Title: Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.

Protocol Version 4.0

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Sponsor and Funder

This study will be funded by philanthropic donations through the LSHTM COVID response fund and UK Department of Health and Social Care.

London School of Hygiene & Tropical Medicine (LSHTM) whose principal place of business is at Keppel Street, London WC1E 7HT will serve as Sponsor for this study

This protocol provides information about procedures for entering participants into LSHTM observational trials. The protocol should not be used as a guide for the treatment of others; every care was taken in its drafting, but corrections or amendments may be necessary.

Problems relating to this trial should be referred, in the first instance, to the Trial Coordination Centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

Signatures

This protocol has been read and approved by:

18-Nov-20

Prof James Logan — Date

Chief Investigator
On behalf of the Trial Coordination Centre, ARCTEC

23-Nov-20

Ms Zoe Leftley — Date

Research Facilitator
On behalf of the Sponsor, London School of Hygiene & Tropical Medicine

Study Synopsis

Name of Sponsor:	London School of Hygiene & Tropical Medicine (LSHTM)		
Title of Study:	**Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.**		
Short Title:	Canine Coronavirus detection		
Protocol Number:	LSH1285	**Version:**	4.0
Chief Investigator:	Prof James Logan, LSHTM		
Primary/Secondary Objective(s):	***Primary objective:*** Determine whether trained dogs can distinguish between people with asymptomatic, mild and moderate symptomatic infections with SARS-CoV-2 and uninfected individuals, estimating sensitivity and specificity with enough precision (±5%) to allow the value of dogs as a diagnostic tool to be assessed. ***Secondary objectives***: 1. Assess the inter-observer reliability between trained dogs to detect people with asymptomatic, mild and moderate symptomatic infections with SARS-CoV-2. 2. Identify the volatile profile that is specific to asymptomatic mild and moderate symptomatic participants with SARS-CoV-2 compared with uninfected individuals.		
Study Design / Methodology:	A double-blind experimental study using samples of breath and body odour collected from adults undergoing screening for SARS-CoV-2.		
Number of Participants:	Samples will be collected from approximately 16,250 adults screened for SARS-CoV-2 with the aim of collecting from a total of 325 SARS-CoV-2 positive adults and 675 SAR-CoV-2 negative adults. Three batches of samples will be used, as follows: 1) Pilot study: 25 positive and 75 negative samples. 2) Training phase: 100 positive and 400 negative samples. 3) Testing phase to establish sensitivity and specificity: 200 positive and 200 negative samples.		
Active Study Duration:	8 months		

Inclusion Criteria:	• Due to have a coronavirus swab test or have had a swab test conducted in the previous 72 hours • Aged ≥ 16 years • Have suspected mild or moderate COVID-19 symptoms, or have been exposed to COVID-19, or have received results of a positive COVID-19 swab test conducted in the previous 72 hours, or are NHS staff, or household member of NHS staff • No evidence of previous* laboratory confirmed SARS-CoV-2 • Written informed consent provided • Willing and able to wear a face mask for at least 3h+ • Willing and able to wear nylon socks for at least 12 h • Willing and able to wear a shirt for at least 12 h + • Willing and able to provide access to or a copy of their coronavirus swab test result *Prior to the date of the swab test reported to this trial +Any participant unable to wear a mask or shirt for medical reasons would still be eligible to participate.
Exclusion Criteria:	• Aged < 16 years • Evidence of severe illness with symptoms compatible with SARS-CoV-2 infection which require mechanical ventilation • Receiving palliative care • Previous* clinical diagnosis of COVID-19 • Previous* laboratory confirmed SARS-CoV-2 infection • Written informed consent not provided • Unable or unwilling to wear a facemask for at least 3 h + • Unwilling or unable to wear nylon socks for at least 12 h • Unwilling or unable to wear a shirt for at least 12 h + • Unwilling or unable to provide access to or a copy of their coronavirus swab test result *Prior to the date of the swab test reported to this trial +Any participant unable to wear a mask or shirt for medical reasons would still be eligible to participate.
Endpoint(s):	***Primary Endpoint:*** Evaluation of whether trained dogs can detect people with asymptomatic, mild or moderate symptomatic SARS-CoV-2 infection by volatile organic compounds profile with sufficient sensitivity and specificity precision (±5%) to allow the value of dogs as a diagnostic tool to be assessed. ***Secondary Endpoints:*** 1. Assessment of the inter observer variability between trained dogs to detect SARS-CoV-2. 2. Identification of the volatile profile that is specific to asymptomatic, mild or moderate symptomatic participants with SARS-CoV-2 compared with uninfected individuals.

Safety Endpoint(s):	Adverse events (AE) and serious adverse events (SAE) will be recorded for participants and research staff whilst sample collecting and for staff doing training and testing with samples. SAEs will be reported within 24 h to the Trial Steering Committee and the CI.
Statistical Methods:	Comparisons between indication rates for positive and negative will be made. Sensitivity and specificity with exact binomial confidence intervals will be calculated for each dog, assuming real-time RT-PCR-determined infection status to be the gold standard. Logistic regression with a fixed effect for each dog will be used to assess individual dog differences in sensitivity and specificity.
Investigation Site(s):	***Multi-centre*** Collection of field specimens: Acute NHS hospitals and COVID-19 testing centres, United Kingdom. International sample collections detailed in Addenda to this protocol. Storage of samples: London School of Hygiene & Tropical Medicine, UK Dog-training: Medical Detection Dogs, Milton Keynes, UK

Roles & Responsibilities

Staff	Organisation	Role	Responsibility
Prof James Logan	LSHTM	Chief Investigator	Overall project oversight
Dr Anna Last	LSHTM	Epidemiologist/Infectious Diseases Clinician (Medical Monitor)	Study design, clinical oversight & liaising with NHS, including reporting of adverse events
Prof Immo Kleinschmidt	LSHTM	Epidemiologist/Statistician	Study design & statistical analysis
Dr John Bradley	LSHTM	Epidemiologist/Statistician	Study design & statistical analysis
Dr Sarah Dewhirst	LSHTM	Project Manager	Study design, sample collection & study management
Sophie Stewart	LSHTM	Clinical Trial Manager	Study design, sample collection & study management
Dr James Hourston	LSHTM	Trial Manager	Sterilisation management
Dr Josephine Parker	LSHTM	Trial Manager	Study coordination
Dr David Allen	LSHTM	Virologist	Virology & sterilisation validation
Prof Steve Lindsay	Durham University	Epidemiologist	Study design
Dr Claire Guest	MDD	Canine Olfaction Research Specialist	Study design & training/testing of dogs

Dr Luke Cottis	MDD (Hampden Veterinary Hospital)	Veterinary Surgeon	Veterinary and animal welfare oversight
Dr Ann Rooney	MDD	Veterinary Epidemiologist	Canine/viral Oversight and welfare manager
Dr Steven Morant	Independent Consultant	Statistician	Study statistician
Prof John Pickett	University of Cardiff	Biological Chemistry	GC-MS and sample collection advisor

List of Acronyms

Acronym	Definition
95% CI	95% Confidence Interval
AE	Adverse Event
ARCTEC	Arthropod Control Product Test Centre
AWERB	Animal Welfare Ethical Review Board
CI	Chief Investigator
CTM	Clinical Trial Manager
CRF	Case Report Form
CRN	Lead Clinical Research Network
CRN	Clinical Research Network
DPIA	Data Protection Impact Assessment
GC-MS	Gas Chromatography – Mass spectrometry
HRA	Health Regulatory Authority
HSE	Health & Safety Executive
ICF	Informed Consent Form
IRAS	Integrated Research Application System
IRB	Institutional Review Board
LSHTM	London School of Hygiene and Tropical Medicine
NIHR	National Institute for Health Research
NHS	National Health Service
OH	Occupational Health
PI	Principal investigator (at Hospitals)
PPE	Personal Protective Equipment
PIS	Participant Information Sheets
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Severe Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBC	To Be Confirmed
TCC	Trial Coordination Centre
UK	United Kingdom
VOC	Volatile organic compound

1. Introduction

When the COVID-19 epidemic wanes in the UK it will be important to prevent the reintroduction of the aetiological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the country, since there will be many susceptible individuals remaining in the UK population. In order to prevent second and third waves of COVID-19, it will be important to screen passengers arriving from high-risk countries. This task would be made simpler if a rapid non-invasive method were available for detecting infected individuals, particularly those with asymptomatic, mild or moderate symptomatic infections with SARS-CoV-2 from those individuals who are not carrying the virus. Thermal screening, practised in many airports and ports around the world, has a low sensitivity since not all patients develop fever. It has received considerable criticism in some quarters (Gostic, Gomez, Mummah, Kucharski, & Lloyd-Smith, 2020; Normile, 2020). The use of trained dogs could provide a rapid primary screen for detecting those potentially carrying the SARS-CoV-2 virus. Travellers indicated by the dogs as likely to be carrying the virus would then be tested by nasal and throat swab, with diagnosis confirmed/excluded using real-time RT-PCR. Using dogs would enable rapid screening, with four dogs able to assess up to 1,000 travellers per hour, saving time and money.

