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. In this study, people attending community settings, such as GP surgeries or coronavirus testing centres, will be invited to join our research study to compare new POCTs for coronavirus with laboratory tests so we can see how good the new tests are in a coordinated and efficient way.

As well as finding out how well these new POCTs work in diagnosing coronavirus in the community, we also want to answer other important questions about the new tests. We need to explore how health care professionals (HCPs)/clinicians are using the tests, which would help us to work out if the tests can be successfully brought into use in other health care settings in the community. This means exploring how easy or difficult clinicians find using them and how the tests fit into the ways clinicians are already working. In this study, we want to observe clinicians as they use the tests and talk to them about it, to get a bigger picture of how the new tests can fit into how coronavirus is diagnosed in the community.

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	NIHR, UK Research and Innovation, Asthma UK, the British Lung Foundation, and the University of Oxford MSD COVID-19 Research Response Fund
Study Design	Prospective Parallel Diagnostic Accuracy Study Qualitative research, employing Focused ethnography methodology (embedded in RAPTOR-C19), including observation and informal interviewing
Study Participants	Community patients with suspected current COVID-19 For the qualitative component, HCPs/Clinicians administering Point-of-Care (POC) tests as part of RAPTOR-C19 diagnostic accuracy study, who give consent to participate, in settings which agree to take part
Sample Size	Dependent on POCT under evaluation and COVID-19 prevalence, but the range of expected participants is 500 to 1000 per test.

	For the qualitative component, this is dependent on number of sites researcher is able to access/number of clinicians who give consent to participate. Would aim to observe 12-15 tests, for each of the POC tests administered by participating clinicians.		
Planned Study Period	04-JUN-2020 to 31-DEC-2022. For the qualitative component, as soon as approval is granted up to 03.10.2022 (fitting with RAPTOR-C19 timeline).		
Planned Recruitment period	04-JUN-2020 to 30-NOV-2022. For the qualitative component, as soon as approval is granted up to 30.06.2022 (fitting with RAPTOR-C19 timeline).		
	Objectives	Outcome Measures	Timepoint(s)
Primary	1. Assess the diagnostic accuracy of multiple current and emerging point-of-care tests (POCTS) for <u>active</u> SARS-COV-2 infection in the community setting.	1. <u>Standard</u> diagnostic accuracy of (POCTS) for <u>active</u> SARS-COV-2 infection with reference to the UK Health Security Agency reference standard or equivalent.	Baseline visit

Secondary	1. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for active SARS-COV-2 infection in the community setting against a composite reference standard.	1. Enhanced diagnostic accuracy of POCTs for active SARS-COV-2 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
	2. Assess the diagnostic accuracy of multiple current and emerging multiplex (POCTS) for either active influenza A/B or respiratory syncytial virus (RSV) infection, or both, where these viruses form an element of a POCT multiplex testing strategy which incorporates SARS-CoV-2.	2. Standard diagnostic accuracy of multiplex (POCTS) for active influenza A/B or RSV infection or both, with reference to the UK Health Security Agency reference standard or equivalent.	Baseline visit
Intervention(s)	SARS-COV-2 POCTs; respiratory multiplex POCTs which incorporate SARS-CoV-2,		
Comparator	Clinical laboratory tests for SARS-CoV-2, influenza A/B and respiratory syncytial virus (RSV), or composite reference standards for SARS-CoV-2		
Aim/Research Questions/Objectives for the qualitative component	Research Aim To explore how clinicians conduct rapid POCTs deployed as part of RAPTOR-C19 in community settings Research Objective To gather data on: • The process of administering the POCTs within the RAPTOR-C19 diagnostic accuracy study by clinicians in community settings. This will include the POCT device preparation, biological sample preparation and collection, analysis of sample, recording of results. • How the POCTs fit into the workflow of the whole testing procedure, including barriers and facilitators to using the POCTs. • Clinician views of the usability of the POCTs and their insights into administering and processing the POC tests. • Clinician views of learning how to use the POCTs and training given.		

4. ABBREVIATIONS

CI	Chief Investigator
CMR System	Customer Relation Management System
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
HCP	Health Care Professional
HRA	Health Research Authority
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IVDs	In Vitro Diagnostics
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
PI	Principal Investigator
PIC	Patient Identification Centre

POCT	Point-Of-Care Test
PIS	Participant Information Sheet
RCGP-RSC	Royal College of General Practitioners Research and Surveillance Network
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance, University of Oxford
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase 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
UKHSA	UK Health Security Agency (formerly PHE)

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 SARS-COV-2.

