

RESEARCH PROTOCOL



**Facilitating AcceLerated Clinical evaluation Of Novel diagnostic tests for
COVID-19 (FALCON-C19)**



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The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

For and on behalf of the Study Sponsor:

Signature:

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Date:

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Name (please print):

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Position:

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Chief Investigator:

Signature:

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Date:

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Name: (please print):

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Manchester University

NHS Foundation Trust

1. RESEARCH TEAM & KEY CONTACTS

IRAS Project ID: 284229

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2. SUMMARY

Long Study Title	Facilitating AcceLerated Clinical evaluation Of Novel diagnostics for COVID-19	
Short Study Title	The FALCON C-19 study	
Nature of Study	Multi-centre Observational Prospective Parallel Diagnostic Accuracy Study	
Participants	Adults with suspected current or past COVID-19	
Setting	Secondary and Tertiary Care: Hospitals in the United Kingdom	
Intended number of participants	Dependent on diagnostic test under evaluation, but the range of expected participants is 400 to 10,000	
Planned Study Period	01-JUN-2020 to 01-JUN-2021	
	Objectives	Outcome Measures
Primary	<ol style="list-style-type: none"> 1. Evaluate the diagnostic accuracy of multiple current and emerging tests for <u>active</u> COVID-19 infection in the secondary/tertiary care setting. 2. Evaluate the diagnostic accuracy of multiple current and emerging tests for <u>past</u> COVID-19 infection in the secondary/tertiary care setting. 	<ol style="list-style-type: none"> 1. “Standard” diagnostic accuracy of tests for <u>active</u> COVID-19 infection with reference to the Public Health England reference standard. 2. “Standard” diagnostic accuracy of tests for <u>past</u> COVID-19 infection with reference to the Public Health England reference standard.
Secondary	<ol style="list-style-type: none"> 1. Evaluate the diagnostic accuracy of multiple current and emerging tests for <u>active</u> COVID-19 infection in the secondary/tertiary care setting against an <u>enhanced reference standard</u>. 	<ol style="list-style-type: none"> 1. “Enhanced” diagnostic accuracy of tests for <u>active</u> COVID-19 infection assessed against a <u>composite reference standard</u> using multiple tests, linked electronic health records data, and patient follow-up optimised for different clinical applications, allowing for imperfections in the reference test: <ul style="list-style-type: none"> ○ Clinical scenario requires ruling out infection (e.g. healthcare workers return to work, decisions about de-isolation) ○ Clinical scenario requires ruling in infection (e.g. decisions about isolation)

	<p>2. Compare the diagnostic accuracy of multiple current and emerging tests for <u>past</u> COVID-19 infection in the secondary/tertiary care setting against an <u>enhanced reference standard</u>.</p> <p>3. Compare viral load and diagnostic accuracy between saliva and combined nose/throat swab samples</p>	<p>2. “Enhanced” diagnostic accuracy of tests for <u>past</u> COVID-19 infection assessed against a <u>composite reference standard</u> using multiple tests, linked electronic health records data, and patient follow-up, optimised for different clinical applications, allowing for imperfections in the PHE reference tests:</p> <ul style="list-style-type: none">○ Clinical scenario requires ruling out infection (e.g. healthcare workers return to work, e.g. de-isolation)○ Clinical scenario requires ruling in infection (e.g. decisions about isolation) <p>3. Method comparison between saliva samples and the reference standard method (combined nose/throat swab)</p>
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3. BACKGROUND

In response to the COVID-19 pandemic, multiple in vitro diagnostics tests (IVDs) have been rapidly developed to detect SARS-CoV-2 infection or immunity. To meet the urgent demand for increased testing capacity, many IVDs have received emergency use authorization. However, clinical evaluations to date have mainly been single-centre, employing differing reference standards with variable protocols. There remains an urgent need for a multi-site, rapid, and methodologically robust approach to in-context clinical validation.

