Study Title: Expanding national RAPid community Test evaluation capacity fOR COVID-19.

Internal Reference Number / Short title: RAPid Testing fOR Covid-19 (RAPTOR-C19)

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Chief Investigator Signature:	

There are no potential conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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2. LAY SUMMARY

The NHS urgently needs quick, accurate rapid diagnostic tests to diagnose people with coronavirus or to confirm that people do not have the infection. Point-of-care Tests (POCTs) can be used in community settings where there is no easy access to a specialist laboratory. They provide quick results that allow people to get immediate advice about self-isolation and treatment, potentially blocking further spread of infection in the community. Companies are quickly developing new rapid diagnostic tests, but we do not know how well they work. Some tests give a result like a pregnancy test by using a drop of blood from a finger prick. Others use saliva, or a swab to collect a sample from the nose or throat.

Companies check tests work in their laboratories, but usually tests do not work as well when used in the field with real patients. Accurate rapid diagnostic tests are important so that people are not falsely reassured when they are infected, and are not wrongly diagnosed when they are not really infected.

Our team manages a national surveillance system with a network of community settings including GP practices from all over England that report directly to the Department of Health and Social Care about a wide range of infections. These GP practices have been testing for coronavirus since January 2020 with samples sent for laboratory tests. In this study, practices in the network will quickly compare new POCTs for coronavirus with laboratory tests so we can see how good the new tests are in a coordinated and efficient way. National COVID-19 Test centres may also support the research project.

3. SYNOPSIS

Study Title	Expanding national RAPid community Test evaluation capacity fOR COVID-19.		
Internal ref. no. / short title	RAPid Testing fOR Covid-19 (RAPTOR-C19).		
Study registration	https://doi.org/10.1186/ISRCTN14226970		
Sponsor	University of Oxford Joint Research Office Boundary Brook House, Churchill Drive Oxford OX3 7GB 01865 616480 ctrg@admin.ox.ac.uk		
Funder	UKRI/MRC COVID-19 Rapid Response Rolling Funding Call University of Oxford MSD COVID-19 Research Response Fund (awaited)		
Study Design	Prospective Parallel Diagnostic Accuracy Study		
Study Participants	Community patients with suspected current or past COVID-19		
Sample Size	Dependent on POCT under evaluation and COVID-19 prevalence, but the range of expected participants is 500 to 1000 per test.		
Planned Study Period	04-JUN-2020 to 03-JUN-2021.		
Planned Recruitment period	04-JUN-2020 to 03-APR-2021.		
	Objectives	Outcome Measures	Timepoint(s)
Primary	1. Assess the diagnostic accuracy of multiple current and emerging	1. Standard diagnostic accuracy of (POCTS) for active COVID-19 infection with	Baseline visit.

	point-of-care tests (POCTS) for active COVID-19 infection in the community setting.	reference to the Public Health England (PHE) reference standard or equivalent.	
Secondary	1. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for past COVID-19 infection in the community setting. 2. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for active COVID-19 infection in the community setting against a composite reference standard. 3. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for past COVID-19 infection in the primary care setting against a composite reference standard.	1. Standard diagnostic accuracy of (POCTS) for past COVID-19 infection with reference to the PHE reference standard. 2. Enhanced diagnostic accuracy of POCTs for active COVID-19 infection assessed against a composite reference standard using multiple tests data, linked EHRs data, and patient reported outcomes data 3. Enhanced diagnostic accuracy of POCTs for past COVID-19 infection assessed against a composite reference standard using multiple tests data, linked EHRs, and patient reported outcomes data.	Baseline visit. Baseline visit, follow-up visit (day 28) and follow-up in EHR Baseline visit, follow-up visit (day 28) and follow-up in EHR
Intervention(s)	COVID-19 POCTs; serology		
Comparator	Clinical laboratory tests for COVID-19 or a composite reference standards for COVID-19		

4. ABBREVIATIONS

CI	Chief Investigator
CMR System	Customer Relation Management System
CTRG	Clinical Trials & Research Governance, University of Oxford
CONDOR	COVID-19 National DiagnOstic Research and Evaluation Platform
COVID-19	Coronavirus Disease 2019
CRN	Clinical Research Network
DHSC	Department of Health and Social Care

DSP	Data Security and Privacy
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
EMIS	Egton Medical Information Systems
ETL Process	Extract, Transform, Load Process
FN	False Negative
FP	False Positive
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IVDs	In Vitro Diagnostics
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LFIA	Lateral Flow Immunoassay
NDPCHS	Nuffield Department of Primary Care Health Sciences
MIC	NIHR Community Healthcare MedTech and In vitro Diagnostics Co-operative
NHS	National Health Service
NHSX	NHS User Experience
NIHR	National Institute for Health Research
OMOP CDM	Observational Medical Outcomes Partnership Common Data Model
OP/NP swab	Oropharyngeal/Nasopharyngeal swab
ORCHID	Oxford Royal College of General Practitioners Clinical Informatics Hub
PC	Primary Care
PHE	Public Health England
PI	Principal Investigator
POCT	Point-Of-Care Test
PIS	Participant Information Sheet
RCGP-RSC	Royal College of General Practitioners Research and Surveillance Network
REC	Research Ethics Committee
RT-PCR	Real-Time Polymerase Chain Reaction
SAP	Statistical Analysis Plan

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SNOMED CT	Systematized Nomenclature of Medicine -- Clinical Terms
SOP	Standard Operating Procedure
STARD	Standards for Reporting Diagnostic Accuracy Studies
TN	True Negative
TP	True Positive
TPP	The Phoenix Partnership

5. BACKGROUND AND RATIONALE

There are currently no rapid diagnostic tests that have been evaluated as fit-for-purpose in NHS primary care that aim to identify whether adults are currently, or have been, infected by COVID-19.