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 SARS-COV-2, improving surveillance of NHS and social care staff, accurate prevalence estimates, and understanding of SARS-COV-2 transmission dynamics in the population. Multiplex POCTs for respiratory pathogens which incorporate tests for SARS-CoV-2 and other respiratory viruses such as influenza A/B and RSV may support differential diagnoses in patients with respiratory symptoms, ensuring that advice and treatment decisions are appropriate to the cause of disease.

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 UKHSA 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.

However, as well as determining how well these new POCTs work in diagnosing SARS-CoV-2 in the community compared with the reference standard, there are other questions about the new tests which are important and play a role in determining whether they can be successfully implemented. Such questions include their acceptability to the clinicians administering them, the practicalities of conducting the new POCTs, as well as how the new POCTs fit into the context within which the clinicians are working. Such issues reach beyond clinical effectiveness and cost-effectiveness and cannot be fully explored or understood using quantitative designs alone. There has been warning that unless qualitative research is adopted in diagnostic evaluation there will be inadequate appraisal and unnecessary expense, with tests being both poorly evaluated and implemented (1).

The aim of the qualitative component is to explore how clinicians conduct rapid POCTs, deployed as part of RAPTOR-C19 in community settings, to understand wider issues around their practicality and usability.

A focused ethnographic approach has been chosen to explore these issues and data collection methods will include direct observation of clinicians conducting COVID testing and unscheduled, informal interviews with clinicians about the testing process.

There are no potential risks to clinicians who choose to participate, other than allowing their conduct of the testing to be observed and being prepared to have conversations with the researcher about the testing. As the focus will be on the testing procedures, it is not anticipated that any of the conversations are likely to include topics which would be sensitive, embarrassing or upsetting nor that criminal or other disclosures requiring action could occur.

The population under study would be the clinicians in the community settings taking part in RAPTOR-C19 who would be prepared to take part.

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 SARS-CoV-2 infection in the community setting.	1. Standard diagnostic accuracy of (POCTS) for active SARS-CoV-2 infection with reference to the UK Health Security Agency reference standard or equivalent.	Baseline visit.
Secondary		
1. Assess the diagnostic accuracy of multiple current and emerging (POCTS) for active SARS-CoV-2 infection in the community setting against a composite reference standard. 2. Assess the diagnostic accuracy of multiple current and emerging multiplex (POCTS) for either active influenza A/B or respiratory syncytial virus (RSV) infection, or both, where these viruses form an element of a POCT multiplex testing strategy which incorporates SARS-CoV-2.	1. Enhanced diagnostic accuracy of POCTs for active SARS-CoV-2 infection assessed against a composite reference standard using multiple tests data, linked EHRs data, and patient reported outcomes data 2. Standard diagnostic accuracy of multiplex (POCTS) for active influenza A/B or RSV infection or both, with reference to the UK Health Security Agency reference standard or equivalent.	Baseline visit, follow-up visit (day 28) and follow-up in EHR Baseline visit
Aim of the qualitative component 1. To explore how clinicians conduct rapid POCTs, deployed as part of RAPTOR-C19, in community settings.	Objectives of the qualitative component: 1. To explore the process of administering the POCTs within the RAPTOR-C19 diagnostic accuracy study by clinicians in community settings. This will include the POCT device preparation, biological sample preparation and collection, analysis of sample, recording of results. 2. To examine the POCTs fit into the workflow of the whole testing	

	procedure, including barriers and facilitators to using the POCTs. 3. To explore clinicians' views of the usability of the POCTs and their insights into administering and processing the POC tests. 4. To explore clinicians' views of learning how to use the POCTs and training given.	

7. STUDY DESIGN

RAPTOR-C19 incorporates a series of prospective observational parallel diagnostic accuracy studies of SARS-CoV-2 POCTS against laboratory and composite reference standards in patients with suspected current COVID-19 attending community settings.

Scenario 1.

For adult patients (≥ 16 years old) with suspected, current COVID-19 who are having an oropharyngeal/nasopharyngeal (OP/NP) swab for laboratory SARS-CoV-2 Reverse Transcriptase 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 SARS-CoV-2, or POCTs which incorporate SARS-CoV-2 as an element of a multiplex panel or testing strategy for respiratory viruses including either influenza A/B, RSV, or both
3. agree to results of their clinical test being shared with researchers
4. the study team accessing their NHS EHRs for one year
5. further contact from the study team to track symptoms and health status (daily after the first study visit until the second visit)

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 SARS-CoV-2 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 SARS-CoV-2, or POCTs which incorporate SARS-CoV-2 as an element of a multiplex panel or testing strategy for respiratory viruses including either influenza A/B, RSV, or both
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)

Scenario 2.

