University Hospital Southampton NHS
NHS Foundation Trust

Evaluating the clinical impact of routine molecular point-of-care testing for COVID-19 in adults presenting to hospital: A prospective, interventional, non-randomised, controlled study (CoV-19POC)

Sponsor: University Hospital Southampton NHS Foundation Trust

Chief Investigator: Dr Tristan Clark

Protocol Version 2.0, 3rd June 2020

Signature Page

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 publically 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.

Chief Investigator:

Signature Date

…….. ……

Name (please print)

……..

For and behalf of the Study Sponsor:

Signature Date

…….. ……

Name (please print)

……..

Position

……..

Protocol Modification History

Version	Date	Key Modifications	Author(s)
1.0	19th February 2020	N/A	Tristan Clark, Nathan Brendish
1.1	12th March 2020	As requested by REC: - Updated Section 6. Recruitment and Study processes, to clarify that potential participants will be first approached by clinical team members - Updated Section 8. Sample Size - Updated REC reference details - Removed reference to GP letter (no longer needed)	Nathan Brendish, Tristan Clark
2.0	3rd June 2020	- Updated the timeframe in which the control group is obtained to improve comparability to intervention group - Updated SAE reporting definitions - Clarified participant end date in the study - Updated study title to reflect control group timeframe changes - Streamlined outcome measures in view of pandemic	Nathan Brendish, Tristan Clark

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Registrations

Internal Study Code: RHM MED1696

ISRCTN: 14966673

Date registered: 18/03/2020

IRAS Project ID: 280621

CPMS ID: 45292

Ethical Approval

Regional Ethics Committee (REC): South Central – Hampshire A

REC reference: 20/SC/0138

Date approved: 16/03/2020

Funding

Support from QIAGEN in the form of equipment and consumables free of charge. University Hospital Southampton NHS Foundation Trust.

Contents

1. Synopsis

Trial site

Southampton General Hospital, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD, UK.

Trial locations

Emergency department (ED), Acute Medical Unit (AMU), Respiratory High Dependency Unit (RHDU), General Intensive Care Unit (GICU), medical wards and other locations, within University Hospital Southampton NHS Foundation Trust (UHS).

Aim

To evaluate the clinical impact and real-world diagnostic accuracy of routine molecular point-of-care testing for respiratory viruses including SARS-CoV-2 (the cause of COVID-19) in adults presenting to hospital with suspected COVID-19 and/or acute respiratory illness (ARI).

Design

Non-randomised, interventional, controlled study.

Population

Adults aged 18 years old and over presenting to hospital with suspected COVID-19 and/or ARI.

Sample Size

1000 participants (500 participants in the intervention group and 500 in the control group).

Intervention

Combined nose and throat swab (and lower respiratory tract samples where available) tested by QIAGEN QIAstat-Dx Respiratory SARS-CoV-2 Panel at the point-of-care with results communicated to clinical and infection control teams in real time.

Control

Routine clinical care with testing for SARS-CoV-2 by laboratory RT-PCR performed in regional Public Health England (PHE) laboratory contemporaneously, in patients not included in the intervention.

Key Assessment

Evaluation of clinical outcome measures, implementation feasibility, and real-world diagnostic accuracy.

Timing

12 months: March 2020 to April 2021 (with up to 6 months for patient recruitment)

Plus a further five years after patient recruitment has ended for data and laboratory analysis of specimens

2. Overview

Background

Coronavirus disease 2019 or COVID-19 (formally known as 2019-nCoV acute respiratory disease) is an infectious disease caused by SARS-CoV-2, a novel coronavirus closely related to the SARS virus. The World Health Organisation (WHO) declared COVID-19 to be a Public Health Emergency of International Concern on the 30th of January 2020. At the time of writing there have been nearly 90,000 confirmed cases worldwide with nearly 3000 deaths worldwide involving over 50 countries. Although to date most cases and deaths have occurred in China, large outbreaks have been now reported in South Korea, Iran and Italy demonstrating sustained person-to-person spread in other countries. There have been over 50 confirmed cases in the UK so far and thousands have been tested. It seem likely that the virus will continue to spread causing a full scale pandemic and that the UK will see many more suspected and confirmed cases over the coming weeks and months. The current diagnostic strategy of the UK uses centralised laboratory RT-PCR testing but laboratory capacity is limited and results are delayed by up to several days, leading to unsustainable pressures on the NHS. We have previously proven that molecular point-of-care testing (mPOCT) for respiratory viruses is feasible and associated with improved clinical management and outcomes for patients compared to standard of care laboratory testing. Testing patients presenting to secondary care using a novel mPOCT for SARS-CoV-2 may dramatically reduce the time to results, improve clinical management and relieve pressures on laboratories and NHS clinical services during the next phase of the outbreak.

Aims

This study will evaluate the clinical impact, implementation feasibility and real-world diagnostic accuracy of routine syndromic mPOCT for respiratory viruses, including SARS-CoV-2, in adults presenting to hospital with suspected COVID-19 and/or acute respiratory illness (ARI).