The COVID-19 National Diagnostic Research and Evaluation Platform (CONDOR) will contribute to the coordinated national effort to improve COVID-19 diagnostics by providing a collaborative national platform for clinical evaluation. The Facilitating Accelerated Clinical evaluation of Novel diagnostics for COVID-19 (**FALCON-C19**) study feeds into the CONDOR programme by evaluating novel diagnostic tests for COVID-19 in hospital settings. Meanwhile, a separate study, called the Expanding RAPid community Test evaluation capacity FOR COVID-19 within the RCGP Research and Surveillance Centre (RCGP-RSC) network (**RAPTOR-C19**) study will separately evaluate novel diagnostic tests for COVID-19 in a community setting.

FALCON will provide in-context clinical validation for multiple IVDs in a hospital setting, specifically applied to high-priority use cases. This collaborative platform will also place the UK in a unique position to rapidly evaluate and adopt novel diagnostics into clinical practice when faced with future pandemics.

4. STUDY OBJECTIVES

4.1 Co-primary objectives

In this platform study, which is designed to add new evaluations of IVDs for COVID-19 as the study progresses under this umbrella protocol, we will evaluate two co-primary objectives, as follows:

- (1) To determine the diagnostic accuracy of novel commercially supplied IVDs for active infection with SARS-CoV-2
- (2) To determine the accuracy of novel commercially supplied IVDs for monitoring the development of antibodies against SARS-CoV-2.

We will evaluate this in secondary and tertiary care settings, commencing at the first point of contact with secondary healthcare organisations, and also in settings where patients have been identified as positive for SARS-CoV-2 PCR through national laboratory infrastructure. In this platform study, we aim to evaluate multiple commercially supplied assays including assays that may not be available at the beginning of the study.

4.2 Secondary Question/Objectives

1. To evaluate the feasibility and acceptability to end users of novel diagnostic tests for the detection of infection, response and immunity to SARS-CoV-2.
2. To compare the SARS-CoV-2 viral loads between saliva and combined nose/throat swabs



5.1 Design

This is a prospective, multi-centre diagnostic test accuracy study including patients suspected to have past or present infection with SARS-CoV-2. The study is observational in nature, meaning that the healthcare provided to participants will not be altered as a result of their participation in the study. All patients will have appropriate investigations that are standard of care to determine SARS-CoV-2 status which will be used to determine ongoing care. The work will be divided into three work streams (A, B and C) to permit evaluations in different settings.

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

5.2 Index tests under evaluation

In this adaptive and pragmatic study we endeavour to evaluate a number of new tests, some of which will become available after approval. Tests to be evaluated will have been identified and prioritised, for example by the National Test Advisory Group (NTAG), the Viral Detection Test Advisory Group (VDTAG), the Serology Task Force (STF) or (since August 2020) the Technology Validation Group (TVG) each of which was set up by the Department of Health and Social Care, or (at a later stage in the pandemic response) by the CONDOR steering committee. The CONDOR steering committee will include two lay representatives, key stakeholders from primary and secondary healthcare settings and test evaluation methodologists.

In order to be accepted for inclusion in this platform study, novel tests must have clear potential to benefit patients and healthcare organisations in the NHS during the current SARS-CoV-2 pandemic. Prioritisation may also be informed by the findings of a forthcoming national survey of clinicians, who will be invited to define their priorities to improve diagnostic testing for patients with suspected or confirmed infection with SARS-CoV-2.

For each IVD to be evaluated within the FALCON study, there will also be an associated use case. The use case describes how the IVD will be used in clinical practice, if the evaluation is successful. An example of a use cases relevance to this study would include: early identification of COVID-19 by testing at the time of arrival in patients presenting to the Emergency Department or acute medical unit with symptoms that may be caused by COVID-19 who may need hospital admission, in order to triage patients, along with clinical assessment, to an appropriate area within the hospital (COVID-19 or low risk COVID-19 area). For serology testing, a typical use case may include identification of the development of antibodies in order to determine immunity to COVID-19. For each use case, a different evaluation is required. This study will collect all data and has the facility to collect all sample sets required to evaluate the various use cases anticipated. In some circumstances, not all of the samples described in the protocol will be required for a particular evaluation. In that instance, the steering committee will decide (prior to commencing the relevant evaluation) upon the minimum sample set required to evaluate the relevant IVD for the appropriate use case. Should additional samples be required for a particular evaluation, we will apply for a substantial amendment to the protocol.