For community settings, such as national testing centres that are not trialling a POCT under their own

governance or providing an appropriate oropharyngeal/nasopharyngeal (OP/NP) swab for laboratory Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) as part of clinical care:

Adult patients (≥ 16 years old) with suspected current COVID-19 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 SARS-CoV-2, or POCTs which incorporate SARS-CoV-2 as an element of a multiplex panel or testing strategy for respiratory viruses including either influenza A/B, RSV, or both
3. having a oropharyngeal/nasopharyngeal (OP/NP) swab for laboratory respiratory virus (including SARS-CoV-2) Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
4. the study team accessing their NHS EHRs for one year.
5. further contact from the study team to track symptoms and health status (daily after the first study visit until the second visit)

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 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 SARS-CoV-2
3. having a oropharyngeal/nasopharyngeal (OP/NP) swab for laboratory respiratory virus (including SARS-CoV-2) Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
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)

Scenario 3.
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).

Study Design for the qualitative component

Ethnography has the capacity to generate information-rich, detailed accounts of complex clinical and organisational issues, including professionals' approaches to practice and service delivery, professional and interprofessional relationships in health care and how professionals interact with patients (2,3). It can provide a subtle understanding of organisations and how they operate and can highlight differences between what people say and what they do (4,5,6).

A flexible, ethnographic methodology will be used in this study. In recent times, the concept of 'focused ethnography' (7) has emerged as a means of capturing data on specific topics in healthcare in order to improve care and care processes. Certain features of focused ethnography will be utilised in this study, including short-term, intermittent field visits rather than full-time immersion in the particular field and an emphasis on data analysis involving the whole research team rather than an individual researcher alone (8).

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

- adults aged ≥16 years old presenting to community settings with suspected, current COVID-19.
- for those at GP surgeries, having clinical OP/NP swabs for laboratory SARS-CoV-2 RT-PCR
- children aged <16 years old presenting to community settings with suspected, current COVID-19

8.2. **Inclusion Criteria**

Adults (≥16 years old)

- males or females
- with suspected, current or SARS-CoV-2 infection*
- for those at GP surgeries, having OP/NP swab for laboratory SARS-CoV-2 RT-PCR as part of clinical care
- willing and able to give informed consent for participation in the study

Children (< 16 years old)

- males or females
- with suspected, current SARS-CoV-2 infection*
- for those at GP surgeries, having OP/NP swab for laboratory SARS-CoV-2 RT-PCR as part of clinical care
- parent or legal guardian is willing and able to give informed consent for participation in the study

8.2.1. *Suspected current 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 COVID-19 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 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 (9).

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 (10) (Figure 7.2.1).

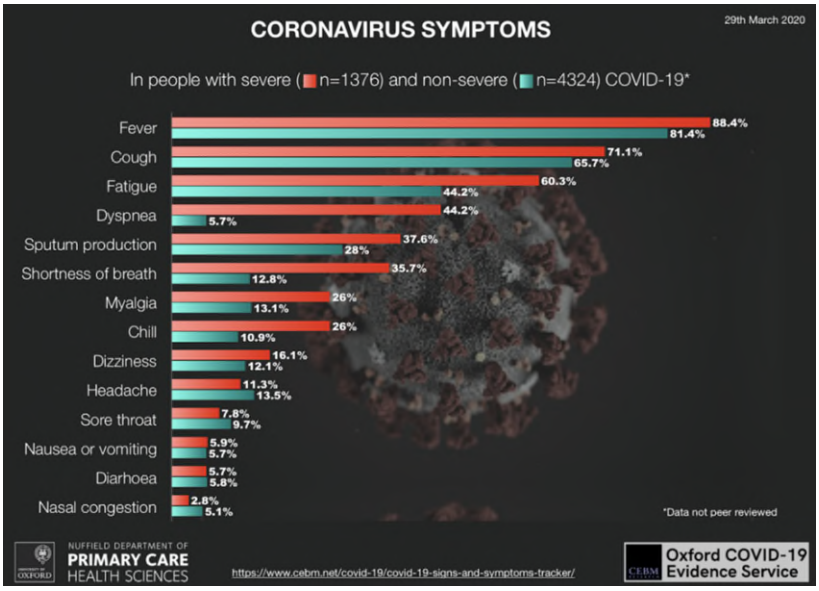


Figure 7.2.1. Symptoms reported in non-severe and severe COVID-19

The working definition of suspected current COVID-19 will be based on the current advice (11) to consider COVID-19 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 SARS-CoV-2, 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. HCP Participant identification