Methods

We will undertake a prospective, interventional, non-randomised, implementation study of mPOCT for COVID-19 in adults presenting to University Hospital Southampton NHS Foundation Trust. A brief validation and training phase will be followed by the post-implementation phase where patients will be recruited and tested at the point-of-care using the QIAstat-Dx Respiratory SARS-CoV-2 Panel. We will initially test patients suspected of COVID-19 based on current PHE case definitions and then progress to testing all patients with ARI as the outbreak becomes more widespread in the UK and the risks of admitting patients to hospital with unsuspected COVID-19 are high. Clinical and infection

control teams will be informed of these results in real time. The control group will consist of patients who were tested for SARS-CoV-2 by laboratory PCR but not recruited to the study during the same time period. This allows us to have a comparable control group as the outbreak progresses and hospital pathways change, as opposed to a pre-implementation group which predominantly is expected to consist of community-based patients tested in hospital for containment reasons. Only anonymised, routinely collected hospital data will be obtained for the control group. Outcome measures will be by assessed by retrospective case note analysis and will include: time to result, time in isolation facilities, detection of COVID-19 cases not initially suspected (based on current PHE case definition), antibiotic use, antiviral use, length of hospital stay, ward closures and hospital resource use. Multivariate analysis will be used to control for the effect of confounding variables between the groups.

Potential benefits to patients and the NHS

We hypothesise that the use of a routine mPOCT for respiratory viruses including SARS-CoV-2 in adults presenting to hospital with suspected COVID-19 and/or ARI will dramatically reduce the time from patient presentation to results, compared to the current standard of PHE laboratory RT-PCR. We expect that timely detection or exclusion of COVID-19 will lead to improvements in early directed isolation facility and enhanced PPE use or de-isolation/de-escalation, in addition to other potential benefits such as reduced length of stay, improved use of antibiotics and antivirals and resource use and cost for the NHS. The detection of COVID-19 positive cases presenting to hospital and not initially suspected based on current the PHE case definition will prevent widespread nosocomial transmission of SARS-CoV-2 and associated hospital ward closures.

3. Abbreviations and Definitions

AE: Adverse Event

AMU: Acute medical unit

ARI: Acute respiratory illness

CES: School of Clinical and Experimental Sciences, Faculty of Medicine University of Southampton

CI: Chief Investigator

COVID-19: Coronavirus disease 2019

CRF: Case Report Form

ED: Emergency Department

GICU: General Intensive Care Unit

HRA: Health Research Agency

ICU: Intensive care unit

mPOCT: Molecular Point-of-Care test

PCR: Polymerase Chain Reaction

PHE: Public Health England

PI: Principal Investigator

POCT: Point-of-Care Test

PPE: Personal Protective Equipment

REC: Regional Ethics Committee

RHDU: Respiratory High Dependency Unit

RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

SAE: Serious Adverse Event

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

UHS: University Hospital Southampton NHS Foundation Trust

WHO: World Health Organisation

4. Introduction

COVID-19

COVID-19 (previously known as 2019-nCoV acute respiratory disease) is an infectious disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a novel coronavirus closely related to the SARS virus. The primary mode of transmission is human-to-human spread via respiratory droplets and it has an incubation period of 2-14 days (median of 4 days). Cases were first identified in Wuhan, Hubei province, China in December 2019 and it has subsequently spread to other regions of china and multiple other countries. There have now been nearly 90,000 confirmed cases involving over 50 other counties around the world [1]. The R_0 (average number of secondary case from each primary case) for the virus has been estimated at between 2 and 3 showing that it is highly contagious [2]. The severity of cases ranges from very mild or asymptomatic infection through to severe pneumonia and multi-organ failure [3,4]. So far nearly 3000 deaths have been recorded and early estimates of the case fatality rate are around 1 to 2% [1].

The World Health Organisation (WHO) declared COVID-19 to be a Public Health Emergency of International Concern on the 30th of January 2020. At the time of writing there have been over 50 confirmed cases in the UK. Recent large scale outbreaks have occurred in Iran, South Korea and Italy demonstrated sustained person to person transmission in multiple geographic regions. It seem likely that the virus cannot be contained and will continue to spread leading to a full scale pandemic, and that the UK will see many more suspected and confirmed case, including patients with severe pneumonia, over the coming weeks and months.

Diagnosis of COVID-19

Currently, all diagnostic testing for COVID-19 (SARS-CoV-2) in the UK is takes place in the PHE reference laboratory in Colindale, London, with testing capability being rolled out to regional PHE laboratories in late February 2020. Testing utilises RT-PCR and is thought to be highly accurate but the current diagnostic pathways are unacceptably slow; the time from sampling to results being available is currently around 3-4 days. Even when laboratory testing is rolled out to regional PHE laboratories the turnaround time for results is still likely to be too slow to allow clinical decision making in a meaningful timeframe for clinical and infection control teams. Currently there are small numbers of suspected cases of COVID-19 in the UK and the vast majority of specimens test negative. Suspected cases currently have to spend several days in hospital isolation facilities with staff using full enhanced personal protective equipment (PPE) or self-isolating at home, until results are returned. It is likely

that there will be many more suspected cases of COVID-19 over the coming weeks with high numbers of patients presenting to secondary care and therefore requiring enhanced isolation facility use and testing. In this context the additional resource demand on secondary care and laboratories will be immense and the current diagnostic pathway will be unsustainable.

The current case definition for suspected cases of COVID-19 relies on a recent history of travel to heavily affected areas in Asia and elsewhere. However as the virus is highly contagious, mainly causes mild illness and can even be transmitted by minimally symptomatic patients [5], clusters of infected patients are likely to go unrecognised as the outbreak progresses. There is therefore a high risk of COVID-19 cases that do not fulfil the case definition and so are clinically unsuspected, being hospitalised in the coming weeks. If these are not tested and appropriate isolation facilities used at presentation then widespread nosocomial transmission in hospitals is likely to occur, with devastating consequences for patients and hospitals. There is therefore a compelling argument as the outbreak spreads, for routine testing for SARS-CoV-2 in all patients presenting to hospital with compatible clinical symptoms (i.e. acute respiratory illness) alongside syndromic testing for other respiratory viruses.