The UK and wider world is in the midst of the 2019 novel coronavirus (SARS-CoV-2) pandemic. Accurate diagnosis of infection, identification of immunity and monitoring the clinical progression of infection are of paramount importance to our response, and for all of these diagnostics are central. Widespread population testing has proven difficult in western countries and has been limited by test availability, diagnostic test sensitivity, human resources and long turnaround times (up to 72 hours). This has limited our ability to control the spread of infection and to develop effective clinical pathways to enable early social isolation of infected patients, early treatment for those most at risk and early return to work for those with resolved infection and potential immunity.

POCTs can be used in the community where there is no easy access to a specialist laboratory, in locations such as NHS general practices. POCTs provide quick results that allow people to get immediate advice about self-isolation and treatment, potentially blocking further spread of infection in the community. In-context evaluation of POCTs in the community is important as test accuracy can vary based on the prevalence of disease in the population tested. The severity of the COVID-19 disease in the community is much lower than in hospital patients. Symptomatic acutely unwell hospitalised patient are likely to have higher viral loads that are easier to detect, and may be undergoing invasive procedures to collect samples from the lower respiratory tract, that have a higher yield. Testing only severe patients introduces spectrum bias, and biases the results to overestimate test performance. It is important to diagnose hospital patients, but from a public health point of view the most concerning patients are ambulatory outpatients, who may spread the virus much further in the community if falsely reassured. Evaluations of COVID-19 POCTs are therefore required in each clinical setting. Community based POCTs may lead to additional public health impacts such as reducing onward household transmission of COVID-19, improving surveillance of NHS and social care staff, accurate prevalence estimates, and understanding of COVID-19 transmission dynamics in the population.

RAPTOR-C19 will provide the community testbed to the COVID-19 National DiagnOstic Research and Evaluation Platform (CONDOR). Its platform design will allow for both flexibility in which POCTs are evaluated and for changes in PHE choice of reference standard. All POCTs will be detailed in the Appendices to this protocol. POCTs will only be added after submission to the appropriate approval bodies.

CONDOR is the collaborative national platform for COVID-19 diagnostics research and evaluation. CONDOR will evaluate the analytical performance of in vitro diagnostics (IVDs) (molecular, antigen and antibody

tests) via its laboratory network, and evaluate the in-context clinical performance (diagnostic and prognostic accuracy) of IVDs (self-tests, POCTs and laboratory platforms) in the network of community and secondary care settings. These include the community, emergency departments, acute ambulatory care and acute medicine units, critical care units and hospital at home services.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary		
1. Assess the diagnostic accuracy of multiple current and emerging point-of-care tests (POCTS) for active COVID-19 infection in the community setting.	1. Standard diagnostic accuracy of (POCTS) for active COVID-19 infection with reference to the Public Health England (PHE) reference standard or equivalent.	Baseline visit.
Secondary		
2. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for past COVID-19 infection in the community setting.	2. Standard diagnostic accuracy of (POCTS) for past COVID-19 infection with reference to the PHE reference standard.	Baseline visit.
3. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for active COVID-19 infection in the community setting against a composite reference standard.	3. Enhanced diagnostic accuracy of POCTs for active COVID-19 infection assessed against a composite reference standard using multiple tests data, linked EHRs data, and patient reported outcomes data	Baseline visit, follow-up visit (day 28) and follow-up in EHR
4. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for past COVID-19 infection in the primary care setting against a composite reference standard.	4. Enhanced diagnostic accuracy of POCTs for past COVID-19 infection assessed against a composite reference standard using multiple tests data, linked EHRs, and patient reported outcomes data.	Baseline visit, follow-up visit (day 28) and follow-up in EHR

7. STUDY DESIGN

RAPTOR-C19 incorporates a series of prospective observational parallel diagnostic accuracy studies of COVID-19 POCTS against laboratory and composite reference standards in patients with suspected current or past COVID-19 attending community settings.

At RCGP-RSC NHS General Practices:

Adult patients (≥ 16 years old) with suspected current or past COVID-19 who are having a oropharyngeal/nasopharyngeal (OP/NP) swab for laboratory COVID-19 Real-Time Polymerase Chain Reaction (RT-PCR) clinically will be asked to consent to:

1. answer a short questionnaire about eligibility and their clinical details
2. use at least one, but the intention is to assess multiple, POCTs for COVID-19
3. agree to results of their clinical test being shared with researchers
4. submit blood samples for PHE COVID-19 laboratory antibody testing
5. the study team accessing their NHS EHRs for one year
6. further contact from the study team to track symptoms and health status (daily after the first study visit until the second visit)
7. a second visit for additional blood sampling

The parent or legal guardian of children (< 16 years old) with suspected current COVID-19 will be asked to provide parental consent on behalf of their child who is having an OP/NP swab for laboratory COVID-19 RT-PCR clinically to:

1. answer a short questionnaire about eligibility and their clinical details
2. use at least one, but the intention is to assess multiple, POCTs for COVID-19
3. agree to results of their clinical test being shared with researchers
4. the study team accessing their child's NHS EHRs for one year
5. further contact from the study team to track symptoms and health status (daily after the first study visit for 28 days)

For community settings, such as national testing centres that are trialling the same POCT under their own governance, relevant de-identified data and test results from children and adults with suspected current COVID-19 will be shared with the study team by means of data sharing agreement. Data from evaluations in these settings (both OP/NP swabs and POCT) will be limited to the assessment of standard diagnostic accuracy (primary objective).