Permissions will be sought for the qualitative researcher to be given access to the community settings where the new POCTs are being conducted. Staff already involved in the RAPTOR-C19 study will be made aware of what the ethnographic research is about and invited to take part if they are willing to be observed.

It is anticipated that for each test being evaluated conducted as part of RAPTOR-C19, approximately 12-15 observations would be sought, ideally across sites and across clinicians. If possible, observation will occur until no new issues or information are emerging from the observations and informal conversations.

9.1 Inclusion Criteria

- Clinicians involved in conducting the new POCTs as part of the RAPTOR-C19 diagnostic accuracy study
- Willing and able to give consent for participation in the study.

9.2 Exclusion Criteria

- The inclusion criteria specify the participants who are eligible to take part and the only clinicians to be excluded will be those who do not wish to take part.

10. PROTOCOL PROCEDURES

10.1. 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 staff 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.

10.2. Personal Protective Equipment (PPE)

All RAPTOR-C19 sites will be required to follow the current UKHSA 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.

10.3. Enrolment

This is not a randomised study.

Participants will be selected from RAPTOR-C19 sites, including participating GP surgeries and community testing centres. GP surgeries that have submitted an expression of interest to take part in the study will be selected with the help of the RCGP-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. Testing centres will be selected in discussion with the UK Government's Department for Health and Social Care, or the relevant organisational structures within devolved administrations of the UK.

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 outlined in 10.4 and 10.5 will be followed.

10.4. 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

Qualitative Sampling Strategy

Access for ethnographic field work to different sites participating in RAPTOR-C19 (e.g. GP surgeries and national COVID-19 test centres; PICs not included) will be sought by the research team and sampling will be dependent upon the community health care settings to which the researcher is granted access, creating an opportunistic or convenience sample of sites.

In a similar way, observation of clinicians will be limited to those who are happy to take part and who are available at the times when the researcher is present. The nature of the research topic requires flexibility around sampling but the clinicians who take part will be those who are directly involved in delivering the new POCTs and therefore have current, relevant experience of the phenomenon of interest.

10.5. 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 SARS-CoV-2 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.

10.6. Blinding and code-breaking

There is no blinding and or no code breaking

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

Biological samples to test for SARS-CoV-2 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.

POCTs:

The index POCT will be at least one, but the intention is to assess multiple, candidate POCTs for active (adults (≥16) and children (<16)) infection. If multiple POCTs are being assessed, these may target a combination of current SARS-CoV-2 infection SARS-CoV-2 infection. Candidate POCTs for active infection that incorporate SARS-CoV-2 detection may also target other respiratory pathogens such as influenza A/B and RSV as part of a respiratory testing panel strategy. 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 and children, a reference test sample for current infection will be taken at the first visit.

The priority is to maintain a consistent reference standard across all RAPTOR-C19 participants and sites taking part in the evaluation of an individual POCT.

In settings where the RAPTOR-C19 reference standard for current infection is routinely offered as part of clinical care (section 7, scenario 1, above) these tests will be done as part of clinical care. Participants will receive clear instructions on how to self-sample, as per standard advice. If participants are unable to self-swab a staff member will take the sample. 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 sample material remains at all times the responsibility of the testing laboratory, and not study remit.

In settings where the reference standard for current infection is not routinely offered, these tests will be offered as part of the research. Participants will receive clear instructions on how to self-sample, as per standard advice. If participants are unable to self-swab a staff member will take the sample. The samples will be sent to the central laboratory but remain the responsibility of the study and will not be retained past the end of the study. The results of these tests will be reported to the research team.

The initial reference standard to be used in RAPTOR-C19 is the UKHSA reference standard. We acknowledge that the UKHSA 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 develop composite references standards to mitigate the imperfect 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 contemporaneous RAPTOR-C19 reference standard, an assessment of the suitability of the laboratory and assay used will be conducted by the CONDOR team.

10.8. Description of study procedure(s)

This 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.