Molecular POCT for respiratory viruses

Our previous randomised controlled trials have demonstrated that routine syndromic mPOCT for respiratory viruses leads to the generation of accurate, actionable results in under 2 hours compared with 1-2 days for laboratory testing. Physicians act on these results and mPOCT is associated with a number of clinical benefits including reduced antibiotic use and length of stay [6]. Further analysis shows that a very rapid turnaround time is critical to achieving these improvements and the best outcomes were associated with the quickest results [7], definitively showing that testing for respiratory viruses should take place at the point-of-care rather than in centralised laboratories. In our most recent trial (FluPOC) routine mPOCT for influenza was associated with vast improvements in the detection of influenza and the timely and appropriate use of isolation facilities and antivirals [8] and was also associated with improvements in clinical outcome.

Using syndromic mPOCT to detect COVID-19

The current situation of an emerging pandemic of a novel coronavirus is ideal for using a syndromic mPOCT approach including testing for COVID-19. COVID-19 is clinically indistinguishable from illness caused by other respiratory viruses and so testing syndromically with a single test is clinically desirable and efficient. Accurate testing for COVID-19 at the point-of-care will enable the generation of results in near real-time, allowing early appropriate and directed use of enhanced isolation facilities for

patients and PPE for staff, for SARS-CoV-2 infected patients and rapid de-isolation for those testing negative. Testing for influenza and other respiratory viruses at the same time enables early identification of other important pathogens simultaneously and without the need for duplicate testing or for processing of additional samples in biological safety level 3 (BSL3) facilities.

The QIAGEN QIAstat-Dx is a rapid automated multiplex PCR system designed for syndromic testing for infectious diseases. The CE marked Respiratory Panel contains targets for 20 respiratory viruses and atypical bacteria (Influenza A, Influenza A subtype H1N1/2009, Influenza A subtype H1, Influenza A subtype H3, Influenza B, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Parainfluenza viruses 1 to 4, Respiratory Syncytial virus A/B, human Metapneumovirus A/B, Adenovirus, Bocavirus, Rhinovirus/Enterovirus, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Bordetella pertussis*). Diagnostic accuracy assessment demonstrates high sensitivity, specificity, positive predictive and negative predictive value for all targets [9,10]. The test requires minimal sample preparation, can test on a swab directly or using viral transport medium, and takes around 1 hour to generate a result. Assays for SARS-CoV-2 have been added to the panel and early data from control material (including patient samples) suggesting diagnostic accuracy comparable to the WHO reference standard and a limit of detection of around 400copies/ml. This updated test version is currently approved for research use only (RUO) with application for CE marking to follow rapidly. There is no cross reactivity between the seasonal coronavirus targets (229E, HKU1, NL63 and OC43) and SARS-CoV-2.

Potential clinical impact of mPOCT for SARS-CoV-2

The impact of mPOCT for COVID-19 in hospitals is likely to be large given the very prolonged delay in obtaining laboratory RT-PCR results for suspected cases and the requirement for enhanced infection control procedures including the use of negative pressure side rooms for patients and full PPE for staff, while awaiting results. As most patients with suspected COVID-19 are expected to test negative (at least in the early part of the outbreak) the use of mPOCT is expected to lead to the avoidance of using negative pressure side room or early de-isolation for COVID-19 negative patients and the avoidance or early de-escalation of enhanced PPE for staff. In addition there may be additional benefits of mPOCT such as early cessation of unnecessary antibiotics, early directed antivirals for influenza and early appropriate discharges for certain patients. The early detection of SARS-CoV-2 in patients presenting to hospital with ARI who were not clinical suspected (based on the current PHE case definition) will prevent widespread nosocomial transmission and ward closures. Early, accurate identification of hospitalised COVID-19 positive patients will also allow enrolment into trials of investigational antiviral therapeutics and vaccines, and will allow early directed antiviral therapy once it becomes available.

Alignment with global research priorities

Laboratory testing for COVID-19 by RT-PCR is the current standard diagnostic strategy for all countries. Laboratory testing capacity was rapidly exceeded in China due to the huge volume of cases leading to alternative diagnostic strategies including CT scanning of the chest as a surrogate test for viral pneumonia. Due to the limited laboratory capacity and prolonged turnaround for results alternative diagnostic strategies are urgently needed for COVID-19 across the globe. This study will demonstrate the feasibility and clinical impact of mPOCT for COVID in hospitals as well as studying real-world diagnostic accuracy of the QIAstat-Dx Respiratory SARS-Cov-2 assay.

5. Aim and Objectives

Aims

To evaluate the clinical impact, implementation feasibility and real-world diagnostic accuracy of routine mPOCT for respiratory viruses including SARS-CoV-2 in adults presenting to hospital with suspected COVID-19 and/or ARI.

Objectives

1. To assess the clinical impact of mPOCT for respiratory viruses including SARS-CoV-2 on outcomes measures including: time to test result, time in COVID-19 assessment cohort areas, time to definite ward move, length of stay in hospital, use of antibiotics, use of antivirals, ward closures, and hospital resource use, in adults hospitalised with ARI.

2. To assess the implementation feasibility of mPOCT for COVID-19.

3. To assess the ease-of-use, reliability and real-world diagnostic accuracy of the QIAstat-Dx SARS-2-CoV assay, , using respiratory samples prospectively collected from adults presenting to hospital with ARI, compared to the reference standard of PHE laboratory RT-PCR for SARS-CoV-2.

