nose and throat swab, placed in 1ml of VTM. This will be labelled with the unique participant identification number and frozen at -80°C (+/- 10°C).
- In the event of discordant results, from the reference standard test and the Veros COVID-19 test for a given participant, viral culture will be performed (See *Appendix 2*). Non-discordant samples may also be sent for culture to allow evaluation of infectiousness.
- Remaining samples, identifiable only by the participant's unique participant identification number, will continue to be stored at -80°C (+/- 10°C).

The remaining anonymised stored samples (both *Sample 1* and *Sample 2*) at the end of the study, will continue to be stored, frozen at -80°C (+/- 10°C), within the CI's institution in a secure location, for up to five years. After this point, further application to the relevant ethics committee may be required to continue storing and using the samples, or the CI may deposit the samples in an appropriately licenced biobank or destroy the samples. Access to these stored samples is restricted to the CI's team and relevant laboratory managers.

The consent provided by participants expressly permits further ethically approved research (which may include validation of molecular and other test platforms for SARS-CoV-2, and pathogen sequencing) on the stored samples, should any remain after this study has concluded. This work will primarily occur within the Clinical and Experimental Sciences (CES), Faculty of Medicine, University of Southampton, but collaboration with other institutions is at the discretion of the CI.

7.7 End of trial

The study recruitment period will be for up to 12 months, with up to five years from the end of the recruitment period for laboratory analysis, write up and publication. The exact start date will depend upon staff availability and COVID-19 prevalence but will fall in early January 2023.

7.8 Safety

7.8.1 Serious Adverse Events

Serious adverse events (SAEs) are typically monitored for extended periods and are reportable during the monitoring window if an adverse event results in death, is life threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity or consists of a congenital anomaly or birth defect.

However, within the parameters of this study, the risks of respiratory tract sampling are minimal and where occurring are likely to be mild and of short duration (it is a procedure undertaken daily for many patients throughout UHSNFT). Given the low-risk nature of this respiratory tract sampling, the brevity of the participants' physical involvement in the study and that no changes to routine clinical care are planned for any participants, we do not anticipate any significant increased risk as a result of the study procedures that would require monitoring for SAEs for a prolonged period after physical involvement. As such, SAEs will only be reportable in the event that they are thought to be due to either the process of the participant's enrolment or the process of taking samples. Monitoring for SAEs will be for one hour post sampling. These parameters were discussed and agreed with the Sponsor.

In the event of a study-related SAE being identified by the research team, the Sponsor will be informed within 24 hours and the Research Ethics Committee (REC) will be informed as per Health Research Authority (HRA) regulations.

Should any of the team become aware of SAEs beyond the period of active monitoring that are thought to be linked to the study processes/enrolment, these will also be reported.

7.8.2 Investigator Responsibilities

The CI is responsible for the overall conduct of the study and compliance with the protocol and any protocol amendments. The CI will be responsible for using medical judgement in assigning seriousness of SAEs and causality.

It is the responsibility of the CI to ensure that all SAEs, as previously defined, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event, and to provide further follow-up information as soon as it is available.

Responsibilities may be delegated to an appropriate member of the study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

7.8.3 Notification of deaths

Given that involvement in this study for participating patients is extremely low risk, deaths will only be reported to the Sponsor if the study is assessed as having contributed to the death. This is not anticipated.

7.8.4 Pregnancy reporting

Given that the taking of samples should not confer any additional risk upon pregnant patients, pregnancy is not considered an adverse event. No monitoring or additional management should be required for participants who are pregnant or who later become pregnant.

7.8.5 Reporting urgent safety measures

A Sponsor or investigator may take appropriate urgent safety measures to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. The REC must be notified, in the form of a substantial amendment, that such measures have been taken and the reasons why. This must be done no later than 3 days from the date that the measures are taken.

7.8.6 Letters to General Practitioners

Given that participating patients will not receive any deviation from routine care as a result of this study, and that the results of the Veros COVID-19 tests are not being used to inform patient care or to provide a diagnosis, letters informing GPs of their patient's involvement with the study will not be sent out as it will not add any value to the patient's ongoing care and add to the already significant administrative workload managed in primary care.