There is evidence that viral and bacterial respiratory infections cause the release of specific odours from human cells. For example, research has demonstrated changes in volatile organic compound (VOC) emissions from cell cultures infected with influenza virus subtypes H9N2 (avian), H6N2 (avian), and H1N1 (human) (Aksenov et al., 2014). VOCs given off from human cell cultures infected with influenza A virus showed a significant change related to infection status. N-propyl acetate was associated with viral infection (Traxler et al., 2019). A further study used volatile finger printing to determine differences in VOCs between different human respiratory viruses; respiratory syncytial virus (RSV) and influenza A virus (IAV) (Purcaro et al., 2018). The VOCs given off from cultures of several human respiratory viruses; influenza A, influenza B, adenovirus, respiratory syncytial virus and parainfluenza 1 virus were compared to several bacterial cultures that cause similar respiratory symptoms. They found several VOCs which were significant predictors for determining which of the two infectious agents were present (Qader et al., 2015). Further work on respiratory infections showed that human rhinovirus (HRV) can be detected by analysis of VOCs. Human respiratory cell cultures were either infected or kept clear of HRV and distinct VOC emanations of the subsequent respiratory cell cultures were detected (Schivo et al., 2014). It has even been shown that administration of a live attenuated H1N1 vaccine in humans significantly affects the VOC profile which could be detected up to 7 days post-vaccination (Mashir et al., 2011). There is evidence that dogs can detect and learn the smell of virus-associated volatiles in real time, with sensitivities of up to 96% and specificity of up to 98% (Angle, Waggoner, Ferrando, Haney, & Passler, 2016). These findings demonstrate that trained dogs can differentiate between VOCs associated with viral infection.

We hypothesise that dogs, with their highly advanced sense of smell (Marchal, Bregeras, Puaux, Gervais, & Ferry, 2016) could be trained to detect people infected with the SARS-CoV-2 virus. Medical detection dogs are increasingly being deployed in high-income countries as an efficient, reliable, and mobile diagnostic intervention to recognise volatile biomarkers contained in human breath, skin, and urine that are produced by specific diseases and chronic health conditions. Recent trials have demonstrated that appropriately trained dogs have the capacity to identify cancers of the lung, breast, bladder, and

prostate, and alert people living with type I diabetes to oncoming hypoglycaemia, as well as epileptic seizures (Cornu, Cancel-Tassin, Ondet, Girardet, & Cussenot, 2011; Ehmann et al., 2012; Rooney, Morant, & Guest, 2013; Willis et al., 2004). Importantly, we have also demonstrated that trained dogs were able to identify those carrying malaria parasites with a high degree of accuracy by their smell (Guest et al., 2019). There is also evidence from the laboratory that trained dogs can identify pathogenic viruses by their smell (Angle et al., 2016). We hypothesise that people infected with the SARS-CoV-2, which may be associated with asymptomatic infection, mild or moderate respiratory disease (COVID-19), will produce distinct volatiles from their lungs and through their skin.

Here we propose to carry out a study to determine whether trained dogs could detect asymptomatic, mild or moderate symptomatic coronavirus infections in adults aged ≥ 16 years old. Moderate symptomatic is defined as any symptoms compatible with SARS-CoV-2 infection which are severe enough to require hospital admission and medical treatment specific for COVID-19 but not mechanical ventilation. Severe infections (defined as any symptoms compatible with SARS-CoV-2 infection which are severe enough to require mechanical ventilation) are excluded from the study since: (1) people will not be travelling with severe symptoms, (2) the volatile profile of severely symptomatic COVID-19 patients is likely to be markedly different from patients who are asymptomatic or mildly symptomatic. We have included moderately symptomatic patients due to the low recruitment rate of mildly or asymptomatic people. We expect the profile of someone who is moderately symptomatic to provide a stronger, COVID odour signal, based on other studies (Grandjean, D. et al 2020), and although there may be potential confounding medical conditions or medication, we can deal with these through the experimental design of the dog behaviour, and chemical analysis to rule out confounders.

The overall study will be conducted in three phases. **Phase 1**, is a proof-of-principle study to demonstrate that trained dogs can identify asymptomatic, mild or moderate symptomatic infections with SARS-CoV-2 with high precision, and is the focus of this protocol. **Phase 2**, is an assessment of the capability of our trained dogs to detect people infected with SARS-CoV-2 and **Phase 3** is deployment of trained dogs at UK ports of entry.

In phase 1 we have three main objectives. Firstly, we will carry out a study to determine whether trained dogs can identify a distinct odour from people with asymptomatic, mild or moderate symptomatic infections with SARS-CoV-2; secondly we will assess the variability in detection between individual dogs; thirdly, we will compare odours profiles from asymptomatic, mildly or moderately symptomatic (infected) and uninfected individuals, to illustrate what volatiles the dogs are detecting (and potentially could be used as a basis for developing an electronic detection system).

Samples of exhaled breath odour and skin odour will be collected from approximately 16,250 adults, in order to acquire samples from approximately 325 SARS-CoV-2-infected adults and 675 uninfected adults. Samples will be divided into two study groups: infected/positive group (asymptomatic, mildly or moderately symptomatic participants positive for SARS-CoV-2) and uninfected/negative group (no evidence of SARS-CoV-2). If possible, the sample groups will be divided further into severity and/or different viral loads (high, medium and low) to aid training of the dogs. Samples will also be allocated to one of three phases of the study. Piloting of the study will involve 25 infected/positive samples and 75 uninfected/negative samples. The training phase of the study will use 100 infected/positive samples and

400 uninfected/negative samples. The final batch of samples will be used for testing the dogs (200 infected/positive samples and 200 uninfected/negative samples). Numbers here are the minimum sample numbers required to complete tests. If an excess of viral-negative samples is collected, they will be included, augmenting the pool of uninfected/negative samples that can be drawn from in training.

If this study demonstrates that the dogs can detect SARS-CoV-2-infected adults and we are able to determine the sensitivity and specificity with a high degree of accuracy (±5%) to allow the value of dogs as a diagnostic tool to be assessed, we will develop a separate protocol for testing the ability of dogs to detect the virus in travellers. An additional study will take place to identify which VOCs are associated with an infection with SARS-CoV-2. This research could lead to the development of a rapid and accurate test for people with SARS-CoV-2 infections, which could be used at ports of entry for detecting infected travellers.

This protocol has been submitted for adoption to the National Institute for Health Research (NIHR) Clinical Research Network portfolio (ref CVD1900226). The London School of Hygiene & Tropical Medicine Research Ethics Committee (ref: 22159), LSHTM Animal Welfare and Ethical Review Board (AWERB) (ref: 2020-06) and the Biosciences Ethics Committee, Durham University (ref: C19070520) have approved this project. The NHS Trust Research Ethics Committee North West - Preston (NHS REC ref: 22159) has approved the proposed project through the Integrated Research Application System (IRAS) (ref: 284221).

If our research is successful, we will then move forward to phase 2 of our study, to determine how well-trained dogs can identify people with SARS-CoV-2 by their scent in an operational setting.