6. Recruitment and Study Processes

Overview

This is a non-randomised, controlled, implementation study of mPOCT for respiratory viruses including COVID-19 with prospective recruitment for participants in the intervention phase. The intervention consists of testing respiratory samples from patients at the point-of-care using the QIAstat-Dx Respiratory SARS-CoV-2 Panel. In the contemporaneous control group, routinely collected data on outcomes in patients tested for COVID-19 using laboratory RT-PCR, including time to test result. In the intervention phase patients will be tested using the QIAstat-Dx Respiratory SARS-CoV-2 Panel with results delivered immediately to the clinical and infection control team and outcome and diagnostic accuracy data collected retrospectively. A brief validation phase will precede the intervention phase. Study processes that patient-participants undergo in intervention phase are summarised in Figure 1.

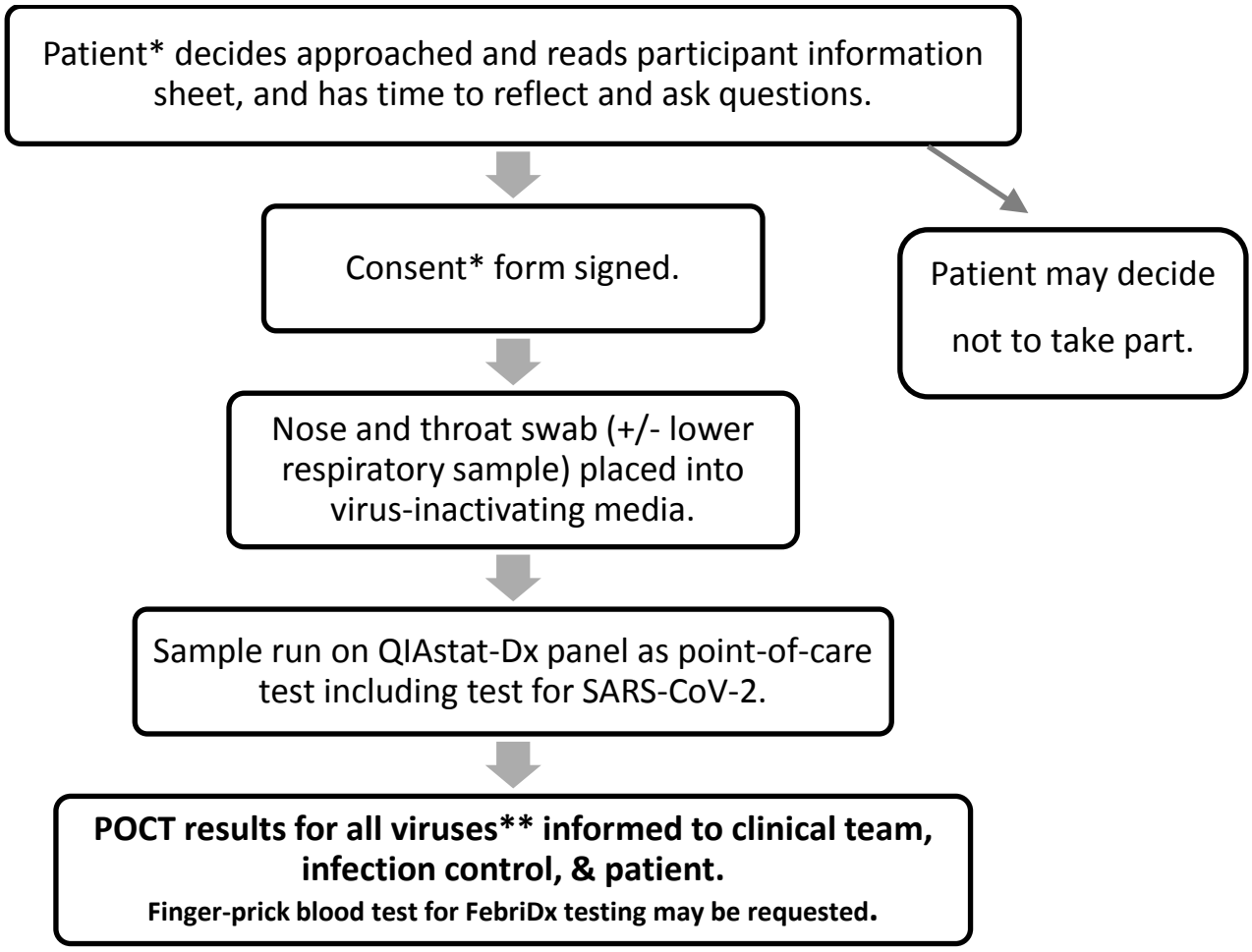

Figure 1: Participant flow through the study

POCT = point-of care test
*if lacks capacity to consent, participant's consultee may be substituted here

Control group

Patients (≥18 years old) presenting to hospital with ARI who have been tested for SARS-CoV-2 during the same time period as part of standard clinical care (but not included in the intervention) via University Hospital Southampton NHS Foundation Trust (UHS) will be identified via (laboratory) information management system and select clinical data will be obtained by electronic records including age, sex, co-morbidity, observations, blood test results, length of hospital stay, and time to test result. Consent is not obtained for these patients, and only anonymised data already collected as part of routine clinical care will be used.

Screening

The clinical teams in the various areas shall identify potentially eligible patients in the clinical areas by regularly reviewing the admitted patients and electronic admission systems against eligibility criteria and informing the research team. Many members of the research team are healthcare professionals who are looking after these patients directly. The initial approach to potential participants will be made by clinical team members and not by additional research staff.

Consent

The study team will obtain written informed consent for those fulfilling eligibility criteria and willing to be recruited for those with capacity, or assent via consultee for those without capacity, using the dedicated study forms. As noted above, in view of the acute nature of patients' illnesses, the potential benefits of rapid identification of viruses including SARS-CoV-2, the usual 24 hour consideration period for a participant or consultee will not apply.