10.9. Baseline Assessments

For adults (≥16 years old), the study visit will follow the same protocol when current COVID-19 is suspected. In each instance, the baseline visit will involve the POCT(s) under evaluation and RT-PCR for laboratory reference testing. For children (< 16), study visits will follow the same protocol as for adults.

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.
4. **Test data**
    a. POCT (repeated subsection if multiples POCTs)
        i. POCT for active 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. Reference standard swab
        i. Test completion
        ii. Time of test
        iii. Self-swab?
        iv.
    c. 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-l of the eCRF, above, and 4a and b.

10.10. 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. This is non-essential for the primary objective to assess standard diagnostic accuracy but contributory for the secondary objectives of enhanced diagnostic accuracy.

10.11. Sample Handling

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

10.12. 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 ($\geq$ 16) refuses to give a venous blood sample

10.13. 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 UKHSA, as prevalence of SARS-CoV-2 is dynamic and affects the sample size required.

11. Protocol procedures for the qualitative component

The RAPTOR-C19 research team will determine which of the GP sites agree to participate in the study. Within each site, clinicians will be provided with material giving information about the study and its focus and be allowed to choose whether they wish to be observed.

All RAPTOR-C19 sites are currently following the current UKHSA infection prevention and control guidance regarding collection and processing of samples at all times including that regarding personal and protective equipment (PPE). Contact between the researcher and the clinicians will be minimised during the consent procedure. The availability of appropriate PPE for the researcher will be ensured.

Observations will be carried out for each of the new POCTs being conducted at the sites. Recruitment:
It is anticipated that the study will be multicentre and that a number of testing sites will be able to take part. The sites will be approached by the RAPTOR-C19 team and informed about the qualitative study and its aims.

The clinicians in the community sites which agree to take part will be made aware of the study and will be asked to give consent. They will be able to choose whether they want to be observed at the times of the researcher's visits.

Where sites agree to take part, a flyer will be circulated to make patients aware of what is happening at those sites and what it means for them (See Advertisement_V 1.0_28.01.2021). They will be able to choose whether or not they want the taking of their sample to be observed by the researcher.

11.1. **Informed Consent**

Before the study begins, clinicians taking part in the RAPTOR-C19 diagnostic accuracy study will be made aware of the exact nature of the qualitative study and what it will involve for them by the research team.

Before any observation begins, the researcher will make it clear to the clinicians that they can refuse to take part or can withdraw from taking part at any point, without the need to give a reason.

The clinicians will be allowed as much time as wished to consider the information, and will have the opportunity to question the researcher, the CI or other independent parties to decide whether they will participate in the study. Formal consent will be taken from each of the clinicians and they will be asked to sign a consent form. Names and signatures will be collected from clinicians as part of the consent process. This will be linked to an anonymised participant ID included in each of the observations so that clinicians will be able to withdraw any data pertaining to them if they choose.

11.2. **Qualitative Data Collection**

A combination of data collection methods will be used including observation and unscheduled/informal interviews exploring the process involved in conducting POCTs as they happen during the time of the researcher's visits to the community health care settings.

Observation is a central activity in ethnography. Often referred to as 'participant observation', although the extent of participation may vary considerably (12), it allows the researcher to spend time with a group of people, learning to see the world through their eyes (the 'emic' perspective') (13). However, as ethnography has been taken up as a methodology in the health care arena, the term 'participant observation' has been called into question. It is claimed that it is not possible for ethnographers to actively participate in ongoing situations and events in hospital or clinical settings *as* a patient or professional etc. (14). Instead it is argued that researchers should see their time in the field instead as 'negotiated interactive observation', placing the emphasis on interaction as a way for the open, sensitive ethnographer to be receptive to ongoing activities, in order to understand the experiences of the people under study.

Initial, broad observation will be guided a list of sensitising topics adapted from a schedule used in previous ethnographic explorations of Point-of-Care testing (included as Appendix C). In all the instances which bring the researcher into contact with patients, verbal consent from patients for the researcher to be present will be sought first. During observations the researcher will write field notes on a computer tablet provided by the research team for this purpose. Field notes will not include names of settings/clinicians or any other identifiable information, excluding any details which might compromise anonymity. Data will be collected on participation of different clinician groups (e.g. nursing staff, GPs) but it will be ensured that this will not compromise anonymity. The researcher will need to achieve a balance between recording immediate, accurate and comprehensive notes of events while not making staff or patients feel awkward or defensive. During the observations there may be occasions when it is appropriate for the researcher to ask the clinicians questions. Such informal interviews or conversations will be written up by the researcher as soon as possible after they take place.