8 STATISTICS AND DATA ANALYSIS

8.1 Sample size calculation

The planned sample size of 400 patients has been chosen as a pragmatic cohort size to achieve in the intended time frame and with the anticipated staffing, while also consisting of sufficient numbers to give a clinically meaningful assessment of test performance. Sense Biodetection Limited has agreed to provide sufficient Veros COVID-19 test kits to achieve this sample size.

A sample size of 400 patients has also been chosen to be consistent with the MHRA TPP recommendations for the evaluation of the performance of COVID-19 POCTs. This specifies that at least 150 positive clinical samples, over a range of viral loads, should be assessed to allow for the establishing of clinical sensitivity of greater than 97% (within confidence intervals of 93-100%) and that at least 250 negative clinical samples should be assessed to allow for the establishing of clinical specificity of greater than 99% (within confidence intervals of 97-100%)[9]. Whilst these high levels of accuracy may not be necessary for the eventual use of the Veros COVID-19 test in routine clinical care, depending on use case, they provide a gold standard framework to assess accuracy with precision.

8.2 Statistical analysis plan

Summaries of all baseline characteristics will be presented using means and standard deviations, medians and interquartile ranges, or frequencies and percentages as appropriate.

Test results from the Veros COVID-19 test and GeneXpert SARS-CoV-2 assay will be compared using standard comparative statistical methods. Sensitivity, specificity, PPV, NPV and overall accuracy of the Veros COVID-19 test (with 95% confidence intervals), compared to the reference standard, will be calculated.

Proportionate reliability/failure rate of the Veros COVID-19 test will be calculated as a percentage.

Time to result, in minutes, will be measured for each of the Veros COVID-19 tests and its GeneXpert SARS-CoV-2 comparator, and the results compared using standard comparative statistical methods (e.g. Student's T test, Mann Whitney U test).

Ease-of-use scores (using the scoring system in *Appendix 1*) will be compiled for the Veros COVID-19 test and the reference standard. Given the clear boundaries of the criteria within the scoring system,

little variance between user responses is anticipated for each testing modality, but where there is variance in response, this will be presented using frequencies and percentages as appropriate.

The proportion of discordant results that are culture positive/negative will be reported. The performance of the Veros COVID-19 test results (sensitivity, specificity, PPV and NPV (with 95% confidence intervals)) will be calculated for high, medium and low viral loads (based on Ct value bins as previously described).

No interim analysis is planned given the very low risk of harm associated with the intervention in this non-CTIMP trial.

Missing data has been minimal in the CI's previous POCT studies and therefore is not expected to be a significant issue in this study. The use of multiple imputation will be considered should missing data exceed 5% of the primary outcome or for key secondary outcomes.

9 DATA MANAGEMENT

9.1.1 Source Data

Source data will be recorded and maintained in keeping with GCP principles to facilitate reporting and analysis, and quality control, audit and inspection.

Baseline and clinical data will be collected on all participants at enrolment, shortly following enrolment (when the Veros COVID-19 test result is available) and retrospectively from the EPR to allow for data collection on all outcome measures. For each participant, this data consists of age, sex, ethnicity, vaccination status, observations and NEWS2, duration of illness, clinical presentation, time of testing, result of the Veros COVID-19 test, result of the reference standard COVID-19 test, times of test results, Ct values and time from sampling to definitive ward area, COVID-19 antiviral administration and discharge from the ED. Viral culture results will be recorded in applicable cases.

The Veros COVID-19 test result and time to result, and the time at which routine COVID-19 testing was performed will be recorded contemporaneously by the research team in the ED, and will be recorded directly into the e-Case Report Form (e-CRF).

Anonymised results of viral cultures will be communicated by the relevant laboratory team to the research team. GeneXpert Ct values (calculated for all positive GeneXpert SARS-CoV-2 assays but not automatically released to the EPR) will be viewed and recorded by members of the research team. The results of the ease-of-use scoring will be obtained through the collation of scores from the questionnaires provided to research team members with experience of using the Veros COVID-19 test, and clinical staff who use the GeneXpert analyser. All other outcome measures will be extracted from the participants' EPRs. All data points will be inputted directly to the e-CRF.

All source documents will allow for the making of accurate copies, if required, to facilitate review, audit or inspection.