2. Objectives

Primary objective:

Determine whether trained dogs can distinguish between people with asymptomatic, mildly or moderately symptomatic infections with SARS-CoV-2 and uninfected individuals, estimating sensitivity and specificity with enough precision (±5%) to allow the value of dogs as a diagnostic tool to be assessed.

Secondary objectives:

1. Assess the inter-observer reliability between trained dogs to detect people with asymptomatic, mildly or moderately symptomatic infections with SARS-CoV-2.
2. Identify the volatile profile that is specific to asymptomatic, mildly or moderately symptomatic participants with SARS-CoV-2 compared with uninfected individuals.

3. Study Design

This is a double-blind experimental study using samples collected from adults undergoing screening for SARS-CoV-2. Asymptomatic NHS staff are currently being tested for the SARS-CoV-2 virus using a validated SARS-CoV-2-specific real-time RT-PCR assay in UK hospitals (NHS, 2020). This study is a multi-centre study involving acute hospitals from a number of NHS acute non-specialist trusts. Discussions

with potential sites over collaboration and access to staff will follow expressions of interest through the lead Clinical Research Network (LCRN) Thames Valley & South Midlands CRN. We will approach all NHS staff who are due to be screened for SARS-CoV-2, using the Occupational Health (OH) structure or equivalent, to enrol participants. If needed to reach the target sample size, recruitment will expand to recruit members of households of NHS staff who are to be tested or have been tested for SARS-CoV-2, to maximise chances of identifying sufficient infected/positive and uninfected/negative individuals. Additional recruitment will be carried out through testing centres (including drive-through testing centres and satellite), testing and tracking programmes, COVID-19 clinically diagnosed non-severe cases discharged home from hospital, patients (outpatients, day patients, inpatients) who are not receiving mechanical ventilation or palliative care but have been exposed to COVID-19 or have suspected COVID-19 symptoms or are COVID-19 positive, self-isolating individuals who are sent home testing kits, and outbreak testing. Participants amongst the general population we will be recruited through a variety of mediums for example, phone, text-messages, emails, leaflets/posters, videos, social media and media. Third-party organisations (e.g. those involved in the test and trace process) may contact or provide contact details of potential participants who have independently consented to being contacted about clinical research. Potential participants may contact or be directed to an individual delegated by the TCC within specific organisations (e.g. a university or factory) who can aid with the distribution and collection of the sample pack. SARS-CoV-2 screening will take place in study hospitals, testing centres or remotely through NHS home testing kits, and swabs processed through the routine NHS channels. Testing carried out through other (non-NHS) testing routes will be assessed on an individual basis and included if robust testing methods and accuracy of results can be ensured. If required, the study will also include participants recruited in different countries, in accordance with this protocol but with SARS-CoV-2 being processed via local pathways. Local ethics approvals will be sought using this protocol and an addendum to cover local procedures, before recruitment commences in each country.

Participants will be asked to: 1) provide access to the result of their swab test for detection of SARS-CoV-2, 2) to wear a face mask for 3 h, a pair of nylon socks for 12 h, and a shirt for 12 h 3) complete a short data collection sheet (eligibility questionnaire). Face mask, shirt and sock odour samples will be processed at LSHTM. Upon confirmation of positive (SARS-CoV-2 detected) or negative (SARS-CoV-2 not detected) swabs, the samples will be divided into two study groups: infected/positive group (asymptomatic, mildly or moderately symptomatic participants positive for SARS-CoV-2 by real-time RT-PCR or equivalent testing methods) and uninfected/negative group (no evidence of SARS-CoV-2 RNA, or equivalent). If possible, the sample groups will be divided into different viral loads (high, medium and low) in order to facilitate training of the dogs.

Each sock and mask will be cut into multiple samples. Initially, a number of progeny sock and mask samples will be presented to the dogs directly for training/testing. One progeny sock and mask sample will be air entrained to collect VOCs and/or eluted using ethanol or isopropanol to produce a liquid extract. These extracts may be used for dog training/testing if necessary, and VOC analysis. The remaining progeny sock and mask samples will be stored for possible later use. Whole shirt samples will be used in Phase 2 testing, although shirts may be cut into progeny samples and may be used in Phase 1 if socks and masks produce a low response.

Initial dog training exercises will be conducted with direct presentation of progeny sock samples in sealed, vented vials which prevent contact between the dog and sample. Sock samples do not present a risk of infection to handlers or dogs and are a closer representation of odours available to trained dogs in an operational setting, where they would be at ground level and so offer the greatest potential for training. Subsequently, mask VOCs will be presented to dogs either directly or as an alcohol extract to establish which sample provides the best opportunity for further training of the dogs and to confirm that the dogs can identify a specific smell associated with SARS-CoV-2. After full training, to improve the accuracy of the dogs, we will test them on a new set of samples in a double-blind trial (200 infected/positive samples and 200 uninfected/negative samples). The researchers setting up the samples for the dogs, and the dog handlers will be unaware of the sample identity until after the dog has been judged to have made an indication. The handler will be unblinded immediately after the indication has been called, utilising specially developed software (MDD-OPRA), in order to reward the dog as appropriate.

An important ancillary study will take place to identify the specific volatile produced by SARS-CoV-2 positive patients using gas chromatography – mass spectrometry (GC-MS) that is not found in uninfected/negative individuals.

3.1. Study Endpoints

Primary Endpoint:

Evaluation of whether trained dogs can detect people with asymptomatic, mildly or moderately symptomatic SARS-CoV-2 infection by volatile organic compounds profile with sufficient sensitivity and specificity precision (±5%) to allow the value of dogs as a diagnostic tool to be assessed.

Secondary Endpoints:

1. Assessment of the inter observer variability between trained dogs to detect SARS-CoV-2.
2. Identification of the volatile profile that is specific to asymptomatic, mildly or moderately symptomatic participants with SARS-CoV-2 compared with uninfected/negative individuals.

3.2. Risks and Benefits

There is a high risk of infection with the virus while handling swabs for SARS-CoV-2 testing, therefore only the participant themselves or trained and delegated staff at NHS or other testing facilities will handle these swabs according to HSE guidelines. There is a low risk of infection with the virus through contact while handling mask samples and a very low risk of infection through contact while handling sock and shirt samples. It is for this reason that samples will be cut into progeny samples in a containment lab at LSHTM and sealed from contact in vials before transporting to Medical Detection Dogs. Dogs and their handlers will not open the vials and so will not come into direct contact with samples. Samples will be returned to LSHTM without opening vials, thereby minimising chance of infection for dog handlers and chaperones. If required, for masks, odours will be eluted in ethanol or isopropanol, before dog training is started, inactivating any infectious virus.

There are unlikely to be direct risks to individuals associated with collection of odour samples from participants, since they will only be wearing facemasks, shirts and nylon socks. For participants who are unlikely to be attending the study site, the risk of infection associated with exposure from attendance at a study site was deemed to outweigh the risk of consenting and participating remotely, therefore those

swabbed via testing centres or invited for NHS home tests will be eligible for participation (those using non-NHS tests will be eligible at investigator discretion following assessment of test and processing methods). All remote participants will be able to contact a delegated member of the study team to discuss any study details or ask any questions they may have.

There is a low risk of allergy to the sample collection substrates (face masks, shirts and nylon socks). Sampling will be stopped if any discomfort is expressed by the participants. The risks of infection to research staff collecting samples and during dog training are described in the risk assessment (Appendix 5). There is a very low risk of infection to dog carers from dogs used in training, however, carers and their families will be made aware of this risk.

There will be no direct benefit to participants. However, the samples collected in this study will help determine whether trained dogs can detect SARS-CoV-2, as a rapid non-invasive method, to help prevent further spread of the virus and prevent deaths in the UK, and potentially, other parts of the world.

4. Participant Entry

Appendix 1 shows three flow charts of how participants will be recruited and enrolled from three groups: participants who can attend an in-person screening appointment at a hospital site i.e. NHS staff and patients, NHS staff household members via a consented NHS staff participant, and participants via remote recruitment i.e. through testing centres, home testing, any participants who can't attend an in-person screening appointment.