Individual clinicians will be observed as they conduct POCTs during the researcher's site visits but it is not possible to anticipate the duration of each of the observations or how many clinicians will be observed during each visit. This is also dependent upon the number of tests being conducted during the time of the researcher's visit.

The researcher will aim to spread observation so that as many clinicians as possible can be involved and to ensure that no clinician is over-burdened by observation.

11.3. Subsequent Visits

If a number of visits are made to participating sites by the researcher it is possible that clinicians who were present on a previous visit will be asked to take part again. On any new occasions and where the clinician is observed more than once, the researcher will check that their original consent is ongoing.

Data collection activities will be exactly the same for subsequent visits to sites.

11.4. Discontinuation/Withdrawal of Participants from Study

During the course of the study a participant may choose to withdraw at any time. Clinicians can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected from them after withdrawal. Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

11.5. Withdrawal of data by a clinician(s), may require additional observations to be conducted.

The reason for withdrawal, if this information is volunteered by the participant, will be recorded by the researcher.

11.6. Definition of End of Sub-study

The end of the qualitative sub-study will be the date of the last site visit by the researcher.

12. SAFETY REPORTING

Nose and throat swabs cause some transient discomfort to patients, but there are no clinically significant risks associated with the procedure. 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.

12.1. 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.

12.2. 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).

13. 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.

13.1. Research Questions

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

- Standard diagnostic accuracy of POCTs for active SARS-CoV-2 infection with reference to the UKHSA reference standard or equivalent
-
- Standard diagnostic accuracy of POCTs for active influenza A/B infection, RSV infection, or any combination, where these pathogens form an element of a POCT multiplex panel or testing strategy which incorporates SARS-CoV-2

- Enhanced diagnostic accuracy of POCTs for active SARS-CoV-2 infection assessed against a composite reference standard using multiple tests data, linked EHRs data, and patient reported outcomes data
-

13.2. 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 respiratory viruses including SARS-CoV-2	POCT index test for active influenza/RSV on panel with COVID-19	Composite reference standard	De-identified data from other settings
Standard diagnostic accuracy of active infection	Yes	Yes – visit 1	Yes – visit 1	Yes – visit 1	No	Yes
Enhanced diagnostic accuracy of active infection	Yes	Yes – visit 1	Yes – visit 1	No	Yes	No

13.3. 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 UKHSA reference standard or equivalent 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 to 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 UKHSA reference (or equivalent) test result for current infection at visit one / increase sensitivity* will also include:
    i. 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
    ii. a positive household contact within 14 days

2. A positive composite reference standard *to minimise the impact of a FP UKHSA reference (or equivalent) test result for current infection at visit one / increase specificity will also include*:
    i. at least two positive UKHSA reference tests for current infection
    ii. EHRs showing COVID-19 hospital admission or death

13.4. 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, first and second secondary outcomes:
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 UKHSA reference test (+/-) or equivalent for active infection.

For the first secondary outcome:
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 13.3 (+/-).

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.

13.5. 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. Where POCTs are evaluated which incorporate SARS-CoV-2 and other respiratory viruses, such as influenza A/B or RSV, sample size calculations will be appropriate for the SARS-CoV-2 element of the assay, with data collected opportunistically for other panel elements only.

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.

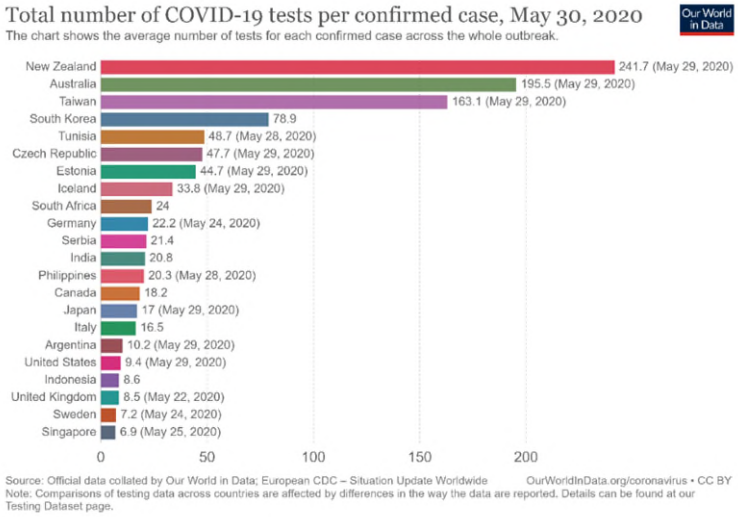
	Prevalence	**40%**	**35%**	**30%**	**25%**	**20%**	**15%**	**10%**	**5%**
Sensitivity	**95% (76 cases)**	190	218	254	304	380	507	760	1520
	90% (144 cases)	360	412	480	576	720	960	1440	2880
	85% (204 cases)	510	583	680	816	1020	1360	2040	4080
	80% (256 cases)	640	732	854	1024	1280	1707	2560	5120
	75% (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% (15). 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.