5.3 Sampling

5.3.1 Work Streams A (in-hospital testing) and C (undifferentiated community testing)

The following samples may be drawn for a given IVD evaluation in the study:

	Baseline (day 0)	Day 1	Days 3, 5, 9, 30, 90
Evaluation of viral detection tests	Nose/throat swab +/- saliva	Nose/throat swab +/- saliva	Option for further nose/throat swab +/- saliva depending on particular evaluation
Evaluation of antibody tests (if required; Work Stream A only)	15ml venous blood	2ml whole blood or fingerstick	2ml whole blood or fingerstick

Blood samples are only required during the evaluation of tests intending to use blood samples for analysis. Not all IVD evaluations will require a full sample set. We will draw the minimal sample set required for evaluation of each IVD, the frequency of which will be determined by the technology under test at the beginning of each evaluation. Some evaluations will only require a baseline nose/throat swab +/- saliva. The precise requirements will be communicated to sites at the beginning of any given test evaluation.

All samples will be collected by staff who are fully trained to don and doff personal protective equipment, and who are wearing full personal protective equipment in accordance with contemporary guidance from Public Health England. Samples will be handled in full accordance with contemporary guidelines for sample handling. Where it is deemed appropriate for a particular IVD evaluation (dependent upon the specified use case), participants may also be asked to self-collect samples.

5.3.1.1 On-site point-of-care device testing

Some point-of-care tests (POCTs) being evaluated will be undertaken in accordance with the manufacturer's instructions locally at the participating site. Infection, prevention and control issues for each POCT will be discussed and implemented according to the test. Training materials will be developed ahead of the evaluation.

In general, for antibody tests this will require the use of whole blood samples (venous and/or finger stick) and for viral detection tests this will require throat/nose swabs or saliva samples. The remaining whole blood samples will be centrifuged at 1,500g for 15 minutes (unless otherwise stated by manufacturer of the point-of-care device being evaluated) and stored as required within 4 hours of collection by local laboratory personnel/research team members. Serum/plasma will be separated into aliquots of approximately 1ml and frozen at -80°C pending future analysis in batches. At the end of the study, the frozen samples will be transported on dry ice to the sponsor to be stored centrally.

5.3.1.2 Central point-of-care device testing

Where POCTs are not available for local on-site testing, samples will be sent to a suitable laboratory (which may be provided by the manufacturer) for testing. In preparation for transport of blood samples (where required) the whole blood will be centrifuged at 1,500g for 15 minutes (unless otherwise stated by manufacturer of the point-of-care device being evaluated) and stored as required within 4 hours of collection by local laboratory personnel/research team members. In general, this will be the transport of serum/plasma aliquots, throat/nose swab and/or saliva samples. Where possible, the manufacturers will arrange for a courier that has the proper certification to handle this classification of samples to transport the research samples to their testing facility. Any remaining samples will then be stored by the manufacturer for future testing in batches for COVID-19 diagnostics.

5.3.2 Work Stream B (known COVID positive and/or COVID negative community testing)

The following samples may be drawn, depending on the nature of the particular IVD evaluation:

- Saliva (approximately 5ml) will be collected on days 1, with an option for further samples on days 2, 3, 4 and 5
- Combined nasal/throat swabs will be collected on days 1 with an option for further samples on day 5
- Breath samples on day 1

Not all IVD evaluations will require a full sample set. We will draw the minimal sample set required for evaluation of each IVD, the frequency of which will be determined by the technology under test at the beginning of each evaluation.

All samples will either be a) collected by staff who are fully trained to don and doff personal protective equipment, and who are wearing full personal protective equipment in accordance with contemporary guidance from Public Health England, or b) self-collected by participants. Samples will be handled in full accordance with contemporary guidelines for sample handling.