9.1.2 Case report forms

The research team members will be responsible for entering study data in the e-CRF. This will be an ALEA e-CRF. It is the investigators' responsibility to ensure the accuracy of the data entered in the e-CRF. The e-CRF will capture only data required by the protocol and will be an accurate representation of the protocol.

As data will be directly entered into the e-CRFs, they will be considered a source document and copies of the e-CRF will be maintained post-study so that an independent account is available to the CI as well as to the Sponsor.

As all metrics discussed during this protocol are either being dedicatedly assessed by the research team members or will be part of the standard documentation of a hospital attendance, it is expected that the generation of complete e-CRFs should not present obstacles.

9.2 Data handling and record keeping

To maintain participant anonymity, upon enrolment in the study all patients will be allocated a unique participant identification number/code. This unique participant identification number/code will be used on samples and documents after screening and recruitment.

The study team will keep an Enrolment Log of each participant's name, hospital ID number, date of birth, and unique participant identification number/code. Only the CI, co-investigators and relevant members of the research team will have access to the Enrolment Log linking participant details to the participant trial number, which will be securely stored within the CI's institution, behind two locked doors. The participant details will also be recorded on the secure NHS EDGE system.

This unique participant identification number/code is used in documentation following enrolment. Documents that are not anonymous (e.g. signed ICFs) will be maintained separately and securely, in strict confidence, in the ISF within the CI's institution.

After enrolment, anonymised study data will be inputted directly to the ALEA e-CRF. Some of these metrics will be recorded at the time of enrolment and a further retrospective collection of data points will be made from the participant's EPR over the next 30 days. Research team members will require their unique UHSNFT usernames and passwords in order to access the participants' EPRs.

The ALEA eCRFs are stored on a secure electronic database. The ALEA components, that will be in use once the study is live, are hosted in Den Bosch, in the Netherlands. This location is a secured ISO 27001 certified data centre operated by InterConnect BV. FormsVisions' Quality Assurance includes formal disaster management procedures for management of issues related to the operational environment. This includes failover, local data recovery and site recovery. Each physical server is equipped with RAID5 disk redundancy, redundant power supply and redundant network connectivity. The server facilities in Den Bosch include both hot standby and cold standby servers. Hot standby servers allow for near instant failover to a running server in case of physical server failure. In case of logical server failure, cold standby servers provide local data recovery in case the site is operational. In case of site failure, the disaster recovery procedure provides transfer of all operational services to

the ALEA hosting facilities in Amsterdam. ALEA is GDPR and GCP compliant. Any changes to data inputted to the e-CRF will have an audit trail maintained explaining why changes have been made.

All research staff are hospital employees (or have appropriate honorary contracts), and all of the medical research staff on this study have dual clinical and research roles, meaning that they access hospital systems and EPRs on a daily basis as part of their clinical roles.

Due to the inputting of all source data directly to the e-CRFs, physical documentation containing identifiable data will consist of the Screening Log, Enrolment Log and ICFs. These will be stored securely in the CI's institution, in the ISF.

9.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audit, or inspection.

9.4 Essential Document Retention & Archiving

Essential documents will include all signed protocols (and any amendments), copies of completed e-CRFs, signed ICFs from all subjects who consented, the Enrolment Log, the Screening Log, REC approvals and all related correspondence including approved documents and study correspondence.

The investigator and/or Sponsor must retain copies of the essential documents in the ISF for a minimum period following the end of the study. This will be for 15 years after completion of the study. Destruction of essential documents prior to this time will require authorisation from the Sponsor. The CI is responsible for, with the Sponsor, ensuring that documents are archived in accordance with local NHS R&D procedure at the close of the study. All essential documents will be stored securely in the CI's institution.

10 MONITORING

Based on the very low risk of harm associated with the intervention in this non-CTIMP trial, no interim analysis, or Data Monitoring Committee is planned.

This study will be monitored and may be participant to monitoring and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor, and other regulatory bodies to ensure adherence to ICH GCP, UK Policy Framework for Health and Social Care Research, applicable contracts/agreements and national regulations. All study related documents will be made available on request for monitoring and audit by UHS, the relevant REC or other licensing bodies.