4.1. Confidentiality

Participants' identification data will be required for the enrolment process. The participating NHS trust and the Trial Coordination Centre will preserve the confidentiality of participants taking part in the study and are registered under the Data Protection Act. All data collected following enrolment will be pseudonymised using participant identification numbers. Data may be shared, where necessary, to the Trial Steering Committee (TSC), regulatory and/or approving ethics boards. Following the study, fully anonymised study data may be published to a data repository to enable future research into viruses or outbreaks such as this. Participants' personal data will be destroyed once the published study outcomes are relayed to participants at the end of the study.

4.2. Participant Recruitment & Consent

Good clinical practice will be conducted throughout these investigations. Hospitals identified as having high throughput of confirmed SARS-CoV-2 cases will be selected for this study. Asymptomatic, mildly or moderately symptomatic NHS staff will be identified through the NHS SARS-CoV-2 screening programme. Participants will be informed of the study through standard recruitment methods, including recruitment posters in staff areas, recruitment emails containing Participant Information Sheets (PIS) sent directly to NHS staff. If it is necessary, recruitment will be expanded to members of households of NHS staff that are eligible for NHS SARS-CoV-2 screening. PIS, Informed Consent Forms (ICFs) and screening materials will be given to a consented member of staff for distribution to household members. Household members will be invited to contact the recruiting member of staff at

the hospital remotely for further discussion and queries, if required. NHS Staff will be identified by presentation of their NHS photo ID card, verified by selected healthcare professionals trained in this study.

Participants will also be recruited amongst the general population being tested for coronavirus infection by the NHS and other testing facilities where appropriate. This includes testing centres, hospital patients and outbreak testing programmes. There are around 50 drive-through testing centres across the UK, at which appointments can be booked for anyone showing symptoms consistent with SARS-CoV-2 infection. These individuals will be given recruitment materials and/or document/sample packs on their visit to the test centre and will be either invited to contact trial staff by e-mail or telephone for further discussion remotely within 72 hours of the swab test, or they will be asked to fill in the contact details form during the visit to the test centre and the Trial Coordination Centre or site will contact them within 72 hours. If contact with participants occurs 72 hours after their swab test, they will still be invited to take part even though the pack may be received greater than 72 hours after the swab test. In addition, a recruitment text, phone call or e-mail message may be sent alongside the test result, inviting potential participants to contact trial staff. Participants who attend testing centres where the participant is given the test to conduct themselves, only samples collected from positive participants will be included in the potential samples for dog training and testing, as swab technique amongst this group will be variable and potentially less rigorous. Participants will also be recruited via testing and tracking programmes via the same methods as with those attending drive-through test centres. In addition, a recruitment text, phone call or e-mail messages may be sent alongside text and e-mails sent by the testing and tracking programmes, inviting potential participants to contact trial staff. Two groups of hospital patients have been identified as potential trial participants. The first consists of patients that have been exposed to covid-19 or present themselves with symptoms consistent with SARS-CoV-2 infection or have received results of a positive COVID-19 swab test conducted in the previous 72 hours, but whose illness is not severe enough to require hospitalisation. These patients are asymptomatic or are mildly symptomatic, but then sent home and monitored. The second group are inpatients who present themselves with symptoms consistent with SARS-CoV-2 infection or have been exposed to COVID-19 or have or have received results of a positive COVID-19 swab test conducted in the previous 72 hours, but do not require mechanical ventilation. If these patients have been admitted due to their COVID-19 symptoms or have been admitted for another condition but are receiving specific COVID-19 treatment i.e Remdasavir or Dexamethasone, these will be classed as having moderate symptoms. As case numbers decline, there are likely to be small localised outbreaks which may prompt blanket testing within a small area. In these situations, participants could be recruited at the point of testing as with those attending drive-through test centres, as participants who have been exposed to COVID-19 if they are not displaying COVID-19 symptoms. We will also seek to recruit members of the public using home test kits, usually because they are self-isolating at home. As swab technique amongst this group will be variable and potentially less rigorous, only positives from home testing will be including in potential samples for dog training and testing. Participants amongst the general population will be recruited through a variety of mediums e.g. phone, text-messages, emails, leaflets/posters, videos and social media. Permission from social media sites will be sought where required. Media e.g. radio and tv interviews, and the other mediums will also be used in order to inform participants of a recruitment phone line and/or e-mail, and/or direct people to recruitment materials and web sites e.g. www.virusdogs.com. All

recruitment material and study documents will be in English. Examples of recruitment wording will be submitted to ethic boards as supporting documents, but variations of this wording may be used. At the time of recruitment, participants may be given information about other relevant research studies with their own ethics approvals and separate consent processes.

Briefing meetings with front-line clinicians and healthcare workers in each potential study hospital will be held to ensure appropriate training for those participating in sample collections. Participants will be fully informed before consent is taken and it will be made clear that they can withdraw from the study at any time. Volunteers will be given and asked to read the PIS which describes the sampling which they will take part in, and two identical copies of the ICF which defines what they are consenting to. Two copies (participant copy and researcher copy) of the ICF must be signed by the participant before eligibility is determined and any data or sample collection commences. Details of the participant, together with a brief medical history and contact information will be taken. A participant study ID number will be allocated for the purposes of pseudonymising participants, this will be recorded on the participant identification log upon consent.

When informed consent and eligibility screening are conducted remotely, particularly on volunteers not associated with a hospital-based study team, staff from the Trial Coordination Centre will be able to conduct these meetings. Verbal meetings i.e. via the phone, will occur to ensure appropriate training for those participating in sample collections and that participants are fully informed before consent. If participants contact the site/TCC via e-mail, the PIS will be e-mailed to them and they will be asked to read it as soon as possible. They will then be asked to confirm if they understand the PIS, if they have any questions, and if they would like a verbal meeting i.e. via the phone, to discuss the PIS. During this correspondence (via phone or e-mail), the participant will be asked when the date of their swab test was/is. Participants who are due to have a coronavirus swab test or have had a swab test conducted in the previous 72 hours will then be given a document pack containing the PIS/ICF, eligibility questionnaire, and a comprehension check along with the sample pack, directly from the testing centre or hospital site, or via the post from the TCC or hospital site. When packs are to be sent to the participant, the participant will be asked to supply their address either verbally over the phone or via e-mail during the meeting. This address will be destroyed as soon as the pack has been sent. In addition, it will be noted on the enrolment log that the ID number has been distributed. Participants who contact the site/TCC 72 hours after their swab test, will be sent a pack even though the pack will be received greater than 72 hours after the swab test. The members of the ARCTEC team designated to data management and monitoring, will not have access to participant personal information, and, therefore, will not be able to conduct informed consent and eligibility screening meeting.

4.2.1. Time to consent

Ideally, potential participants will be approached and provided with a copy of the PIS a minimum of 24 h prior to written informed consent being sought. However, in cases where the recruitment pathway does not allow this e.g. should the participant potentially be SARS-CoV-2 positive and asymptomatic, mildly or moderately symptomatic (therefore eligible) and onset of advancing symptoms and COVID-19 could develop at short notice, there could be potential for harm if testing is delayed, participants will be approached as early as possible. Without defining a strict minimum time, this should be adequate for the potential participant to reflect on the implications of participating, to discuss the study with

friends/relatives (should they wish to), and to request any additional information. This should be judged on a case-by-case basis and should take into account the perceived level of understanding of the information provided to the potential participant as well as their right to choose when they consent. Upon consent, confirmation of sufficient time to consent will be confirmed with the participant. Further guidance concerning time to consent is available from the National Research Ethics Service's Single Issue Ethical Debate paper, "Time to Consent" available from the Health Research Authority (NREAP, 2010).

4.3. Screening Procedures

NHS staff participants and hospital patients who can attend a screening appointment in person, will be consented on-site prior to any further screening procedures being undertaken.

NHS staff and hospital patients who cannot attend a screening appointment, household members of NHS staff and other participants from the general population will be required to submit their eligibility questionnaire, contact details, comprehension check questionnaire and consent form remotely (e.g. via post) or via their household NHS staff worker. If the comprehension check is completed unsatisfactory, the delegated recruiting staff member will be required to contact the participant consenting to determine if informed consent occurred. Participants which opt-out of being contacted and provide an unsatisfactory comprehension check questionnaire, or do not understand the trial after being contacted will be withdrawn from the trial. Consented individuals who do not meet all the criteria for inclusion (section 4.3) or meet any one of the exclusion criteria (section 4.4) will not be eligible to participate and will also be withdrawn at this point. Any remote samples provided will not be used from ineligible participants. The screening procedure will be conducted by trained study staff and a chaperone, witness and/or translator will be available if required. A photocopy of the completed signed Informed Consent Document will be sent (email/post) to the participants who have consented remotely, where contact details are provided.