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

- adults aged ≥16 years old presenting with suspected current or past COVID-19 and having clinical OP/NP swabs for laboratory COVID-19 RT-PCR at RCGP-RSC NHS general practices
- children aged <16 years old presenting with suspected current COVID-19 and having clinical OP/NP swab for laboratory COVID-19 RT-PCR at RCGP-RSC NHS general practices

8.2. Inclusion Criteria

Adults (≥16 years old)

- males or females
- with suspected current or past COVID-19 infection*
- having OP/NP swab for laboratory COVID-19 RT-PCR as part of clinical care/testing at RCGP-RSC NHS general practices
- willing and able to give informed consent for participation in the study

Children (< 16 years old)

- males or females
- with suspected current COVID-19 infection*
- having OP/NP swab for laboratory COVID-19 RT-PCR as part of clinical care/testing at RCGP-RSC NHS general practices
- parent or legal guardian is willing and able to give informed consent for participation in the study

8.2.1. *Suspected current or past COVID-19

The clinical presentation of COVID-19 is broad and remains poorly characterised. Restricting testing to a narrow spectrum of clinical features would lead to a limited evaluation of in-context test utility. In general practice settings, the working definition of suspected current or past COVID-19 infection will be based on the clinical judgment of the primary care practitioner and/or the account of the participant. In all community settings, the clinical characteristics of the participant and reasons for testing will be documented.

The overarching UK Government's case definition for possible COVID-19 infection is: a new continuous cough (coughing a lot for more than an hour, three or more coughing episodes in 24 hours, or if the person usually has a cough it may be worse than usual); and/or a high temperature (feeling hot to touch on the chest or back without needing to record a temperature); and/or a loss of, or change to, your sense of smell or taste (1).

Emerging global evidence shows that the clinical features of COVID-19 are potentially much broader with little discriminatory value between patients who develop severe and non-severe infection (2) (Figure 7.2.1).

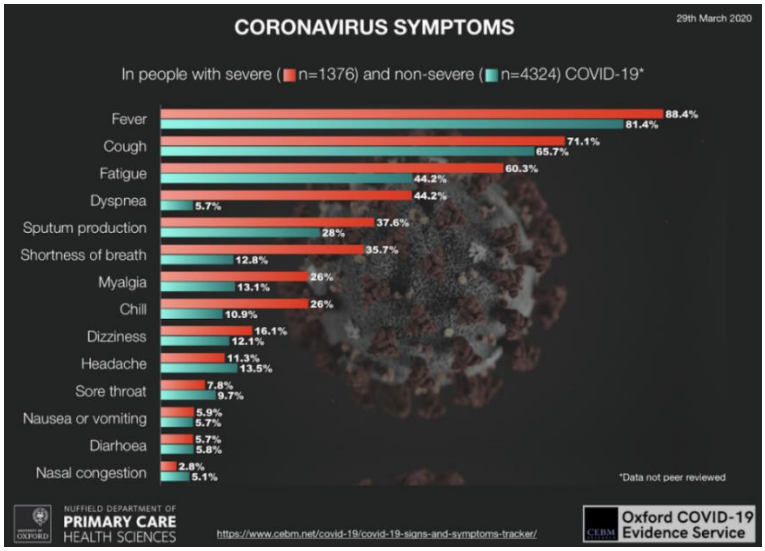


Figure 7.2.1. Symptoms reported in non-severe and severe COVID-19

The working definition of suspected current or past COVID-19 infection will be based on the current advice (3) to consider COVID-19 infection in people who during the COVID-19 pandemic have:

1. symptoms thought to be associated with COVID-19, including but not limited to: fever, cough, fatigue, dyspnoea, sputum production, anosmia, change in sense of taste, shortness of breath, myalgia, chills, dizziness, headache, sore throat, hoarseness, nausea, vomiting, diarrhoea, nasal congestion

2. acute respiratory distress syndrome

3. either clinical or radiological evidence of pneumonia

4. atypical presentations, for example an acute functional decline or frailty syndrome in an older person, if they are immunocompromised

5. lived or worked in close contact with somebody who has tested positive for COVID-19, including NHS staff

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- adults unable to understand the study information and give consent to take part in the study
- need for immediate hospitalisation
- previously enrolled in this study in relation to the individual test being evaluated

9. PROTOCOL PROCEDURES

9.1. Training

Prior to opening recruitment, RAPTOR-C19 staff will use manufacturer's instructions to develop training materials for the tests. RAPTOR-C19 staff will liaise with the manufacturers where clarification is required on use of the POCT. They will arrange training via teleconference with study leads to allow rapid dissemination in compliance with social distancing advice. Online tutorials and/or YouTube videos will be made available. These will be updated as necessary, as new POCTs are introduced into the study. During the study, RAPTOR-C19 staff will be available to support study sites and answer any queries.

9.2. Personal Protective Equipment (PPE)

All RAPTOR-C19 sites will be required to follow the current PHE infection prevention and control guidance regarding collection and processing of samples at all times including that regarding personal and protective equipment (PPE). Contact will be minimised by using electronic and/or verbal consent. The availability of appropriate PPE will be ensured in collaboration with the NIHR Health Protection Unit in respiratory Infections.

9.3. Enrolment

This is not a randomised study.

Participants will be selected from RAPTOR-C19 sites, including participating GP surgeries. GP surgeries that have submitted an expression of interest to take part in the study will be selected with the help of the RGCP-RSC and the NIHR clinical research network (CRN), and will consist of GP surgeries that are willing and able to adhere to the requirements of the trial protocol.