11 ETHICAL AND REGULATORY CONSIDERATIONS

The investigators will ensure that this study is conducted according to the principles of the current revision of the Declaration of Helsinki and in conformity with the ICH GCP and local regulatory requirements.

11.1 Submissions to HRA, REC and local R&D

The protocol, ICFs, PIS and any other document requested will be submitted to the HRA for their processes, including to the REC for written approval. The study will not commence until all necessary HRA and REC approvals are in place.

The CI will submit and, where necessary, obtain approval from the REC for all subsequent substantial amendments to the protocol and ICF. Substantial amendments that require review by the REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the ISF and the REC will be notified at the end of the study.

Local R&D approval will be confirmed prior to the commencement of the study.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within 90 days after the end of the trial (as defined in section 7.10), the CI/Sponsor will ensure that the HRA and the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year of the end of the trial.

All results will be published on a publicly accessible database.

Raw data will be available from the CI after publication, upon reasonable request and for the purposes of ethically approved research.

11.2 Protocol non-compliance and deviations

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective deviations, planned deviations, or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the sponsor. Frequent non-compliances could potentially be classified as a serious breach.

11.3 Serious breaches of GCP or protocol

Serious breaches of GCP or the protocol should be reported, by the investigators and the Sponsor, within 7 days to the MHRA and relevant ethics committee in accordance with current regulations. A 'serious breach' is a breach which is likely to effect, to a significant degree, the safety, or physical or mental integrity, of the subjects of the study, or the scientific value of the study.

11.4 Data protection and patient confidentiality

All data will be anonymised. Participant data will be identified by a unique participant identification number/code in the e-CRF and subsequent data analysis. A separate Enrolment Log containing identifiable information will be stored in the ISF in a secured location within the CI's institution in

accordance with the Data Protection Act 2018. Only the Sponsor's representative and investigators will have access to the information.

11.5 Financial and other competing interests for the investigators

The CI and co-investigators have no ownership interests related to products used in the study, no commercial ties to Sense Biodetection Limited and no non-commercial potential conflicts.

At the time or writing, not all personnel who may be involved in the study have been identified. Should future personnel be identified to have financial or competing interests, this information will be added to the protocol.

11.6 Indemnity

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical trial, when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.7 Amendments

The sponsor will ensure that the trial protocol, PIS, ICF, and submitted supporting documents have been approved by the appropriate regulatory body, Health Research Authority (HRA), main research ethics committee (REC) and that local permission has been obtained prior to any subject recruitment.

All substantial amendments and non-substantial amendments (as determined by the sponsor) will not be implemented until HRA/REC have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial amendments and non-substantial amendments. Relevant approvals must be obtained before any substantial amendment and non-substantial amendments may be implemented at sites.

The CI will submit and, where necessary, obtain approval from the REC for all substantial amendments to the protocol, ICF and PIS. Any amendments to the protocol will be documented, along with date and version number in the most recent protocol version (with previous versions stored for reference). All correspondence with the HRA and the REC will be retained in the Investigator Site File (maintained by the site).

11.8 Access to the final trial dataset

Only the research team and medical statistician will have access to the data prior to publication.

12 DISSEMINIATION POLICY

The investigators and research team will be involved in reviewing drafts of the manuscripts, abstracts and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. All data generated in the process of this study is the property of the CI.

The study results are intended to be disseminated via peer-reviewed journals (which typically have summaries available on the internet) and medical conference posters and presentations. Participants will therefore be able to access the study results via a range of methods. The CI is responsible for the study data.

Funders will be acknowledged in any publications.

Sense Biodetection Limited will support this study by providing financial support and consumables free of charge. They have not had a role in the conception or design of this study and will not have any role in the conduct of the study, data analysis and interpretation, or preparation of manuscripts for submission to scientific journals.

The protocol for this study will be available on ePrints Soton. It is intended that the study be registered on the ISRCTN Registry.

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14 APPENDICES

Appendix 1. Ease of Use Score based on *Nicholson et als'* adaptation[12] of the US Clinical Laboratory Improvement Amendments (CLIA) categorisation criteria to grade systems for their level of complexity.