4.4. Inclusion Criteria

Participants will be members of the general public drawn from populations such as NHS staff identified as having a relatively high exposure to SARS-CoV-2 and people seeking or receiving testing for SARS-CoV-2. Individuals will be included in the study if they meet all of the following criteria:

- Due to have a coronavirus swab test or have had a swab test conducted in the previous 72 hours
- Aged ≥ 16 years
- Have suspected mild or moderate COVID-19 symptoms, or have been exposed to COVID-19, or have received results of a positive COVID-19 swab test conducted in the previous 72 hours, or are NHS staff member, or household member of NHS staff
- No evidence of previous* laboratory confirmed SARS-CoV-2
- Written informed consent provided
- Willing and able to wear a face mask for at least 3h^{+}
- Willing and able to wear nylon socks for at least 12 h
- Willing and able to wear a shirt for at least 12 h^{+}
- Willing and able to provide access or a copy of their coronavirus swab test result

*Prior to the date of the swab test reported to this trial

[+]Any participant unable to wear a mask or shirt for medical reasons would still be eligible to participate.

4.5. Exclusion Criteria

Individuals will be excluded from the study if they meet any of the following criteria:

- Aged < 16 years
- Evidence of moderate to severe illness with symptoms compatible with SARS-CoV-2 infection which require and mechanical ventilation
- Receiving palliative care
- Previous* clinical diagnosis of COVID-19
- Previous* laboratory confirmed SARS-CoV-2 infection
- Written informed consent not provided
- Unable or unwilling to wear a facemask for at least 3 h[+]
- Unwilling or unable to wear nylon socks for at least 12 h
- Unwilling or unable to wear a shirt for at least 12 h[+]
- Unwilling or unable to provide access to or a copy of their coronavirus swab test result

*Prior to the date of the swab test reported to this trial

[+]Any participant unable to wear a mask or shirt for medical reasons would still be eligible to participate.

4.6. Withdrawal Criteria

The study participant has the right to stop their participation at any time without giving a reason. If the participant withdraws their consent during the study, no further samples will be collected. Any information generated from the samples until the time of withdrawal will be used and samples already collected, for which consent has been given, will also be analysed and data used. Participants may also be removed at the discretion of the Chief Investigator (CI) or Principal Investigator (PI), where continued participation may affect the safety of the participant or where there is a development of any condition which might interfere with study participation. No further information or samples will be collected after withdrawal.

5. Enrolment

Samples confirmed to be from asymptomatic, mildly or moderately symptomatic positive individuals or negative individuals and deemed to be suitable for use, will be enrolled for training and testing. Samples will be randomly allocated to the pilot, training and testing sets. Training sets will be stratified by gender (male/female), age group (16-50 years/51-70 years), ethnicity (Black, White, Asian, Mixed/Other) and hospital (A, B, C….) and positive (asymptomatic, mildly, and moderately symptomatic) and negative (uninfected) status. In addition, samples from inpatients will be stratified by the reason for hospital admission and medication received for COVID-19 symptoms where possible.

6. Treatments

No investigational or medicinal treatments will be used.

7. Safety Reporting for Non-Drug Trials

7.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a researcher, delegate or study participant, that occurs after the point of enrolment (following consent) or which was present at the time of enrolment but worsened after enrolment. For study participants, COVID symptoms and viral symptoms will be recorded via the study database and not as an adverse event. For researchers and delegates, only COVID symptoms will be recorded as an AE.
Serious Adverse Event (SAE)	A serious event is any untoward medical occurrence that: Results in death Is life-threatening Requires inpatient hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability/incapacity Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant researcher or delegate or require an intervention to prevent one of the above consequences.

Clinical judgement will be exercised by the Principal Investigator in categorising an AE as serious or not. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant, researcher or delegate or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Reports of COVID-19 and viral symptoms by study participants to delegated staff, on sample receipt and 10-14 days after sample collection will be recorded on the database and not as an AE.

7.2. Reporting

Depending on the nature of the event the reporting procedures listed below should be followed. At study sites, any AEs or SAEs identified will be reported to the hospital Principal Investigator (PI) in the first instance. PIs will then categorise the AE, and report SAEs to the TCC and Medical Monitor for the study, within 24 h of being informed of the SAE. Non-serious AEs from non-ARCTEC sites will be reported to the TCC and medical monitor, at least once a week. PIs are responsible for ensuring participants accurately complete the Adverse Event Monitoring Questionnaire as soon as possible and supply the completed form to the Medical Monitor and TCC.

AEs identified at any other study location, such as at the TCC, in transit or at LSHTM, will be reported to the Medical Monitor within 24 h, who will categorise the AE. The TCC are responsible for ensuring participants, or delegated members of staff, accurately complete the Adverse Event Monitoring Questionnaire as soon as possible and supply the completed form to the Medical Monitor.

If an Adverse Event Monitoring Questionnaire cannot be sent to the participant via e-mail i.e. as the participant has not supplied these details, then delegated study staff can obtain these details verbally i.e. via the phone and study staff can fill in the form. If a postal address has been given, then a copy of the completed form can be sent to the participant if they request a copy. Posting of the blank forms for completion can also be done, but, due to delaying the reporting timeline, this should only be done if this is the only method of obtaining the information.

The CI or delegate will report to the Trial Steering Committee (TSC) and Research Ethics Committees (RECs) as detailed below, who will have the authority to end the study if required. In the event of minor adverse reactions such as skin rashes following mask use, participants will be directed to contact their attending healthcare professional.

7.2.1. Non-serious AEs

AEs categorised as being 'non-serious' will be collated by the TCC who will report to the TSC in aggregate at regular intervals. All AEs should be recorded on the AE Record Form (Appendix 2) and AE Monitoring Questionnaire (Appendix 3) and submitted to the TSC by email. All received questionnaires must be entered into the study database and stored on a secure server with access limited to data entry delegates, and the Trial Coordination Centre (TCC). All adverse events will be reported to the study Sponsor, LSHTM, at the end of the study. Depending on the nature of the event the reporting procedures below should be followed, see Appendix 4 for a flowchart of safety reporting.

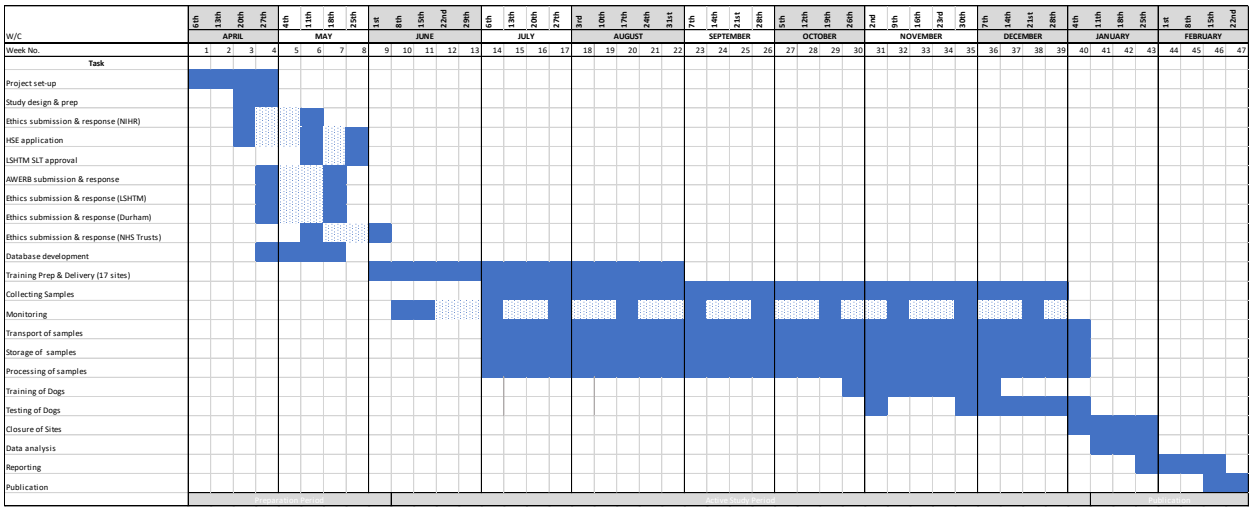
7.2.2. Serious AEs

SAEs must be reported to the medical monitor and to the CI (via the TCC) within 24 h, who will report it immediately to the TSC and, if required, to the Ethics Committees. Regardless of the relation of the AE event to study participation, the event must be reported as an SAE event if it meets any of the definitions in section 7.1. SAEs that are assessed by the Medical Monitor as being both related and unexpected (Suspected Unexpected Serious Adverse Reaction, SUSAR), must be reported to the NIHR, LSHTM Ethics Committee and Durham University's Department of Biosciences Ethics Committee within 15 days of the Medical Monitor becoming aware of the event.