RAPTOR-C19 has a bespoke data collection solution hosted by uMed and developed by the RAPTOR-C19 team and uMed. Through a series of secure webpages, the platform will allow the participant, or the researcher on behalf of the participant, to record eligibility and to document consent. If the participant consents to be included in the study they will be asked for further study specific information, which will be entered into the eCRF. RAPTOR-C19 will provide study sites with a wireless Wi-Fi and 4G enabled Tablet. However, eligibility, consent and additional participant information will be collected from eligible participants using forms accessed via any internet enabled device.

Participants will be asked if they are happy to take part in the study and if they indicate they are, the recruitment process out lined in 9.4 and 9.5 will be followed.

9.4. Screening and Eligibility Assessment

There are two routes to potential participants being screened for eligibility: opportunistic and virtual. Opportunistic screening follows a patient initiated contact with the RAPTOR-C19 study site. Virtual screening would be supported by the uMed platform for patients identified as at-risk or in an at-risk group. Overall, potential participants will be assessed for eligibility if they meet one of the following criteria:

1. current infection
   a. they attend or contact the RAPTOR-C19 site in relation to suspected current COVID-19
   b. clinical suspicion of current COVID-19 occurs during an assessment for an unrelated problem
   c. current infection is suspected through EHRs review
   d. they have been in close contact with a positive COVID-19 case
   e. they respond to study promotional materials

2. past infection (adults (> 16) only)
   a. they have previously been assessed for active infection as part of this study or have a previous positive result for active infection from a separate encounter
   b. clinical suspicion of past COVID-19 occurs during an assessment for an unrelated problem
   c. past infection is suspected through EHRs review
   d. they have been in close contact with a positive COVID-19 case
   e. they respond to study promotional materials

9.5. Informed Consent

The RAPTOR-C19 site will ask eligible and willing patients (or their parent/carer, where applicable) to complete an e-consent process.

Informed consent will be obtained in line with Good Clinical Practice (GCP) guidelines. It is imperative that all non-essential contact between the participants, researchers, and practice staff is prevented in order to minimise the risk of COVID-19 transmission.

To achieve this, we will use a combination of digital written consent and/or researcher recorded verbal consent in this study. Written information will be available in the form of posters at the RAPTOR sites, and as electronic participant information accessible online, and included on the uMed platform and RAPTOR-C19 Tablet. Consent could be completed in discussion with the RAPTOR team in person, over video-link, or on the telephone.

For participants using the uMed platform, it will guide the participant, or the participant's parents / guardians, through the consent questions, or the researcher will read out the questions from the form, recording the participant's responses electronically. The completed consent form will be exported into a .pdf document and emailed securely to the participant.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the researcher or other independent parties to decide whether they will participate in the study. All answers will be stored electronically and securely.

9.6. Blinding and code-breaking

There is no blinding and or no code breaking

9.7. Description of study intervention(s), comparators and study procedures (clinical)

Biological samples to test for COVID-19 will be collected from all participants. Participants will be asked to submit samples as appropriate for each candidate POCT being evaluated. These may include OP/NP swab, saliva, and finger prick blood drop only from those over 10 years. Adults will have blood sampling on two occasions.

POCTs:

The index POCT will be at least one, but the intention is to assess multiple, candidate POCTs for active (adults ($\geq$16) and children (<16)) or past (adults) infection. If multiple POCTs are being assessed, these may target a combination of current COVID-19 infection and past COVID-19 infection. The order in which the tests are conducted will not be randomised but the sequencing of the tests will be documented in the eCRF. For qualitative POCTs, a photograph of the result will be captured in the eCRF to allow independent classification.

Participants will be asked to submit samples as appropriate for each candidate POCT being evaluated by following the POCT instructions provided by the manufacturer (these will be edited if deemed necessary by the RAPTOR-C19 and PPI group). For POCTs that require assistance to complete, the researcher will assist the participant whilst adhering to safe PPE use. The participant will complete the tests observed by the researcher to monitor POCT ease of use and identify safety issues.

All POCT consumables will be discarded as clinical waste as soon as the POCT is complete and the results have been captured. No POCT samples will be retained by the RAPTOR-C19 team. POCT results must not be shared with the patient and they must not be used to make any clinical decisions.

Reference laboratory tests:

For adults, both a reference test sample for current infection and a reference test sample for past infection will be taken at the first visit. For children, a reference test sample for current infection will be taken at the first visit.

Reference tests for current infection will be done as part of clinical care. Individuals can have these done whether or not they agree to be part of research. Participants will be agreeing that results of these clinical tests can be shared with the research team.

The current PHE reference standard for active infection is an OP/NP swab for laboratory COVID-19 RT-PCR. Participants will receive clear instructions on how to self-sample, as per PHE standard advice. If participants are unable to self-swab a staff member will take the sample. The sample material will fall under PHE or other central testing laboratory and not study remit, and PHE may retain the swab for up to five years.

The PHE reference standard for past infection is currently serology for laboratory antibody testing. Participants will be asked to submit two blood samples for COVID-19 antibody testing. Samples taken by a staff member or researcher who has received appropriate training will be taken under sterile conditions. Once taken, the samples will be put in the regulation container packaging, double bagged, and sent to the PHE laboratory or other central testing centre laboratory that is supporting the study using their existing, safe, quality compliant processes. Participants will be able to discuss the result of this test with their GP. Participants will have the option to agree to this sample being retained for future research use.

We acknowledge that the PHE reference standard may change throughout the study as more accurate reference tests are adopted. POCTs will always be benchmarked against the current best practice. We will also compare POCTs to a change in serology and develop composite references standards to mitigate the imperfect PHE reference tests. We will adjust our statistical analysis to reflect these potential changes.