5.3.2.1 On-site sample testing

Some point-of-care tests (POCTs) being evaluated will be undertaken in accordance with the manufacturer's instructions at the place of testing. Infection, prevention and control issues for each POCT will be discussed and implemented according to the test. Training materials will be developed ahead of the evaluation. In general, this will require the use of throat/nose swabs and saliva samples. The remaining samples will be sent for storage at national testing laboratories

5.3.2.2 Central sample testing

Where tests are not available for use at the place of testing, samples will be sent for testing at suitable central laboratories. In general, this will be the transport, throat/nose swab and/or saliva samples. Where possible, the central laboratories will arrange for a courier that has the proper certification to handle this classification of samples to transport the research samples to their facility. Any remaining samples may then be stored by the laboratories for future testing in batches for COVID-19 diagnostics.

6. STUDY PARTICIPANTS

Participants will be identified:

- presenting or referred to secondary/tertiary healthcare organisations such as Emergency Departments, Urgent Care Centres, Ambulatory Care Units, Acute Medical Units, Critical Care services and Acute Hospital at Home services or because they are staff members having tests at their organisation (work stream A),
- as positive or negative for SARS-CoV-2 PCR through national laboratory infrastructure overseeing community testing (work stream B)
- as require testing in the community (work stream C).

6.1 Inclusion Criteria

6.1.1 Work Stream A (in-hospital)

In work stream A we will include two groups of participants – those that present/are referred to secondary/tertiary care with suspected SARS-CoV-2 infection (Group 1) and patients that have been admitted for non SARS-CoV-2 reasons but have been identified as positive for SARS-CoV-2 (Group 2).

Group 1:

We will include participants (patients or staff):

1. That are 18 years or older
2. That will require testing for COVID-19 in the opinion of the treating clinician
3. That may have presented with acute symptoms of COVID-19 (e.g. fever, cough, dyspnoea, anosmia) or chest x-ray changes or they may be asymptomatic but require testing for other reasons

Group 2:

We will include participants:

1. That are 18 years or older
2. That have been admitted for another reason other than suspected SARS-CoV-2 infection, but when routinely swabbed they have been identified as positive for SARS-CoV-2 PCR

6.1.2 Work Stream B (known COVID-positive and/or COVID-negative community testing)

In work stream B we will include patients that have been identified as positive or negative for SARS-CoV-2 PCR through the national laboratory infrastructure (Group 3).

Group 3:

We will include participants:

1. That are 18 years or older

EITHER:

2. They have been identified as positive for SARS-CoV-2 PCR through testing at national laboratory infrastructure

OR

3. They have been identified as negative for SARS-CoV-2 PCR through testing at national laboratory infrastructure

6.1.3 Work Stream C (undifferentiated community testing)

In work stream C we will include participants in the community who are undergoing testing for COVID-19, as follows:

Group 4:

We will include participants:

1. That are 18 years or older
2. Who are undergoing testing for COVID-19, whether they are symptomatic or asymptomatic for COVID-19

6.2 Exclusion Criteria

We will exclude the following patients:

- Impossible or unsafe to obtain the required research samples
- Prisoners
- Patients where sampling is not feasible

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

6.3 Recruitment

6.3.1 Work Stream A (in-hospital; Groups 1 and 2)

Potential participants will be identified when they present or are referred for medical attention delivered by a secondary/tertiary healthcare organisation, whether that be in an Emergency Department, Medical Assessment Unit, COVID-19 cohorted area (e.g. inpatient ward or nightingale hospital) or in an ambulatory care environment such as an Urgent Care Centre, Ambulatory Care Unit or an acute/critical care medicine service. Alternatively, participants may be NHS staff who require testing for COVID-19 at the relevant organisation.

Participants who are successfully screened for potential inclusion will be asked to provide consent. Given the known challenges of obtaining full written informed consent in this setting, patients may participate in the trial if any of the following is provided:

- (1) Tacit or verbal consent, which requires that participants have been given the participant information sheet, have been able to read and understand it, that their understanding has been verified, that they have had the opportunity to ask questions and that they agree to provide samples for the purposes of the study.
- (2) Full written informed consent, in the event that this is feasible and participants have full mental capacity
- (3) Assent provided by a professional legal representative or relative, where both the researcher and an independent professional representative or a patient relative agree that participation in the study is likely to be in accordance with the wishes of the patient, in the event that the patient does not have sufficient mental capacity to decide.