Discussion of the study will be provided to patients, or their consultee for those lacking capacity, by study staff. This includes supply of a participant information sheet for the participant or witness to read and retain.

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

Each patient will be assumed to have capacity unless it is established that they lack capacity. For patients unable to consent for themselves, this study complies with the Mental Capacity Act 2005 and in such cases, the patient's family member, carer or friend may be asked to act as the personal consultee and provide assent. In the event of a personal consultee not being available a nominated consultee (usually the consultant caring for the patient and independent from the study) will be asked if they would provide assent. Both the person taking assent and the consultee must personally sign and date the relevant form.

The personal / nominated consultee will be advised to set aside their own views and take into consideration the patient's wishes and interests. Advance decisions and statements made by the patient about their preferences and wishes will always take precedence.

In the event of the patient recovering capacity following enrolment by consultee, the patient will be asked to read the patient information sheet and provide consent for themselves. The patient may give consent, withdraw but have data and/or samples collected so far retained, or withdraw and have their data and/or samples destroyed (but signed consultee declaration forms, minimal personal identifiable information to record the withdrawal, and any point-of-care test result will be retained).

For potential participants with infection control concerns, consent and consultee declaration forms may be marked with initials and signatures written with a finger or stylus on an electronic device that is subsequently cleaned (e.g. an iPad or similar), rather than paper. In these situations, participants and/or their consultees are still provided with a paper copy of any signed forms.

Validation phase

The study intervention starts with the validation/verification phase which will last approximately 1-2 weeks. The QIAstat-Dx Respiratory SARS-CoV-2 Panel with be validated using the specific control material from Zeptopetrix (NATRVP-QIA) which contains targets for all non SARS-CoV-2 pathogens on the panel, as per the manufacturers recommendations and using their suggested protocols. The SARS-CoV-2 assays will be validated using control material provided by Qiagen (single stranded DNA fragments homologous to the SARS-CoV-2 genes – the E-gene and Rdp gene - targeted by the assays) and from SARS-CoV-2 positive patient samples. The validation will take place in the Clinical Research Facility laboratory under BSL2 conditions and will also test the diagnostic accuracy of the assays on control material placed in molecular media compared to viral transports media (see below).

Intervention phase

Once the analysers have been fully validated using control material and the research staff adequately trained in use of the QIAstat-Dx and fully PPE trained, the validation phase will end and move in the intervention phase. Providing the validation phase is successful (and/or CE marking has been granted) the study will move in the intervention phase where all patients presenting to UHS with ARI will be approached (including those fulfilling the PHE case definition for suspected COVID-19). The intervention recruitment phase will last up to 6 months.

Procedures

Participants will be enrolled and assigned a unique participant identification number consecutively. Respiratory samples will be collected from patients by an appropriately trained member of research staff wearing full PPE as defined by UHS infection prevention and control policy. A combined nose and throat swab, and if available, a lower respiratory tract sample (sputum, or for patients in critical care units BAL or ET secretions) will be obtained and tested. Samples will be immediately placed in a sigma MWMM (molecular medium) or similar tube (containing detergent and Guanidine thiocyanate) to rapidly and completely inactivate any virus present (within 1 minute). The sample will then be loaded in the test kit and tested on the QIAstat-Dx analyser housed in the acute area. The result will be available in around 1 hour and will be delivered to the clinical and infection control teams as soon as results are available. The system will be de-contaminated prior to and after use in accordance with the manufactures instructions.

All participants may be approached for a finger-prick blood test with the FebriDx (RPS, Fl., USA) and a second nose and throat swab in viral transport media (participants may opt out of one or both of these).

Patients testing positive for COVID-19 and for 'seasonal' non-COVID-19 coronaviruses may be approached for additional respiratory samples and/or blood samples for additional virological, serological and host response analysis at various time points (see Table 1 and laboratory analysis plan).

Participant involvement end date

Participant involvement in the study is considered ended once their last physical interaction with the research team has finished, although some retrospectively collected outcome measures will still be collected from records after this time (e.g. 30 and 60 day mortality). For patients testing negative for coronaviruses this is expected to be the same day as enrolment. For patients testing positive for a coronavirus, this may be the same day as enrolment if no further samples are collected, or the date of the last additional samples acquired (see Table 1). Participant withdrawal is discussed separately.

Day 0 (enrolment day) +/- 72 hours	Day 14 (+/- 4 days)	Day 28 (+/- 4 days)
Blood test (max 22ml)	Blood test (max 22ml)	Blood test (max 22ml)
Additional nose & throat swabs +/- lower respiratory sample	Nose & throat swabs	Nose & throat swabs

Table 1. Optional additional tests for those testing positive for SARS-CoV-2 or any endemic coronavirus

Inclusion / exclusion criteria

Inclusion criteria:

- Is a patient in ED, AMU, HDU, GICU, medical wards, or another location within Southampton General Hospital, University Hospital Southampton NHS Foundation Trust (UHS)

- Aged ≥18 years old

- Can be recruited to the study within 24 hours of presentation to hospital

Plus:

- Has acute respiratory illness (ARI)*

OR

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

OR

- Does not have ARI or fulfil the PHE case definition of a suspected case but testing for SARS-CoV-2 is considered necessary by the responsible clinical team

*An episode of acute respiratory illness is defined as an acute upper or lower respiratory illness (including rhinitis, rhino-sinusitis, pharyngitis, pneumonia, bronchitis and influenza-like illness) or an acute exacerbation of a chronic respiratory illness (including exacerbation of COPD, asthma or bronchiectasis). For the study, acute respiratory illness as a provisional, working, differential or confirmed diagnosis must be made by a treating clinician.