8. Methodologies

Here we describe the study methodology in chronological order (Table 1). Appendix 1 shows three flow charts of the process of sample collection and follow-up for the three recruitment groups: participants who can attend an in-person screening appointment at a hospital sites i.e. NHS staff and patients, NHS staff household members via a consented NHS staff participant, and participants via remote recruitment i.e. through testing centres, home testing, any participants who can't attend an in-person screening appointment

Table 1. Study timeline.



8.1. Sample Collection

After providing full and informed signed consent and deemed eligible to participate, enrolled participants will attend their allotted NHS swab appointment to be sampled for SARS-CoV-2 infection (confirmed by validated diagnostics used by the NHS at the time of the study (NHS, 2020)) or their non-NHS testing appointment, to be assessed for robustness of test methodology and accuracy of test result by investigator discretion. Retrospective enrolment of participants may occur up to 72 hours after the swab test. Participants will be provided with a sample pack containing: a single-use face mask (in a biobag-1), a shirt (in a press seal bag) and a pair of single-use nylon ankle socks (in a press seal bag), four single use alcohol wipes, four sample labels (prepopulated with participant ID), three sheets of aluminium foil for wrapping collected samples. Samples of breath odours will be passively collected while participants wear the mask while breathing naturally, for at least 3 h. Skin odours will be passively collected by participants wearing the shirt and nylon socks for at least 12 h. A button up shirt or T-shirt will be provided. Participants will be instructed to avoid contact between the shirt or T-shirt and their face whilst changing in and out of the shirt or t-shirt. Odours should be collected as soon as possible after the swab and preferably within 72 hours. Participants who are not able or willing to wear a mask or t-shirt for medical reasons will still be eligible to participate.

Participants will be advised not to apply any cosmetics associated with a strong scent, such as deodorant, perfume, or make-up that will rub onto the mask, shirt or socks. They will also be asked to avoid getting the mask, socks and shirt dirty or wet and to avoid areas where they could be contaminated with other odours i.e. when cooking. Socks and shirt should be in contact with bare skin therefore participants will be asked not to wear over other clothing, although participants can wear bras. Clothing and shoes can be worn over the socks and shirt.

Samples will be collected and used from consented and eligible participants. After the sample period, the face masks, shirts and socks will be wrapped in labelled aluminium foil, labelled and packaged in separate polythene bags by the participant and returned either to a designated study researcher at the hospital, or sent by post using a pre-paid envelope provided to the trial coordination centre within 14 days of collection. On receipt of the samples, it will be recorded by the site or TCC, if the samples have

been packaged and labelled correctly, and if not, the actions taken to rectify the issue. This will not be notified as a protocol deviation, but the TCC will monitor this data and determine if the samples can be presented to the dogs. Sample packs should only be opened by the TCC. At the point of return, a brief medical history (presence of fever, coughing since consent) will be recorded and the study participant identity confirmed by their study ID number.

The storage conditions of the sample at site, whether frozen, refrigerated, room temperature or other, will be recorded.

Samples will be grouped to either the SARS-CoV-2 positive or SARS-CoV-2 negative group. If possible, they will be further grouped by viral load. Inconclusive results may be repeated where possible or, if not possible, the participant will be deemed ineligible and withdrawn from the study (see section 4.4). Participants will be notified of their SARS-CoV-2 result when it becomes available, using local SARS-CoV-2 screening protocols. They will also be followed up to provide details of any ill health or development of symptoms since consenting to determine if they have become symptomatic. Results of follow-up will be used to define whether participant should be classified as asymptomatic or symptomatic.

Volatile samples from 325 SARS-CoV-2 positive participants and at least 675 SARS-CoV-2 negative participants are required. Dependent on the prevalence rate, this may mean we potentially need to screen between 10,834 (3% prevalence) and 16,250 participants (2% prevalence), but by targeting recruitment to, for example, high risk individuals, individuals with anosmia, or trusts where rapid PCR screening occurs where positive sample are identified within 2-3 h of testing i.e. Cepheid GenXpert, it is expected this number will be much lower.

8.2. Sample Storage & Transport

Participants will be asked to return socks, shirts and masks to study staff as soon as possible following collection, and preferably within 14 days. Self-isolation orders may impact sample return; if participants are obliged to self-isolate, test positive, or become symptomatic between consent and return of samples, they will be advised not to attend the study site and continue to self-isolate. Samples may be stored in domestic fridges or freezers, and returned either in person to recruitment site or to the trial coordination centre using a pre-paid envelope at the end of isolation. Samples should be returned preferably within 14-days after collection. If participants are unable to return the samples, and collection cannot be arranged, they will be advised to carefully dispose of their samples.

Where required by the HSE, samples will be packaged for transport according to IATA UN3373 – biological sample, category B guidelines, where they would be packaged in suitable primary and secondary containers. Sample packaging will remain sealed during transport and only opened by trained and authorised individuals.

Sealed samples can be kept at room temperature. Therefore, provided samples are properly sealed as above, they can be sent through the post to LSHTM for processing. Where samples maybe stored before sending, then cold storage is recommended. This can be refrigeration at <5°C, or freezing under -20°C. Once at LSHTM, samples will be stored in a freezer maintained under -20°C. The storage and transport conditions of each sample will be recorded including the length of time (days) spent under each temperature condition. Samples will be signed in upon receipt of delivery, and each sample accounted

for. After the study, odour samples will be stored by the study team for up to 3 years, where they may be used to support other research in the future, and may be shared anonymously with other researchers, for their ethically-approved projects. All approved projects will seek approval from the involved NHS Trust Research Ethics Committees.

8.3. Sample Processing

Worn sock samples are not considered to be infectious as viral shedding is not known to occur through the skin of the feet. Therefore, sock samples will initially be presented to dogs directly, contained in sealed, vented vials which prevent direct contact with the sample. This reduction in sample handling and assured prevention of direct contact with the samples diminishes the risk of infection.

Each sock pair and mask sample will be cut or separated into progeny samples for: direct presentation to the dogs, where deemed safe; VOC extraction using elution in ethanol or isopropyl alcohol, where necessary or air entrainment; storage. In case alcohol extract VOC concentration is not strong enough for canine detection, alternative sterilisation methods using irradiation will be explored. Any such changes in protocol will be accompanied with appropriate validation steps.

In order to be able to train the dogs in a safe and timely fashion, training will begin by direct presentation of the sock samples to the dogs. For mask samples it is expected that any viral contaminants would be inactivated during the storage period before processing, allowing for direct presentation using sealed, vented vials which prevent direct contact with the sample as detailed above. Air entrainment of samples using a porous polymer such as Porapak eluted with a solvent i.e. diethyl ether will also occur in order to extract VOCs. Where necessary, due to safety reasons, we will process the samples to extract VOCs with either isopropyl alcohol or ethanol, and by air entrainment of samples using a porous polymer such as Porapak eluted with isopropyl alcohol or ethanol. By extracting the VOCs into alcohol solvents, we mitigate the risk of viral infection by inactivating the virus. The vials containing the solvent extracts can also be cleaned with alcohol to disinfect. Once deemed safe for handling at containment level 2, ARCTEC will then distribute the solvent based extractions to the laboratory at Medical Detection Dogs charity in Milton Keynes and to LSHTM for GC analysis and Cardiff University for GC-MS profiling in the UK. The samples will be stored at -20°C.