Participants who are included based on tacit or verbal consent may subsequently withdraw from the study if they wish, as specified in the participant information sheet.

For patients enrolled based on the assent of an independent professional representative or relative, but who regain capacity at the time of follow-up, deferred written consent will be sought.

Where consultee consent cannot be provided in person, we have made provisions for this to be completed over the phone.

If a patient gives consent, then loses capacity and subsequently regains capacity during the study period, then enduring consent will be confirmed by obtaining further written informed consent at the next follow-up visit after they regain capacity.

6.3.2 Work Stream B (known COVID-positive and/or COVID-negative community testing; Group 3)

Potential participants will be identified by a national laboratory infrastructure (lighthouse laboratories). Patients presenting to community testing centres to undergo testing for COVID-19 are routinely asked to consent to be contacted about potential participation in current research studies. Patients who have provided consent to be contacted and who test positive for COVID-19 at the associated lighthouse laboratories (where their samples are tested) will be approached for participation in the study and for sharing of their name, contact details and initial swab-based qRT-PCR result data with the research team. This will either be done by telephone or face-to-face at a national testing centre.

For some evaluations, we may also require COVID-negative participants to identified via this route. In that instance, people who have tested negative for COVID-19 at the national laboratory infrastructure (lighthouse laboratories) will be approached as detailed above.

6.3.2.1 Testing centres

A member of the research team will contact the participant at which time verbal consent will be obtained for participation in the study. Continued consent will be confirmed at each patient contact.

6.3.2.2 Home testing

Due to the observational and low risk nature of this evaluation (requiring only the provision of additional samples for analysis), we will seek tacit consent from potential participants. Home testing kits will be sent out to the participants that have been identified as previously described. The kit will contain the participant information sheet for the participant to read, with an email address included in case they have any questions about the study. By sending samples they are consenting for their samples to be used for the purposes of the study, as stated in the participant information sheet.

6.3.3 Work Stream C (undifferentiated community testing; Group 4)

Potential participants will be identified when they present for testing for COVID-19. Because of the observational and low risk nature of this evaluation (requiring only the provision of additional samples for analysis), we will seek tacit consent from potential participants. This requires that participants have been given the participant information sheet, have been able to read and

understand it, that their understanding has been verified, that they have had the opportunity to ask questions and that they agree to provide samples for the purposes of the study.

6.4 Participant withdrawal

Participants can withdraw consent at any time without giving any reason, as participation in the research is voluntary, without their care or legal rights being affected. Samples will be securely disposed of; however, any data that is collected up to this point will be retained.

7. OUTCOME MEASURES

7.1 Active SARS-CoV-2 infection (co-primary outcome)

In accordance with current Public Health England guidance, the reference standard for active infection will be a nasal/throat swab tested for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR). All patients will undergo reference standard testing on the day of inclusion. Patients who remain in hospital on day 3 have a higher pre-test probability of COVID-19 and repeat sampling is feasible. Therefore, the sample will be repeated on day 3 for patients who remain in hospital.

Samples for reference standard testing will be analysed in the Public Health England laboratory that is supporting the study using their existing quality compliant processes. This sample material will be retained by Public Health England and, line with its current processes, may be retained for up to 5 years.

7.2 Past SARS-CoV-2 infection (co-primary outcome)

The current Public Health England guidance suggests that laboratory-based serology testing is the reference standard for past infection. We recognise that the reference standard assay used to verify past infection may change as the study progresses. To accommodate this, we will switch reference standard as the study progresses in order that novel IVDs are always evaluated against the contemporary reference standard assay, as recommended by Public Health England. Blood sampling for serology will be undertaken at Baseline (Day 0) and on days 1, 3, 5, 9, 30 and 90 if required by the IVD under evaluation

7.3 Secondary outcomes

Recognising that the current reference standards for active and past COVID-19 have imperfect sensitivity (1), we will run sensitivity analyses to explore the possibility that novel tests outperform the current reference standard. To do this, we will evaluate the secondary outcomes of active and past infection using an 'enhanced', composite reference standard (2). The composite reference standard will be determined by expert consensus. The current working version of the composite reference standard combines the reference methods described above with radiological findings (chest radiography and/or computed tomography) but may be updated as the study progresses. We will use the contemporaneous version of the composite reference standard to determine diagnoses.