Exclusion criteria:

- Not fulfilling all the inclusion criteria

- Declines nasal / pharyngeal swabbing

- Consent declined or consultee consent declined

- Already recruited to the study in the last 14 days

Further inclusion / exclusion notes

Concurrent, prior, or subsequent enrolment in another study is not necessarily an exclusion criterion; this is at the discretion of the chief investigator and will be assessed on a case-by-case basis. Local R&D measures including a "12 week exemption form" must be in place and agreed with the chief investigator that may facilitate co-enrolment in other studies.

The inclusion of pregnant women is permitted in the study. No additional risk is perceived to pregnant women or their offspring by any of the study procedures. No additional data collection or monitoring is therefore anticipated in this group. It may be especially important to include pregnant women in COVID-19 research, as infection with influenza is associated with worse outcomes in pregnancy [11]. Data on abnormalities at birth or congenital defects and other serious adverse events are collected and may be reportable (see relevant section on Safety).

Staff testing

Non-hospitalised hospital staff members may be included in the intervention phase of the study, if they satisfy the other inclusion & exclusion criteria. The same consent and study procedure processes are followed. However, their results will not be included in analyses of most outcome measures, with the exception of time to result. Days away from work may be used as an additional outcome measure.

Participant Withdrawal

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

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

Any patient, or their consultee where a patient lacks capacity, who is withdrawing from the study has the options withdraw and have data and/or samples collected so far retained, or withdraw and have their data and/or samples destroyed (but signed consultee declaration forms, minimal personal identifiable information to record the withdrawal, and any completed point-of-care test result will be retained).

Although the study procedures are very brief, if a patient loses capacity after enrolment but before the study procedures are completed, consultee consent must be sought to continue with any study procedures, or the participant must be withdrawn.

A note to file would normally be sufficient to record any withdrawal.

7. Outcomes

Primary outcome

- The primary outcome measure is the time from COVID-19 test being requested to the result being available to clinical teams.

Secondary Outcomes

- The time from presentation to hospital to COVID-19 test result
- Time spent in COVID-19 assessment cohort area
- Time to definitive ward move
- Number of bed moves
- Duration of hospitalisation
- Number and proportion of clinically unsuspected COVID-19 positive patients detected
- Proportion of patients treated with antibiotics
- Proportion of patients treated with single doses or brief courses (<48 hours) of antibiotics
- Duration of antibiotic use, days
- Proportion of all influenza antiviral use occurring in influenza positive patients
- Proportion of all influenza antiviral use occurring in influenza negative patients
- Time from admission to influenza antiviral commencement
- Duration of influenza antiviral use, days and doses
- Proportion of patients with ICU or RHDU admission
- Proportion readmitted to hospital within 30 days
- In hospital, 30 and 60 day mortality
- Reliability (proportion of run failures), ease-of-use scores [12], and implementation feasibility assessment (narrative) of QIAstat-Dx Respiratory SARS-CoV-2 Panel, used at the point-of-care.

Sensitivity, specificity, positive predicted value, negative predictive value, percentage positive agreement, percentage negative agreement, percentage overall agreement, and overall diagnostic accuracy of QIAstat-Dx SARS-CoV-2 assay (as part of QIAstat-Dx Respiratory SARS-CoV-2 Panel) compared to laboratory PCR using the PHE RdRP assay.

All outcomes are measured for the duration of hospitalisation or up to 30 days (whichever is shortest) unless specified otherwise and include medication (antibiotics and antivirals) that patients are discharged home with.

Exploratory Outcomes

Changes in viral load over time (kinetics) in upper and lower respiratory tract samples for COVID-19 positive patients.

Antibody levels and changes over time (kinetics) in blood for COVID-19 positive patients and patients positive for other 'seasonal' non COVID-19 coronaviruses.

Presence or absence of MxA at presentation in fingerpick whole blood (as tested by FebriDx) in patients with and without COVID-19.

Host response (transcriptomic) at presentation and over time in patients with and without COVID-19.
Time to administration of experimental antiviral (if and when available)

8. Sample size

Proposed sample size

The sample size of 500 patient-participants is chosen pragmatically based on the current availability of the QIAstat-Dx Respiratory SARS-CoV-2 Panel test kits. The manufacturer has agreed for us to purchase this number. The kits are in high demand given the epidemic situation with limited supply.

500 patients would give a clinically meaningful assessment of a range of clinical outcome measures including time to results, time in COVID-19 assessment cohort areas, time to definitive ward move, and duration of hospitalisation. It will also allow a robust assessment of the reliability and ease-of-use of the platform. Aiming to recruit more than 500 patients may delay analysis and dissemination of results of this study and subsequent policy changes the study results may bring, especially in a fast-paced outbreak situation.

Accepting that the prevalence of COVID-19 during the study is highly speculative at present, and so formal samples size calculation for diagnostic accuracy studies are not possible, testing 500 patients will allow us to make an ongoing assessment of the real-world diagnostic accuracy of the QIAstat-Dx Respiratory SARS-CoV-2assay compared to the current reference standard of laboratory PCR testing using the PHE RdRP assay.

The control group will be 500 patients for an adequate comparison.

9. Data collection

Demographic and clinical data will be collected for all patients at enrolment including: age, sex, ethnicity, smoking status, vaccination status, co-morbidities, medication use, symptoms, duration of illness prior to hospitalisation, observations (pulse rate, respiratory rate, blood pressure, oxygenation status), laboratory results, radiology results, antimicrobial and antiviral use prior to hospitalisation and provisional diagnosis. Data will be recorded on a Case Report Form, which we intend to be electronic (ALEA). Once patients have been discharged or after 30 days (whichever is soonest), clinical data will be collected retrospectively from electronic and physical case notes including: use of antivirals, duration of antivirals, time from assessment to antiviral use, use of antibiotics, duration of antibiotic use, use of side room facilities, time from assessment to isolation facility use, time to clinical stability, duration of supplementary oxygen use, duration of hospitalisation, complications including ICU and RHDU admission, representation and readmission to hospital within 30 days, final diagnosis and mortality. The number of diagnostic tests and procedures performed will also be recorded and data will also be collected on the turnaround time of respiratory virus test results in each group.