Research staff training the dogs will take a precautionary approach to infection and wear PPE recommended for the perceived risk. Note that the risk of infection in the dogs is extremely low and that they will not directly contact the samples. Samples will be presented directly to the dogs using sealed, vented vials which prevent direct contact with the sample. Any solvent based extractions will be presented to the dogs by drying onto filter paper to allow solvents to evaporate and VOCs to remain. All dogs, handlers and chaperones will be followed up for AEs. If any staff appear symptomatic for SARS-CoV-2, they will be offered testing. We have a veterinary surgeon as part of our team to oversee the animal handling, safety and welfare.

Samples will be divided into three groups: piloting, training and testing. In total, 325 SARS-CoV-2 positive samples and 675 SARS-CoV-2 negative samples will be required for both face masks and socks i.e. 325 positive face mask samples and 675 negative face mask samples, and 325 positive sock samples, and 675 negative sock samples. The pilot will comprise 25 SARS-CoV-2 positive samples and 75 negative samples of each of the face masks and socks. Training will require 100 SARS-CoV-2 positive samples and

400 negative samples for both face masks and socks. Testing will require 200 SARS-CoV-2 positive samples and 200 negative samples for both face masks and socks. Where a surplus of samples is collected, they may be incorporated into testing and training: values given here are minimum batch numbers required to complete each phase.

Whole shirts will be wrapped in foil and will be stored separately in press sealed bags for use in Phase 2 testing, although shirts may be cut into progeny samples and may be used in Phase 1 if socks and masks produce a low response.

8.4. Dog training & testing – *a pilot study*

A pilot study to confirm that dogs can distinguish between 25 positive samples taken from asymptomatic, mildly or moderately symptomatic participants infected with SARS-CoV-2 and 75 samples from uninfected subjects will take place over a few weeks. Face masks and socks will be presented to dogs to determine which offers the best discrimination. A number of dogs, carefully selected by the charity Medical Detection Dogs, and which have been pre-trained for this type of work, will be trained on our SARS-CoV-2 samples. If the dogs cannot identify a SARS-CoV-2 odour, either the study will be terminated or we will explore using the masks and socks which have been processed in other ways. Dogs will initially be presented with masks and socks in sealed and vented vials. If necessary, samples which have been extracted and disinfected with alcohol may also be presented. Failing that, non-extracted masks and socks will be sterilised with ^{60}Co γ- irradiation as a method of inactivating the virus. This will need validation in the laboratory and a separate protocol will be developed if this scenario seems likely. Samples used in the pilot study will be re-used in main study training.

8.5. Dog training & testing - *main study*

The main study is a progression of the pilot study and is designed to measure the sensitivity and specificity of the dogs to detect participants infected with SARS-CoV-2. The same dogs that have been pre-trained to discriminate between samples from human participants with and without SARS-CoV-2 will be further trained for a period of 6-8 weeks. Additional dogs will also be trained, to a minimum number of 6. Early recognition of the scent of a SARS-CoV-2-positive sample by a dog will be achieved using search and find games, which will gradually be replaced by discrimination phases. During training the reaction of each dog to a positive sample will be observed (i.e. standing, sitting or lying down) and this indicating behaviour reinforced by rewarding the dog with food or ball-play, in conjunction with the use of an audible clicker. Samples from 100 SARS-CoV-2-positive/infected individuals and 400 negative/uninfected individuals will be used in training.

The experimental set-up used for training and testing consists of a number of stainless-steel retort stands, each holding an arm with a sealed and vented glass vial containing a sample. A grill placed over the mouth of the vials prevents the dog touching the specimen. Each glass vial will contain either 1 positive or 1 negative sample. If using unprocessed samples, these will be presented in in sealed, vented vials. Where alcohol samples are used, these will be applied to filter paper, the alcohol allowed to evaporate off, then it will be inserted into the vial. Cross contamination from one run to the next will be prevented by cleaning the plates after every run using a commercial glasswasher at a minimum of 85°C,

and leaving them to air dry or drying with paper towel before being used again. Glass vials may also be autoclaved if deemed necessary to prevent cross-contamination. Clean arms will be used for every sample change. The dog's behaviour at the stand will be noted as full alert (indication), heavily investigated (hesitation), weakly investigated (interest) or ignored (no interest). The handler calls the final decision as an indicated sample or blank. A dog will be rewarded with food or a ball, when it correctly indicates either positive or a negative run. If no response is achieved with the unprocessed, or alcohol samples, testing may be repeated with irradiated samples.

8.5.1. Dog assessment to measure sensitivity and specificity

The dog's diagnostic accuracy will be determined in a double-blinded study. Here the trainer and technician using the computer to record the results of the study are blinded to the identity of each sample until the trainer calls the final decision (positive or negative) based on the response of the dog to the sample.

Samples from 200 SARS-CoV-2-positive/infected individuals and 200 negative/uninfected individuals will be tested. Specially designed computer software (Medical Detection Dogs – Olfactory Performance Recording Application) will be used to randomly allocate samples to the stand. Each sample will be presented to each dog once. To prevent cross-contamination between samples, the researchers will use disposable gloves throughout the testing and changed each time a new sample is prepared for testing. All test runs will be carried out in an air-conditioned room at temperature range of 14.2-20.6 °C and 38-53 % relative humidity.

The handler allows each dog to smell each sample, noting any response. Dogs can make a maximum of three passes at the handler's discretion before calling a sample as positive or negative. The handler's decision and the dog's behaviour will then be recorded. If a dog indicates a sample, this will be recorded as positive by the handler. If the dog leaves the apparatus without indicating, the handler calls negative. The blinded researcher in the room enters the findings into the database. This unlocks the secure data area and reveals to the researcher whether the evaluation was correct, who then advises the handler of the result, who in turn rewards the dog immediately for a correct decision.

8.5.2. Randomisation and masking

An unblinded independent researcher, not involved in dog handling or testing of the dogs, will be responsible for accessing the randomisation codes, and preparing the randomisation schedule for the trial. This information will be held within a locked and password protected database and will not be accessible to any other user. The blinded researcher takes the samples, once concealed, to the testing area and loads them onto the apparatus following the coded schedule provided. All those involved with testing will be blinded to the identity of the samples. During each test run the handler stays behind a one-way screen so that the dog cannot receive visual cues from the handler.

8.6. Gas chromatography – mass spectrometry

The dogs will be trained to detect, and report the detection of, volatile chemical markers diagnostic of human infection with the virus, SARS-CoV-2. For quality control and thereby robustness of this approach to establishing non-invasive early stage diagnostics for COVID-19, there will be initial chemical characterisation of volatile marker compounds to which the dogs will be trained. This analytical

approach also enables the identification of SARS-CoV-2 biomarkers which could be used in future biosensors or the development of a pseudo-odour to facilitate the upscale of dog training.

An aliquot of all the extracts will be taken for analysis (see section 8.3) by gas chromatography (GC) and gas chromatography-coupled mass spectrometry (GC-MS). For storage and transport, samples will be sealed under nitrogen in glass ampoules using protocols already established by LSHTM. The GC-MS work will be done on the newly commissioned ThermoFisher Exactive GC Orbitrap GC-MS, at Cardiff University, which has extremely high sensitivity for volatile compound detection and characterisation. Some GC work may be done at LSHTM. Mass spectral databases and direct interpretation of mass spectra, for which the study team have very considerable expertise, will provide tentative identification of compounds showing differential presence or quantification between samples from infected and non-infected participants. Confirmation of the tentative identifications will be by further comparison by GC and MS using authentic compounds. Such compounds will be obtained commercially or synthesised at Cardiff University keeping where possible to sustainable sourcing, e.g. from renewable botanical material, for longer term developments.

Dogs are highly sensitive to volatile cues and the chemical markers of SARS-CoV-2 infection will be present at extremely low levels. This can be expected to be accommodated by the sensitivity of the MS detection and sample acquisition with increased sample size providing a potential solution. Detection of differences between samples relating to virus infection should accommodate artefacts of sampling and disinfection.