13.6. Description of analysis of the qualitative component

The ethnographic data from observations in the form of field notes and data from interviews/conversations with clinicians will form the basis of the analysis. The only participant data used in the analysis will be the field notes of observations and informal conversations with the clinicians, as well as indications of which staff groups are involved. No personal data will be included in the analysis.

The researcher will draw on the clinical expertise and research experience of the RAPTOR-C19 team in developing the coding framework and critically discussing ideas for categories emerging from the data, to ensure trustworthiness (16).

The thematic analytic approach chosen will take into account issues identified from the literature and clinical research context, as well as inductively allowing new themes and ideas to emerge from the data (17). Analysis will be guided by the constant comparative method (17, 18), which will include reading and familiarisation with the field notes and transcripts, noting and recording initial themes and then conducting systematic and detailed open coding using NVivo, a qualitative data analysis software package which assists in the organisation and retrieval of data. Analysis will be iterative, where initial data collected will be analysed to inform ongoing data collection and analysis. Thus, the coding of the first set of notes/conversations will generate an initial coding framework, which will be further developed and refined as observation and analysis proceed.

This will involve consideration of the following issues:

- *Credibility* – *t*he emerging findings from the study will be checked, in terms of how they resonate with the experiences of other clinicians in the research team and with the existing literature around clinician experiences of using POCTs.
- *Transferability* – careful description of the context in which the study took place will enable others to determine the extent to which the research study's findings are applicable to other contexts, including similar clinicians and similar settings.
- *Confirmability* – a careful audit trail setting out the decisions taken in data collection and data analysis will be made, which will enable the wider research team to examine the study findings and confirm their basis in the participants' responses and not in the personal biases or motivations of the researcher conducting the ethnography.

14. 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.

14.1. 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 to a server within the NDPCHS secure network. On all study-specific documents except the consent form, the participant will be referred to by the study participant ID number, not by name.

14.2. 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.

14.3. Data Handling and Record Keeping

uMed conforms to the requirements of UK General Data Protection Regulation (UK 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 a server within the NDPCHS secure network at least once a week.

All data handling and management will follow 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 anonymised 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 SystemOne 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 (19). 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 under scenario 3 (section 7) will be de-identified. There will be no linkage to ORCHID or any other data.

14.4. 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 2018 and EC Directive 95/46/EC, and the subsequent UK General Data Protection Regulation (UKGDPR). 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. The University of Oxford 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 settings such as testing centres will be held securely on the database server within the NDPCHS secure network.

15. Data management for the qualitative component

Access to Data

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

Data Recording and Record Keeping

Hard copies of data (such as consent forms) will be securely stored in a lockable filing cabinet in the NDPCHS. Where it is not practical to immediately store data at this location a lockable filling cabinet in the researcher's home will be used for the shortest time possible. Observation data will be related to individual participants so an identifier key will be required.

Field notes and records of conversations/informal interviews will be made during visits to the community sites on a University-owned tablet computer (which can be wiped clean to reduce possibility of transmission of SARS-CoV-2). The notes will include anonymised participant ID only and will not contain information which could identify individual participants.

Field notes will be checked and written up in password protected Word documents and the original notes deleted from the tablet computer. The original field notes and written up versions will be stored on the researcher's University-owned hard-disk encrypted laptop and transferred if possible onto a study-specific University shared drive. The relevant files will be uploaded into NVivo12 on the same University laptop for analysis.

No transcription is required in this study.

Anonymised data will be available to other members of the research team where this is necessary. All data will be destroyed within 10 years of completion of the study.

16. 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.

17. 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

18. 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.

19. 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.