10. Data Management

The subjects' anonymity will be maintained. The study team will keep a log of each subject's name, hospital ID number, date of birth, and unique participant trial number. The participant details will be recorded on the secure NHS Edge system in a similar manner, including NHS number. This participant trial number is used on documents after screening to maintain confidentiality. Documents that are not anonymous (e.g. signed informed consent forms) will be maintained separately, in strict confidence.

The study staff will be responsible for entering study data in the Case Report Form (CRF). It is the investigators' responsibility to ensure the accuracy of the data entered in the CRF.

Only the research study team will know the identity of subjects and have access to the list linking participant details to the participant trial number.

Essential Document Retention

Essential documents, as defined by ICH GCP, include all signed protocols and any amendment(s), copies of the completed CRFs, signed informed consent forms from all subjects who consented, hospital records, and other source documents, REC approvals and all related correspondence including approved documents, study correspondence and a list of the subjects' names.

The investigator and/or sponsor must retain copies of the essential documents for a minimum period following the end of the study. This period is defined by local guidelines where the research is being conducted. For all subjects that are entered into the study, the medical notes and electronic systems may be marked in line with local R&D guidelines to alert other users of the notes and systems to the patient's enrolment in this study.

The chief investigator is responsible for, with the sponsor, ensuring that documents are archived in accordance with local NHS R&D procedure at study close. Documents are expected to be archived for 15 years.

Data monitoring

On the basis of the very low risk of harms associated with the intervention in this non-CTIMP trial, no data monitoring committee or interim analysis is planned.

11. Statistical Analysis Plan

Trial results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. Statistical analysis will be performed by a dedicated medical statistician from the University of Southampton, independent from the study team (Dr Sean Ewings). No interim analysis is currently planned.

Patients in the groups will be compared using standard descriptive and comparative statistical methods using Prism version 7.0 (GraphPad Software Inc; La Jolla, California), and Stata version 16 (StataCorp, College Station, Texas) or more updated software versions where available.

Missing data was minimal (<2%) in the CI's previous POCT studies and therefore is not expected to be significant issue in this trial. The use of multiple imputation will be considered should missing data exceed 5% for the primary outcome or for key secondary outcomes.

Summaries of all baseline characteristics will be presented using means and standard deviations, medians and interquartile ranges, or frequencies and percentages, as appropriate. The groups will be compared using chi-square tests for equality of proportions for binary data (e.g. proportion of cases of influenza detected) and using independent-samples t-tests or non-parametric equivalent as appropriate for continuous data (e.g. duration of isolation facility use, etc.).

The primary outcome measure (median duration of isolation facility use) will be compared between the groups using the Mann-Whitney U test. Multivariate analysis will be performed to adjust for confounding variable in view of the non-randomised nature of the study.

12. Safety

Serious Adverse Events

The risks of respiratory tract sampling and additional blood tests being taken are minimal and where occurring are likely to be mild. No additional adverse events related to mPOCT for respiratory viruses including COVID-19 are anticipated. However active monitoring and reporting of severe adverse events will be undertaken. A Serious Adverse Event (SAE) is any adverse event that:

- Results in death

- Is life-threatening

- Requires hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity

- Consists of a congenital anomaly or birth defect

In the event of a SAE, a study doctor will consider the likelihood of the event being related to the study based on the documented evidence from the treating clinicians. SAEs will be reported via the sponsor's standard forms and processes. SAEs will be reported within 24 hours of the study team learning of the SAE. In the event of a SAE, the PI will be involved in deciding whether this was a study-related event. In the event of a study-related SAE, the REC will be informed as per HRA regulations.

Participants already admitted to AMU, or another hospital ward including high dependency or an intensive care unit, or are in ED but with a decision already made to admit, are considered already hospitalised. However, an adverse event leading to prolongation of their existing hospitalisation will be counted as an SAE.

Only SAEs occurring within 30 days of enrolment or hospital discharge, whichever comes soonest, will be reported to the sponsor, with the exception of any congenital anomaly or birth defect. Congenital anomalies or birth defects will be actively recorded up to 30 days post enrolment but if discovered after this period will still be reported to the sponsor. The trial procedures are very brief and very low risk, and pregnancy commencing during the trial procedures or follow up period is both unlikely to occur and is not expected to be reported to the sponsor or REC.

Participants in high dependency or intensive care units are at high risk of expected death, and therefore participants recruited in these locations who die will not be reported as an SAE to the sponsor, unless it is deemed related to the study by the PI.

The SAE conditions noted were prompted by previous respiratory virus molecular POCT studies including one that showed around 60 SAEs for just over 300 patients. A large proportion of the patient group had conditions making readmission likely and had a high background likelihood of mortality. Not a single SAE was in any way related to the study, but significant resources were taken up in reporting of the SAE without any benefit or impact upon safety. Similar criteria have been used in two previous POCT studies. Therefore, the caveats to SAE reporting for this trial have been developed to streamline the reporting process, promote efficiency and maximise safety.

Urgent safety measures

A sponsor or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. The REC must be notified immediately and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

Protocol non-compliance and deviations

Events of protocol non-compliance or deviation will be considered by the Chief Investigator on a case-by-case basis. Where deemed necessary by the CI, advice from trials mangers, facilitators, or governance staff within UHS R&D, and as the sponsor, will be sought.