Additional data

De-identified data received from other sources, only for assessment of standard diagnostic accuracy (primary objective), will comprise demographic data POCT and reference test results. If a data provider does not use the PHE laboratory to conduct laboratory testing, an assessment of the suitability of the laboratory and assay used will be conducted by the CONDOR team.

9.8. Description of study procedure(s)

This is a platform study is being set up to evaluate multiple POCTS, including those selected by DHSC and triaged for community evaluation by CONDOR.

When RAPTOR-C19 identifies which further tests are to be evaluated, prior to evaluation of the POCT, a substantial amendment will be submitted describing the POCT, instructions for use, safety characteristics, and any maintenance required. All POCTs will be conducted and all material left at the study site.

9.9. Baseline Assessments

For adults (≥16 years old), study visits will follow the same protocol whether current or past COVID-19 infection is suspected: the analysis will be different. In each instance, the baseline visit will involve the POCT(s) under evaluation and both antigen and serology tests for laboratory reference testing; the second visit will be for additional serology. For children (< 16), as only those with suspected current COVID-19 will be included, only a single baseline visit will be required.

Following consent being provided, the eCRF will then be used to capture study data. Section 1 and 2 will be automatically completed to ensure that each participant has a unique number. Section 3 can be completed by the participant alone or with assistance from the RAPTOR-C19 team. Section 4 will be completed by the RAPTOR-C19 team.

The following data from each participant:

1. **Study site number**
2. **Participant number**
3. **Spectrum of disease data** (for criticism of spectrum bias)
    a. gender
    b. age
    c. ethnicity
    d. comorbidities
    e. current date
    f. symptoms
    g. duration of symptoms
    h. household COVID-19 contacts
    i. clinical observations (if available)
    j. immediate place of care
    k. care home resident
    l. vaccine status (experimental or new COVID vaccine)
    m. past COVID tests with results
4. **Test data**
    a. POCT (repeated subsection if multiples POCTs)
        i. POCT for active or past infection
        ii. Test ID
        iii. Time of test
        iv. Who is performing the POCT (for inter-operator reliability)
        v. Results
            - a description and photo of qualitative results
            - a continuous quantitative result with units of measurement
        vi. Acceptability of test (Likert scale)
        vii. Problems (errors / indeterminate results / not done / failed with reason)
    b. COVID-19 swab
        i. Test completion
        ii. Time of test
        iii. Self-swab?
    c. Antibody blood sample
        i. Test completion
        ii. Time of test
        iii. Problems with venepuncture
    d. Sequencing of tests

Where de-identified data from other settings is to be provided to the study under a data sharing agreement, this will include 3a-h and k-m of the eCRF, above, and 4a and b.

9.10. Subsequent Visits

Where feasible, adult (≥ 16) participants will also be invited to attend a second visit, or visited at home by a research nurse, 28 days following the first visit, to allow repeat antibody testing using a blood test as outlined above for the purposes outlined in the sections that follow. This may not be feasible if a second visit is not possible at the study setting.

9.11. Enhanced Follow-up.

The uMed research platform also supports symptom tracking, and patient reminders. Where feasible, symptom tracking will be used to gather additional contextual data, on a daily basis between the first and second study visit. This is non-essential for the primary objective to assess standard diagnostic accuracy but contributory for the secondary objectives of enhanced diagnostic accuracy. Patient reminders may be used to remind participants to attend for their 28-day follow-up blood test appointment.

9.12. Sample Handling

Sample handling is outlined in the parallel index and reference testing section above.

9.13. Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the study at any time. Withdrawn participants will not be replaced. Participants are not required to give a reason for withdrawal. The Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- ineligibility (either arising during the study or retrospectively having been overlooked at eligibility assessment)
- significant protocol deviation
- withdrawal of consent
- if the participant refuses to do any POCTs, or if an adult (≥ 16) refuses to give a venous blood sample

9.14. Definition of End of Study

The end of study will be the last data capture for the last participant for the last test evaluated. Recruitment will be reviewed by the RAPTOR-C19 team, using the latest prevalence data from PHE, as prevalence of COVID-19 is dynamic and affects the sample size required.

10. SAFETY REPORTING

Safety reporting is not applicable given the low risk of point-of care tests.

Nose and throat swabs cause some transient discomfort to patients, but there are no clinically significant risks associated with the procedure. Fingerstick blood sampling may cause transient discomfort and localised bruising at the sampling site, however there are no clinically significant risks associated with the

procedure. Venous blood sampling causes discomfort and may result in bruising and localised swelling at the sampling site. Provision of saliva samples is unlikely to cause discomfort to any participants.

To mitigate these risks, self-sampling will be supported where appropriate, otherwise these procedures will be carried out by personnel who have received training in these procedures or who carry out these procedures as a routine element of their duties.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan (SAP). The SAP will be finalised before any analysis takes place.

11.1. Research Questions

RAPTOR-C19 will allow "Standard" and "Enhanced" diagnostic accuracy studies for active and past infection:

- Standard diagnostic accuracy of POCTs for active COVID-19 infection with reference to the PHE reference standard
- Standard diagnostic accuracy of POCTs for past COVID-19 infection with reference to the PHE reference standard

- Enhanced diagnostic accuracy of POCTs for active COVID-19 infection assessed against a composite reference standard using multiple tests data, linked EHRs data, and patient reported outcomes data
- Enhanced diagnostic accuracy of POCTs for past COVID-19 infection assessed against a composite reference standard using multiple tests data, linked EHRs, and patient reported outcomes data

11.2. Data Sources

Table 9.2 below outlines which data sources used to address each research question. It is important to stress, that de-identified data from other settings such as national testing centres will only be used to determine standard diagnostic accuracy of active infection.

Table 9.2 Data sources.