Ease of Use – After using the Veros COVID-19 test kits or GeneXpert analyser, for each criterion, select the most appropriate of the three choices. Answers in first column are assigned a score of 1, answers in the second column a score of 2 and in the third column, a score of 3.

Equipment	The test doesn't need specialised equipment and is easily transferred between facilities.	Intermediate between the descriptions on either side	The test needs essential non-portable specialised equipment.
	☐	☐	☐
Test Site	The test is used at the point-of-care.	Intermediate between descriptions on either side	The test needs a facility with purpose-built accommodation, ventilation systems and dedicated space.
	☐	☐	☐
Materials and Reagents	The test kit's components are stable, pre-packaged, pre-measured and don't need special handling or storage.	Intermediate between descriptions on either side	The test kit's components are labile, need special storage or special handling steps. Preparation requires manual steps (e.g. volumetric assessment).
	☐	☐	☐
Operational steps	The test is easily and rapidly executed with minimal hands-on time or pipetting steps.	Intermediate between descriptions on either side	The test needs close special preparation, precise temperature control or timing, accurate pipetting or extensive calculations.
	☐	☐	☐
Training, experience & knowledge	The test needs minimal scientific and technical knowledge or experience. Learning to perform the test can be done with on-the-job instruction.	Intermediate between descriptions on either side	The test needs specialised scientific and technical knowledge, with substantial experience needed to use it.
	☐	☐	☐

Calibration & Quality Control	Calibrating the test is either automatic or not needed. Quality control materials are included, or readily available, and are stable.	Intermediate between descriptions on either side	Materials for calibrating & quality control may be labile/ unavailable or technical expertise is needed for calibration.
	☐	☐	☐
Interpretation and Judgement	The test needs minimal interpretation and judgement.	Intermediate between descriptions on either side	The test needs extensive interpretation and judgement.
	☐	☐	☐
Test system troubleshooting and equipment maintenance	The test system's trouble shooting is automatic, self-correcting or clearly described. It requires minimal judgement.	Intermediate between descriptions on either side	The test system's trouble shooting is not automatic or self-correcting and needs decision making to resolve most problems. Equipment maintenance needs special knowledge, skills and abilities
	☐	☐	☐
Time to reporting of results	Test results are reported within 30 minutes of collection of almost all specimens	Intermediate between descriptions on either side	Test results are reported at ≥2 hours from collection of almost all specimens
	☐	☐	☐
Health and safety	The test is completed using low levels of PPE	Intermediate between descriptions on either side	The test has ≥1 steps that need bio-safety level >Category 3
	☐	☐	☐
Storage and disposal of waste test materials and reagents	The test's waste materials & reagents are stored/disposed of using standard clinical waste plastic bags/sharps containers.	Intermediate between descriptions on either side	The test's waste materials or reagents include hazardous materials that require special attention
	☐	☐	☐

Total Score: ___/33

Appendix 2: Laboratory protocol for SARS-CoV-2 cell culture

A combined nose and throat swab will be taken and placed in 1ml of sterile Viral Transport Media (VTM) to assay for viable virus. This swab will be frozen at -80°C (+/- 10°C) promptly (in a manner that allows it to be later transferred to the CL3 -80°C freezer without experiencing a freeze-thaw cycle).

When ready, the VTM swab will be thawed and the 1ml subject to centrifugation at 13,000 revolutions per minute for 30 seconds to pellet particulates and bacteria/yeast. It will then be subject to plaque assay, or foci forming assay, using Vero TMPRSS2 cells. If plaque assay is used, dilutions undertaken will be 1:2, 1:4, 1:10, 1:100 and 1:1,000 using 2 wells per dilution. (The reason for starting with 1:2 and 1:4 if the risk of toxicity/microbial contamination at the lower dilutions).

1ml of neat supernatant, diluted with 3ml Dulbecco's Modified Eagle Medium (DMEM), will also be used to inoculate a 75cm^2 flask of cells to look at recovery of viable virus. Cells will be left for 4 days, the supernatant harvested and then used to inoculate a second flask. The presence of cytopathic effect in the first flask and the second flask, coupled with detectable nucleocapsid in the second passage supernatant (as determined by enzyme-linked immunosorbent assay (ELISA)) will be the readout used.