20. ETHICAL AND REGULATORY CONSIDERATIONS

20.1. Declaration of Helsinki

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

20.2. Guidelines for Good Clinical Practice

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

20.3. 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.

20.4. 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.

20.5. Transparency in Research

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

20.6. Participant Confidentiality

The study will comply with UK General Data Protection Regulation (UK 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. 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.

20.7. 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.

21. FINANCE AND INSURANCE

21.1. Funding

Funding for RAPTOR-C19 has been secured through NIHR, UK Research and Innovation, Asthma UK, British Lung Foundation, and the University of Oxford MSD COVID-19 Research Response Fund

21.2. 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).

21.3. Contractual arrangements

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

22. 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.

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

Not applicable.

24. ARCHIVING

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

25. REFERENCES

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APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1 [substantial amendment 1]	2.0	13/08/20	Brian Nicholson	Add testing centres, remote consent, collection of ethnicity and comorbidity data, and test 1 (SD Biosensor).
2 [minor amendment 1]	2.0	15/10/20	Brian Nicholson	Modification of detail about current data processing arrangement of RCGP-RSC database.
3 [amendment 3]	2.0	22/10/20	Brian Nicholson	Addition of Dudley Integrated Health and Care NHS Trust and North Cumbria Integrated Care NHS Foundation Trust as study sites.
4 [substantial amendment 2]	3.0	06/01/21	Brian Nicholson	Add test 2 (BD Veritor)
5 [substantial amendment 3]	4.0	28/01/21	Brian Nicholson	Add qualitative component, qualitative researcher, and recruitment poster.
6 [substantial amendment 4]	5.0	14/03/21	Brian Nicholson	Add testing centres as point of recruitment, with attendant participant information materials; genericise reference standard information, add test 3 (Abbott ID Now), and extend study duration.
7 [substantial amendment 5]	6.0	17/12/21	Brian Nicholson	Add text relevant to the inclusion of multiplex POCTs which incorporate SARS-CoV-2 and other respiratory pathogens. Remove references to past SARS-CoV-2 infection and associated blood sampling and serology. Add test 4 (LumiraDx). Extend study duration.
8 [Substantial amendment 6]	6.1	11/05/22	Sharon Tonner	Extend recruitment duration to 01 Sept 2022 and updated SMS message.
9 [Non Substantial Amendment 3]	6.2	08/08/22	Sharon Tonner	Extend recruitment duration to 30 Nov 2022 and planned study period to 31 DEC 2022

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
BD Veritor	Becton, Dickinson and Company	LFIA with reader	Yes	The BD Veritor™ System for Rapid Detection of SARS-CoV-2 is a chromatographic digital immunoassay intended for the direct and qualitative detection of SARS-CoV-2 nucleocapsid antigens in nasal swabs from individuals who are suspected of COVID-19 by their healthcare provider within the first five days of the onset of symptoms.	500050809(01)_CE-IVD VERITOR_SARS-C 8091498_Veritor Plus_IfU(06).pdf
Abbott ID Now	Abbott Diagnostics Scarborough, Inc	Instrument-based isothermal test (molecular) for the detection of SARS-CoV-2	Yes	The Abbott Diagnostics ID Now COVID-19 is a rapid, automated, instrument-based assay that employs isothermal amplification technology for the qualitative detection of SARS-CoV-2 nucleic acids (RNA) from nasal, nasopharyngeal and throat swabs taken from patients suspected of COVID-19. The assay is comprised of disposable, receiver, transfer, and reaction cartridges, and the ID Now Instrument.	IN191000 v1.0 ID NOW COVID-19 Test
LumiraDx SARS-CoV-2 & Flu A/B Test	LumiraDx Limited	Instrument-based viral antigen detection test for	Yes	The LumiraDx SARS-CoV-2 & Flu A/B test is an instrument-interpreted rapid microfluidic immunofluorescence assay for the simultaneous	flu-ab-product-insert-ce-english.pdf

		SARS-CoV-2 & Influenza A/B		qualitative detection and differentiation of SARS-CoV-2, Influenza A, and or Influenza B viral antigens from self or clinician collected nasal swabs or clinician collected nasopharyngeal swab specimens, from patients suspected of respiratory viral infection. The assay is comprised of the SARS-CoV-2 & Influenza A&B disposable test strips, LumiraDx platform, and assay control materials. Updated to reflect name changes of Public Health England to UK Health Security Agency & University sponsor office from CTRG to RGEA	

25. APPENDIX C: OBSERVATION SCHEDULE