Serious breaches of GCP or protocol

Serious breaches of GCP or the protocol should be reported, by the investigators and the sponsor, within seven days to the Medicines and Healthcare products Regulatory Agency and relevant ethics committee in accordance with current regulations. A “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

Update to SAE reporting with Protocol Version 1.2

As of 3rd June 2020, 131 SAEs of deaths, life-threatening events, and readmissions have been reported to the sponsor with more expected to be found and therefore need reporting. All SAEs have been unrelated to the study procedures. Given the high rate of poor clinical outcomes during the COVID-19 outbreak unrelated to the study, and the high and unnecessary administrative burden without any

safety benefit, SAE reporting for this trial urgently needs to be updated. Therefore, as of the date of approval of this amendment, the only SAEs to be reported to the sponsor are death during the hospital admission in which the participant was recruited (up to 30 days after admission; and not reportable if recruited in HDU/ICU setting), or congenital anomaly or birth defect occurring at any time. Other SAE categories shall not be reported to the sponsor unless they are related to the study. The publishing of safety outcome data for this trial is unchanged by this update.

13. Ethics, Oversight and Approvals

Declaration of Helsinki

The Investigators will ensure that this study is conducted according to the principles of the current revision of the Declaration of Helsinki.

ICH Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted in full conformity with the ICH Good Clinical Practice (GCP) and local regulatory requirements.

Submissions to HRA, REC and local R&D

The protocol, informed consent forms, participant information sheet (and any other document requested) will be submitted to the Health Research Authority (HRA) for their processes including Regional Ethics Committee (REC) for written approval, and the study will not commence until all necessary HRA and REC approvals are in place. The Chief Investigator will submit and, where necessary, obtain approval from the REC for all subsequent substantial amendments to the protocol and informed consent document. Local R&D approval will be confirmed prior to study start.

Participant Confidentiality

All data will be anonymised: volunteer participant data will be identified by a unique study number in the CRF and database. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the Data Protection Act 1998. Only the Sponsor's representative and investigators will have access to the information.

Investigator Responsibility

The Chief Investigator is responsible for the overall conduct of the study and compliance with the protocol and any protocol amendments. Responsibilities may be delegated to an appropriate member

of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

Monitoring

UHS as sponsor will put in place study monitoring based on study risk assessment at study set-up stage. Study monitoring will be conducted by UHS R&D Clinical Trials Project Managers as per the monitoring plan.

Publication Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

14. Finances and Indemnity

This is an NHS-sponsored study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

15. Role of QIAGEN

The manufacturer of the QIAstat-Dx platform, QIAGEN (Hilden, Germany) will support this study by providing equipment and consumable free of charge. They have had no role in the conception or design of this study and will not have any role in the conduct of the study, data analysis and interpretation, or preparation of manuscript for submission to scientific journals. Only the research team and medical statistician will have access to the data prior to publication.

16. Laboratory analysis plan

Exploratory assays will be carried out on the samples collected in this study at the discretion of the Chief Investigator, with the purpose of studying localised and systemic infection and the human immune responses to infection. The samples acquired from participants and subsequent laboratory analysis will continue after participant recruitment has closed for a period of up to five years. After this period, further application to the relevant ethics committee may be required to continue storing and using the samples, or the Chief Investigator may deposit the samples in an appropriately licenced biobank, or destroy the samples.

The samples will be stored long-term in appropriate, storage conditions (e.g. -80°C freezers) within the Chief Investigator's institution. Access to these samples is restricted to the Chief Investigator's team and relevant laboratory managers.

The samples collected in this study may be used to evaluate the diagnostic accuracy of other infection-related diagnostic tests including those testing for COVID-19.

The gold standard assay for respiratory virus quantification is quantitative polymerase chain reaction (qPCR). qPCR will be used to detect and quantify pathogen presence and quantity in the various samples collected and measure changes in load over time (kinetics).

Samples may be used for host response gene expression studies, where messenger RNA (mRNA) from cells is measured to obtain a "snapshot" of which genes are being expressed. qPCR and whole genome high-density arrays may be used to compare gene expression examining for markers of infection. Techniques such as ELISA and ICS may be used to confirm the results. No studies concerning diseases or traits not connected with respiratory disease will be performed on these samples.

Other exploratory assays potentially include next generation sequencing of samples for detection of possible pathogens that are not conventionally tested for or are novel. In these studies, human genomic material will not be analysed and will be removed computationally by reference-guided mapping.

Samples may be also be tested for antibodies to coronaviruses (serology) and other respiratory viruses, and other immune responses including but not limited to cytokines, C reactive protein, and procalcitonin.

All samples are anonymised of personal identifiable information, and identified by the participant's study number. Anonymised clinical parameters collected can be correlated with these results. The consent provided by participants expressly permits further research on these samples. This work will primarily occur within the Clinical and Experimental Sciences (CES), Faculty of Medicine, University of Southampton, but collaboration with other institutions is at the discretion of the PI.

17. Other personnel and sponsor

Key study personnel in addition to the Chief Investigator & Co-investigators include:

- Clinical Research Fellows and other doctors in Infectious Diseases, Emergency medicine, and Acute Medicine, UHS.
- Research Nurses and Research Assistants at UHS.

The sponsor is University Hospital Southampton NHS Foundation Trust.

For the sponsor and R&D contact: Emma Perry, Clinical Trials Project Manager – UHS Sponsored Studies. 023 8120 3920; emma.perry@uhs.nhs.uk or sponsor@uhs.nhs.uk.

18. References

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