Data Source / **Question**	eCRF	POCT index test for active COVID-19	Laboratory reference test for active COVID-19	POCT index test for past COVID-19	Laboratory reference test for past COVID-19	Composite reference standard	De-identified data from other settings
Standard diagnostic accuracy of active infection	Yes	Yes – visit 1 *Active and past suspects*	Yes – visit 1 *Active and past suspects*	No	No	No	Yes
Enhanced diagnostic accuracy of active infection	Yes	Yes – visit 1 *Active and past suspects*	Yes – visit 1 *Active and past suspects*	No	Yes – visit 2 *Active and past suspects*	Yes	No
Standard diagnostic accuracy of past infection	Yes	No	No	Yes – visit 1 *Active and past suspects*	Yes – visit 1 *Active and past suspects*	No	No
Enhanced diagnostic accuracy of past infection	Yes	Yes – visit 1 *Active and past suspects*	Yes – visit 1 *Active and past suspects*	Yes – visit 1 *Active and past suspects*	Yes – visit 1 & 2 *Active and past suspects*	Yes	No

11.3. Composite Reference Standards to Mitigate Imperfections in the Reference Standard

An assumption of diagnostic accuracy studies is that the reference standard is infallible. This constrains the performance of the index test to the performance of the reference standard and assumes every time the tests get different results the reference is correct and the index is incorrect. In reality, the PHE reference standard is unlikely to be perfect, so we will undertake further analyses using composite reference standards.

Composite reference standard 1 will be designed to minimise false negatives (FNs), and composite reference standard 2 will be designed minimise false positives (FPs). Both composite reference standards will be constructed considering other test results (Table 9.3), patient reported outcomes, and linked EHRs for outcomes related to COVID-19, such as hospitalisation or death.

For POCTs for current infection:

1. A positive composite reference standard to *minimise the impact of a FN PHE reference test result for current infection at visit one / increase sensitivity* will also include:
    i. paired PHE antibody testing suggesting active infection at visit one (positive Immunoglobulin G (IgM)) and past infection at visit two (positive Immunoglobulin G (IgG)), or
    ii. EHRs showing a confirmed COVID-19 diagnosis (in another setting), such as COVID-19 hospital related admission or death in the following 28 days, or
    iii. a positive household contacts within 14 days identified via RCGP-RSC

2. A positive composite reference standard *to minimise the impact of a FP PHE reference test result for current infection at visit one / increase specificity will also include*:
    i. at least two positive PHE reference tests for current infection, or
    ii. paired PHE antibody testing suggesting active infection: visit one (positive for IgM) and visit two (positive IgG), or
    iii. EHRs showing COVID-19 hospital admission or death

For POCTs for past infection:

1. *A* positive *composite reference standard to minimise the impact of a FN PHE reference test result for past infection at visit one / increase sensitivity will also include:*
    i. positive visit two IgG positive PHE antibody tests, or
    ii. EHRs showing a confirmed past COVID-19 diagnosis (in another setting), such as positive PHE test for active COVID-19 infection, hospital COVID-19 related admission, or
    iii. a previous household COVID-19 contact identified via RCGP-RSC

2. A positive composite reference standard *to minimise the impact of a FP PHE reference test result for past infection at visit one / increase specificity will also include*:
    i. Paired PHE serology: visit one (positive IgG) and visit two (positive IgG), or
    ii. Electronic health records showing COVID-19 hospital admission

Table 9.3. Potential use of other tests to enhance the reference standard.

	Minimise FN for Current infection		**Minimise FN for Past infection**	
Visit (day)	*1 (0)*	*2 (28)*	*1 (0)*	*2 (28)*
COVID-19 Antigen	Negative (FN)	N/A	Negative	N/A
COVID IgM	Positive	Negative	Negative	Negative
COVID IgG	Negative	Positive	Negative (FN)	Positive
	Minimise FP for Current infection		**Minimise FP for Past infection**	
Visit (day)	*1 (day 0)*	*2 (28)*	*1 (day 0)*	*2 (28)*
COVID-19 Antigen	Positive (FP)	N/A	Negative	N/A
COVID IgM	Positive	Negative	Negative	Negative
COVID IgG	Negative	Positive	Positive (FP)	Positive

11.4. Statistical analysis

Results will be presented according to the Standards for Reporting Diagnostic accuracy studies (STARD) guidelines for reporting diagnostic studies.

Descriptive analysis:

Characteristics of recruited participants will be summarised using tables and graphs. If applicable, these will be compared to estimates from the general population. Number of total valid tests by POCT and reference standards will also be reported (actual and percentages), stratified by children vs adults and by age groups (if feasible dependent on total counts).

Summary statistics of diagnostic accuracy:

Sensitivity, specificity, positive and negative predictive values for each POCT will be calculated with exact 95% confidence intervals. Results will be stratified for adults vs children and by age groups and spectrum of disease data (if feasible dependent on total counts).

For the primary outcome and first secondary outcome:
For consecutive POCTs for active infection, the diagnostic accuracy of each POCT will be summarised independently using 2x2 tables for POCT (+/-) and the current standard PHE reference test (+/-) for active infection. For consecutive POCTs for past infection, the diagnostic accuracy of each POCT will be summarised independently using 2x2 tables for POCT (+/-) and the current standard PHE reference test (+/-) for past infection.

For the second and third secondary outcomes:
For consecutive POCTs for active infection, the enhanced diagnostic accuracy of each POCT will be summarised independently using 2x2 tables for POCT (+/-) and the composite reference standards as defined in 10.3 (+/-). For consecutive POCTs for past infection, the enhanced diagnostic accuracy of each POCT will be summarised independently using 2x2 tables for POCT (+/-) and the composite reference standards as defined in 10.3 (+/-) for past infection.