Other secondary outcome measures, to be determined at follow-up on days 30 and 90 include mortality, length of hospital stay, the development of multi-organ failure, critical care admission,



8. DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

Basic data will be collected from participants about their demographics, presenting symptoms, past medical history, relevant vaccinations, physical examination findings, vital signs and the results of any routine tests that they undergo as part of their clinical care. On follow-up visits for sampling, we will also collect details of the participant's condition (e.g. mortality status, requirement for intensive care, organ support and oxygen treatment).

During initial telephone or face-to-face recruitment of Group 3 participants, basic personally identifiable information (name, address, telephone number/email addresses) will be collected to allow the research team to follow up with them. Additionally, the sample ID code of their initial national testing programme swab sample will be collected to allow individuals with a positive test result to be identified and to allow the initial qRT-PCR result data to be shared with the research team.

Data will be collected and stored on Castor Electronic Data Capture system, which is fully GCP compliant. The local research teams will be given access to this system to input the study data. Once data entry is complete the dataset will be downloaded onto NHS servers at Manchester University NHS Foundation Trust in Excel format. Data will be pseudonymised prior to analysis and anonymised once the study has closed and analysis is complete. The link for the pseudonymised dataset will be kept on NHS computers and will only be accessed by the central study team based at Manchester University NHS Foundation Trust.

Anonymised datasets will be sent to Newcastle University and University of Oxford or to other collaborators subject to relevant agreements being in place for statistical analysis. Anonymised datasets may also be sent to University of Leeds, University of Manchester and/or University of Oxford or other collaborators (subject to the relevant agreements) for health economic analysis. These datasets may be stored on encrypted non-NHS computers with the required statistical software. Anonymised clinical data will also be sent to the manufacturers of the point-of-care devices; however, they will not have access to the full database. They will only be sent information for the participants where samples were collected for the evaluation of their device.

Un-redacted copies of participant consent forms will also be sent to the central study team as part of the remote monitoring plan, as onsite monitoring will not take place for this study. This will allow for the sponsor to confirm that all participants have been recruited on to the study according to Good Clinical Practice. Consent forms will be sent via encrypted emails, preferably via NHS.net accounts.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical 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.

9.1.1 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 for both the index test and reference standards will also be reported (actual and percentages).

9.1.2 Summary statistics of diagnostic accuracy

The study will use measures of diagnostic accuracy and descriptive statistics to analyse the different testing methods. Each index test will be tested against standard of care laboratory investigations for SARS-CoV-2. These will include sensitivity, specificity, likelihood ratios and negative and positive predictive values (presented alongside prevalence). We will also report 95% confidence intervals for these values. The process will be repeated for sensitivity analyses against the composite reference standard for active and past COVID-19 infection (as described above, under Outcomes).

9.1.3 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.

9.2 Sample Size**9.2.1 Work Stream A**

We will pragmatically enrol all patients who are eligible, within a safe capacity which will be defined by the local principal investigators. The total number of participants will depend on the number of tests to be evaluated. The requirements for the evaluation of a single test are based on POC-test desired performance, which are currently based on thresholds for minimum sensitivity and specificity of 80% and 98% respectively (value for the lower limit of the 95% confidence Interval). Assuming a test with 100% Sensitivity and a pre-test probability of .3, we would require approximately 100 participants (30 positives) to meet the minimum thresholds as stated above. Assuming a test with 97% sensitivity with a pre-test probability of .3, we would require approximately 120 patients (35 positives). If, after recruiting 30 positives for a particular IVD evaluation, the observed sensitivity is 100%, then we will terminate recruitment for that evaluation and analyse the data. If the observed sensitivity is below 100% but futility criteria (below) are not fulfilled, then we will continue to recruit approximately 120 patients (35 positives).

Some evaluations (for example, those prioritised by the Technology Validation Group) will require a sample size that is consistent with the MHRA target product profile. For point of care tests to detect SARS-CoV-2, that requires a minimum of 150 positive cases (who have COVID-19) and 250 negatives (who do not have COVID-19).