Missing data

Missing data for test results including reference tests will be reported. Potential associations between patient characteristics (e.g. age, gender, etc.) and pattern of missing will be evaluated and reported using tables and graphs. Robustness of the estimates for accuracy will be evaluated using sensitivity analyses.

11.5. Number of Participants

Required sample sizes will be calculated using standard methodology based on minimum clinically relevant sensitivity or specificity (whichever is the most critical for the intended placement in the care pathway), instead of expected values from preliminary work.

For example, based on POC-test desired performance, thresholds for minimum sensitivity and specificity of 80% and 98% respectively (value for the lower limit of the 95% Confidence Interval), can be used to determine sample size requirements and a strategy for early identification of poorly performing tests.

Assuming a test with 90% Sensitivity, a 99% Specificity, and a pre-test probability (prevalence) of 30%, we would require 600 participants to meet the minimum thresholds as stated above. This would also mean that

tests with more than 19 false negatives OR five false positives could be immediately dropped from the study. This would allow us to exclude tests with sensitivities of 50%, 60%, 70%, or 80% after the first 130, 160, 210, and 320 participants recruited. For tests with poor specificities of: 80%, 85%, 90% or 95% these would be identified after 35, 50, 70, and 145 participants recruited.

This sample of 600 would still be adequate based on small changes in prevalence. For example, a change from 30% to 15% would mean that the minimum threshold for sensitivity would move from 85% to 82% while for specificity it would shift marginally upwards from 97.5% to 97.7%.

Table 9.5.1. presents illustrative sample sizes to achieve a range of POCT sensitivities based on a standard error of 2.5%. A standard error of 2.5% will give a confidence interval of 5% on either side of the sensitivity estimate.

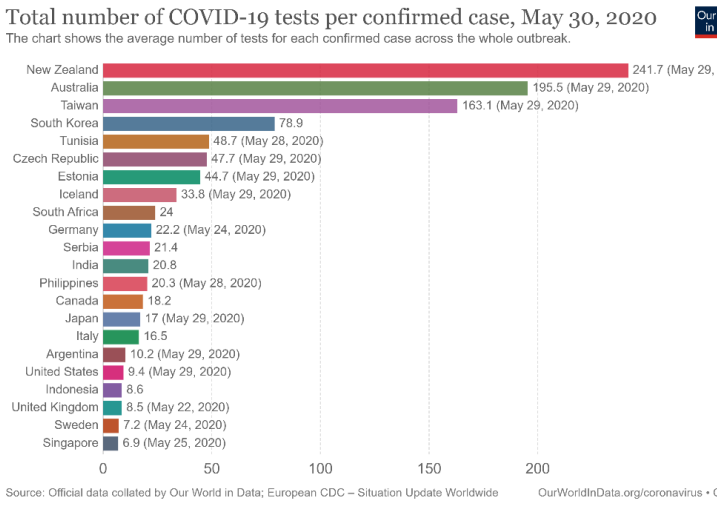
	Prevalence	**40%**	**35%**	**30%**	**25%**	**20%**	**15%**	**10%**	**5%**
Sensitivity	**95% (76 cases)**	190	218	254	304	380	507	760	1520
	90% (144 cases)	360	412	480	576	720	960	1440	2880
	85% (204 cases)	510	583	680	816	1020	1360	2040	4080
	80% (256 cases)	640	732	854	1024	1280	1707	2560	5120
	75% (300 cases)	750	858	1000	1200	1500	2000	3000	6000
	70% (336 cases)	840	960	1120	1344	1680	2240	3360	6720

Table 9.5.2. presents the expected standard error if the sample size was fixed 200:

	Prevalence	**40%**	**35%**	**30%**	**25%**	**20%**	**15%**
Sensitivity	**95%**	2.4	2.6	2.8	3.1	3.4	3.9
	90%	3.4	3.6	3.8	4.2	4.7	5.4
	85%	3.9	4.3	4.6	5.0	5.6	6.5
	80%	4.5	4.8	5.2	5.7	6.3	7.3
	75%	4.8	5.2	5.6	6.1	6.8	7.9
	70%	5.1	5.5	5.9	6.4	7.2	8.4

In the tested UK population there have been 8.5 tests performed for every case of COVID-19 confirmed: a prevalence of COVID-19 in the tested population of 12% (4). RAPTOR-C19 will focus on sites identified as higher prevalence surveillance sites including community “Hot-Hubs”.

Figure 9.5.1. Number of COVID-19 tests per confirmed case, April 21, 2020.



12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data). All eCRF data will be uploaded encrypted securely in the ORCHID hub. On all study-specific documents, the participant will be referred to by the study participant ID number, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.1. Data Handling and Record Keeping

uMed conforms to the requirements of General Data Protection Regulation (GDPR), the NHS Data Protection & Security Toolkit, and ISO 27001. The core principle applied throughout the RAPTOR-C19 study and across the wider uMed platform is that uMed always acts as a data processor on behalf of the sites that are taking part in this study. This data processing agreement allows uMed to capture and utilise EHR data from the practice to provide services to support delivery of studies. uMed therefore cannot use or share provider data with any third party without the permission from the practice (data controller in respect of clinical data and care). Consequently, the uMed platform includes provision for an authorisation workflow to enable the practice to give permission(s) for engagement and/or sharing of data in-line with the RAPTOR study protocol. This process also ensures that an audit trail is created such that the Sponsor is able to confirm all required permissions have been given by each site. eCRF data collected by uMed will be uploaded to the secure ORCHID hub at least once a week.

All data handling and management will follow the current RCGP-RSC Data Management Standard Operating Procedures (SOPs) which are aligned with the University of Oxford SOPs. All eCRFs will be completed electronically and uploaded using a secure web based system. Currently, the ORCHID hub will be hosted by NHSX in the Azure environment. This platform allows for a rapid implementation of both storage and computation while ensuring data integrity through network segmentation and encryption. This has the advantage of allowing the service to be flexible in reacting to the demands of the data flows and compute requirements, through bringing on additional servers to improve data processing throughput.

Each unique patient within the ORCHID hub is de-identified at source before their data is extracted from individual practices using a computer generated patient ID number. The ORCHID hub holds no identifiable data and only hashed NHS number. This pseudonymised patient level data extracted from general practice

CMR systems such as EMIS (Egton Medical Information Systems, UK) and SystmOne TPP (The Phoenix Partnership, UK),will include demographic data, clinical event data coded with SNOMED CT (SNOMED International, UK), medication data coded with dm+d and free text entries. Encrypted data will be transported securely to the protected ORCHID hub, initially through providers such as the Azure environment (Microsoft Corporation, USA) hosted by NHSX. In this environment, we will create an extract, transform, and load (ETL) process that will convert the EMIS and TPP data in to the OMOP Common Data Model (CDM) and map to the Standardized Vocabularies (5). The implementation will be carried out using a collection of automated scripts (i.e. SQL) to enable the ETL process to be repeatable.

Data shared by non-RSC settings, such as testing centres, will be de-identified. There will be no linkage to ORCHID or any other data.

12.1. Data Security

uMed applies the latest cloud based security principles to ensure that data is held securely on uMed's Amazon Web Service (AWS) infrastructure. In addition to conforming to the standards set by NHS Digital, the uMed platform goes beyond this to create a gold standard for information security of health data. It achieves this by ensuring patient identity information is always separated from the sensitive health data with a multi-stage encrypted communication layer that prevents the complete, identifiable patient record from being accessed by a legitimate or maleficent actor (including uMed's internal staff).

The ORCHID Hub is compliant with Data Protection Legislation, which relates to the protection of individuals with regards to the Processing of Personal Data to which a Party is subject, including the Data Protection Act 1998 and EC Directive 95/46/EC, and the subsequent the General Data Protection Regulation ((EU) 2016/679) ("GDPR"). It is also compliant with the NHS Digital Data Security and Privacy policy and is subject to data sharing agreements with all concerned such as NHSX. Both the University of Oxford and the University of Surrey (where the RSC data has historically been held) are Data Security and Privacy toolkit (DSP) compliant. Pseudonymisation of data will ensure that the work meets the common law right to privacy.
Patient level databases are held in the database server within the NDPCHS secure network which is sited behind a firewall within the University of Oxford's network. It is a standalone, independent network, all in-bounded connections are block, but out-bounded connections are allowed. All staff members of the research group working within the team base work from secure workstations or secure laptops with encrypted drive. Only substantive employees of the University of Oxford will have access to the data and only for the purposes described in this document.

De-identified data shared by non-RSC settings such as testing centres will be held securely on the database server within the NDPCHS secure network.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. The study and its records will be monitored by members of the research team.

The study will be conducted in accordance with the current approved protocol, relevant regulations and standard operating procedures.

14. STUDY COMMITTEES

Study Management Committee

Prof FD Richard Hobbs (Chair)
Dr Brian D Nicholson (Deputy Chair)
Prof Gail Hayward
Prof Simon de Lusignan
Prof Rafael Perera
Dr Philip Turner
Ms Mary Logan

15. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

16. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

17.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

17.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

17.5. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database.

17.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

17.7. Expenses and Benefits

RAPTOR-C19 sites will be reimbursed per patient recruited for their participation in the research. Participants will not be paid for their participation in the research.

18. FINANCE AND INSURANCE

18.1. Funding

Funding for RAPTOR-C19 has been secured through UKRI-MRC.

18.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

18.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

19. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by UKRI-MRC and any other funding that is secured. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

21. ARCHIVING

Research data will be archived for 10 year after the completion of the project.

22. REFERENCES

1. Public Health England. COVID-19: investigation and initial clinical management of possible cases 2020 [Available from: https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection.
2. The Evidence COVID-19 Service. COVID-19 Signs and Symptoms Tracker 2020 [Available from: https://www.cebm.net/covid-19/covid-19-signs-and-symptoms-tracker/.
3. Razai MS, Doerholt K, Ladhani S, Oakeshott P. Coronavirus disease 2019 (covid-19): a guide for UK GPs. BMJ. 2020;368:m800.
4. Our World in Data. Total number of COVID-19 tests per confirmed case, May 30, 2020 2020 [Available from: https://ourworldindata.org/grapher/number-of-covid-19-tests-per-confirmed-case.
5. Abedtash H, Ascha M, Beno M, Blacketer C, Blatt D, Christian B, et al. The Book of Observational Data Sciences and Informatics https://ohdsi.github.io/TheBookOfOhdsi/2020.

23. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.2	13/08/20	Brian Nicholson	Add testing centres, remote consent, collection of ethnicity and comorbidity data, and test 1 (SD Biosensor).

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).

24. APPENDIX B: POCT DETAILS

POCT	Manufacturer	Type	CE Mark	Detail	Supporting document
STANDARD Q COVID-19 Ag	SD Biosensor	LFIA	Yes	STANDARD Q COVID-19 Ag Test is a CE marked test that is reported to be a POCT that can quickly and easily diagnose SARS-CoV-2 structural antigen from an NP swab within 15-30 minutes using a format similar to a pregnancy test. It requires minimal training and no additional laboratory equipment for the testing.	 COVID19 Q Ag_EN.pdf