A sample size calculation for each individual evaluation will be stated in a protocol addendum prior to commencing the evaluation.

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.

9.2.2 Work Stream B

The comparison of RT-PCR from throat swabs with detection of SARS-CoV-2 antigen has not been performed in humans, and empirical data for formal power calculations are therefore lacking. The FALCON study management group, study partners from Oxford University Hospitals NHS Foundation Trust Department of Microbiology and an independent statistician will therefore review data from the first 20 subjects with paired throat qRT-PCR and saliva viral antigen results in order to determine formal powering, which will then be included in the statistical analysis plan.

Following initial review, it was decided that approximately 300 participants would be enrolled to this work stream to provide the required precision around estimates of sensitivity for the tests evaluated. Recruitment was subsequently extended to enable the recruitment of additional participants for the evaluation of additional new tests for SARS-CoV-2.

For other evaluations, sample size will be determined on a case-by-case basis prior to commencing the evaluation, as for Work Stream A.

9.2.3 Work Stream C

The sample size for each individual evaluation within work stream C will be stated in a protocol addendum prior to commencing recruitment. For the evaluation of mass spectrometry assays, it is anticipated that approximately 5,000 participants will be required.

10. DATA MONITORING AND QUALITY ASSURANCE

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

11. SAFETY CONSIDERATIONS AND ADVERSE EVENTS

In this observational study, risks to participants will be minimal. Whenever possible, we will use residual samples drawn for clinical purposes. At other times we aim to draw additional samples at the same time as routine venepuncture undertaken for clinical reasons. Finger stick samples must be drawn in addition to routine clinical samples. It is possible that this may cause some transient discomfort to patients and in rare cases there may be bruising. However, the procedures will be undertaken by staff who are proficient at this procedure, which is a regular component of routine clinical assessments. All IVDs will be assessed prior to use to ensure infection prevention and control advice is considered and followed where applicable. We will minimise risks to healthcare workers by requiring that they practice in full accordance with contemporary national guidelines for infection control, including guidance on the appropriate use of personal protective equipment. By undertaking research sampling at the same time as clinical sampling whenever possible, we will minimise the additional exposure of healthcare workers to affected individuals.



12. PEER REVIEW

The study has been externally peer reviewed by the National Institute for Health Urgent Public Health Committee; and by the UKRI funding panel. It has internally peer reviewed by the NIHR Medtech and In vitro Diagnostic Cooperatives (MICs) specialising in the evaluation of in vitro diagnostics, including two statisticians (Prof Rafael Perera and Dr Sara Graziadio).

13. PPI REVIEW

We are being supported by an experienced patient group associated with the Leeds NIHR Medtech and In vitro diagnostic Cooperative (MIC), led by Graham Prestwich. A group of 24 participants met to discuss this proposal. Their ongoing input will be sought as follows: two lay members will form part of the Trial Steering Committee; the patient group will be consulted with regard to interpretation of our findings, prioritisation of tests for evaluation, and dissemination of our findings.

14. ETHICAL and REGULATORY CONSIDERATIONS

14.1 Approvals

Prior to commencing the study, approval will be obtained from the National Research Ethics Service (NRES), the Health Research Authority (HRA) and participating NHS institutions. The research will be undertaken in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

14.2 Risks

Risks to participants and investigators are described above under safety, but the design of this study ensures that such risks are minimal. A risk matrix has been created to identify risks to study delivery and mitigating factors.

15. STATEMENT OF INDEMNITY

NHS indemnity will apply for participants.

16. FUNDING and RESOURCES

The study has been funded by the UKRI (approximately £1.3 million, May 2020) and will be supported by the NIHR Clinical Research Network via the Urgent Public Health portfolio for the COVID-19 response.

17. PUBLICATION POLICY

We will endeavour to publish the findings of this research openly, whether our findings are positive or negative. This is likely to be in medical journals, and our findings may also be published on relevant websites. We will endeavour to ensure that all findings are published with open access. We also plan to disseminate the findings to the Department of Health and Social Care. The data collected will be made available for individual patient data (IPD) meta-analysis.