9. Statistics and Data Analysis

9.1. Sample size calculation

9.1.1. Sample size for pilot.

To assess the dogs' ability to distinguish samples worn by SARS-CoV-2 carriers from those from virus negative participants, 25 samples from SARS-CoV-19 positive individuals and 75 samples from SARS-CoV-2 negative individuals will be required.

9.1.2. Sample size for training.

Previous experience suggests that 100 samples from SARS-CoV-19 positive individuals and 400 samples from SARS-CoV-2 negative individuals will be sufficient to train the dogs to a sufficient proficiency to proceed to testing.

9.1.3. Sample size for testing.

The number of independent samples (i.e. samples of materials from different study participants) encountered by each dog during testing, determines the precision with which its sensitivity and specificity can estimated. With 200 positive samples (i.e. from individuals positive for SARS-CoV-2 RNA by real-time RT-PCR, or equivalent), and an expected sensitivity of 85%, observed estimate will have a 95% Confidence Interval (95% CI) of 79% to 90%. With 200 true negative samples, and an expected specificity of 90%, observed specificity will have a 95% CI of 85% to 94%.

9.1.4. Sample size of screened individuals.

In order to obtain 325 positive samples (25 for pilot, 100 for training, and 200 for testing) we would need to screen up to 16,250 individuals. Although the prevalence of asymptomatic and pre-symptomatic patients is not known, here we assume a conservative estimate of 2%.

9.2. Data analysis

Sensitivity and specificity will be calculated separately for each trained dog. Exact binomial confidence intervals will be constructed for both sensitivity and specificity for each dog. The between dog range of sensitivities and specificities will be presented. Logistic regression with a fixed effect for each dog will be used to assess between dog differences in sensitivity and specificity.

10. Safety and Data Monitoring

10.1. Risk Assessment

Using the LSHTM 'Monitoring Risk Assessment' tool, the CI has determined studies of this kind to be "high-risk". Day-to-day monitoring will be carried out at the study sites by a member of the study team with delegated responsibility. Due to the current social distancing guidance, where possible, monitoring will be done remotely. See risk register (Appendix 5).

10.2. Adverse events

Participants and research staff will be monitored throughout the duration of the study by investigational staff for any AE. All AEs will be classified for relevance to the study by the Medical Monitor and severity by the Principle Investigator. AEs that occur >14 days after the date of sample collection will be passively monitored. An AE that is ongoing 10-14 days after the date of sample collection will be followed up until it resolves or until 30 days after the date of sample collection, whichever comes first. If the participant withdraws from the study no follow ups will occur after the date of withdrawal. AEs will be tabulated and reported to the TCC, TSC and relevant authorities. AEs occurring after the end of participant participation but before the end of the study will be listed separately.

10.3. Data Monitoring

The informed consent form will be a paper form, containing names and signatures only. These will be stored locally at site or at the TCC, in a secure location. Consent forms at the TCC will be randomly checked by the consent monitor. For the purposes of monitoring sites, some consent forms will be requested from each site. These will be scanned and uploaded as encrypted picture files to the secure study server. All data stored on the server is encrypted using asymmetric encryption keys. This means the data must be downloaded locally and decrypted offline. Separate encryption keys will be used for the consent forms, to the rest of the anonymised data. The Data Manager will not hold the encryption keys for consent forms, these will be held by the Study Administrator.

The contact details form will contain names, and potentially phone numbers, email and postal addresses. These data will be used to contact participants to carry out informed consent, arrange sending of sample packs and collection of samples, follow-up, and to inform of the results of the trial. These will be stored locally at site or at the TCC, in a secure location, and, if collected for remote enrolment, details will be entered into an encrypted database by local site staff and shared with the TCC so the TCC can conduct

screening appointments (informed consent). These data will not be kept beyond the end of the trial, and will be destroyed.

Participants may also contact the hospital sites or the TCC directly by e-mail or phone, in response to recruitment material. Therefore, in order for the document and sample pack to be sent, at the end of the screening appointment (remote informed consent and eligibility screening meeting), they will be asked to provide their name and address. This will be stored on an encrypted database, locally at site or at the TCC, in a secure location. Their details will be destroyed within 24 hours of the document and sample pack being sent. This will be explained to the participant during the meeting. On posting of the samples it will be noted on the enrolment log that the ID number has been distributed and the date the screening appointment occurred.

Participant eligibility questionnaires will hold participant medical history and will be identified using the participant ID number. These paper forms will be completed by the participant and the information read and entered into an encrypted database by local site staff or TCC. The hard copy forms will remain stored locally on site or TCC. This data will be used to confirm eligibility.

The Participant ID logs will hold names and participant IDs. This is the only location where these two pieces of data will be linked. Participant ID Logs will be paper form, and will be stored locally at site or at the TCC, in a secure location.

The consent form, participant eligibility questionnaire and participant ID logs will remain on site or at the TCC for the duration of the trial, depending on who carried out consenting. At the end of the trial, all forms will be archived by the TCC at LSHTM.

All other data will be collected on anonymised encrypted electronic forms which will be uploaded to a secure server (https://ork.lshtm.ac.uk/covid19dogs). Data is encrypted within the form before it is uploaded to the server. It is stored in an encrypted form on the server. An encryption key is required to decrypt data, which must be done offline. Encryption keys are stored on USB devices when not in use, to prevent them being accessed remotely. Use of, access to and management of the database will be linked to standard operating procedures and risk assessments.

As participants numbers predicted to be required to complete the study has increased due to low prevalence rates, documents including the informed consent form, contact details form, eligibility questionnaire, comprehension check and adverse event monitoring questionnaire, may be supplied electronically and e-consent may be given. During this process, participants will be encouraged to contact the site or TCC if they have any questions. All completed documents will be stored on anonymised encrypted electronic forms which will be uploaded to a secure server as mentioned above.

Data to be collected are: Participant number, participant initials and date of screening visit, confirmation of informed consent, date of birth, ethnicity, biological sex, eligibility details, medication for symptoms, reason for being admitted to hospital, SARS-CoV-2 test result and date, type of test, viral load, past medical history, symptoms at point of sample collection and at follow-up, sampling collection date, sample return date, storage and packaging conditions and adverse event monitoring.

A comprehensive data monitoring plan will be developed to ensure anonymity of the study participants and security of the record files. Whereby any PRO data that is collected remains independent e.g. data should be provided by the investigator site/an independent third party to the sponsor so that the source data remains under their control (and not the sponsors).

11. Regulatory Issues

11.1. Ethics approval

ARCTEC will obtain approval from the NIHR, HSE, LSHTM Ethics Committee and AWERB, Department of Biosciences Ethics Committee, Durham University, HRA and relevant NHS trust Research Ethics Committees for this study. ARCTEC will require a copy of the ethics approval letters before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.2. Indemnity

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.3. Audits and inspections

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Trial Coordination Centre and other regulatory bodies to ensure adherence to GCP.

11.4. Data access and sharing

Source data collected during this study will be stored and protected by the NHS Research & Development Department at the recruiting hospitals and shared with the Trial Coordinating Centre at the London School of Hygiene & Tropical Medicine. Study researchers at the TCC will not access personal medical records at any point during this study. Data of SARS-CoV-2 test results will be accessed by sites and shared between NHS Occupational Health service or equivalent and the TCC for the purposes of clinical management for NHS staff workers. The TCC will preserve the confidentiality of participants taking part in this study and is registered under the Data Protection Act. Specific details on study participants will be held separately from the data describing each participant and their medical history. The data used to group the samples collected (section 5) will be shared with Medical Detection Dogs. Following the study, fully anonymised study data may be published to a data repository to enable future research into viruses or outbreaks such as this. Study data, excluding participant contact details, will be held for the statutory period of 10 years.

11.5. Record retention

Personal identifiable data will be destroyed after dissemination of the trial results. Non-identifiable data and all appropriate documentation will be stored for 10 years after the completion of the study, including the follow-up period. Access to archived data will be controlled by the TCC archivist and made available by documented request to members of the trial management group, TSC or regulatory bodies.

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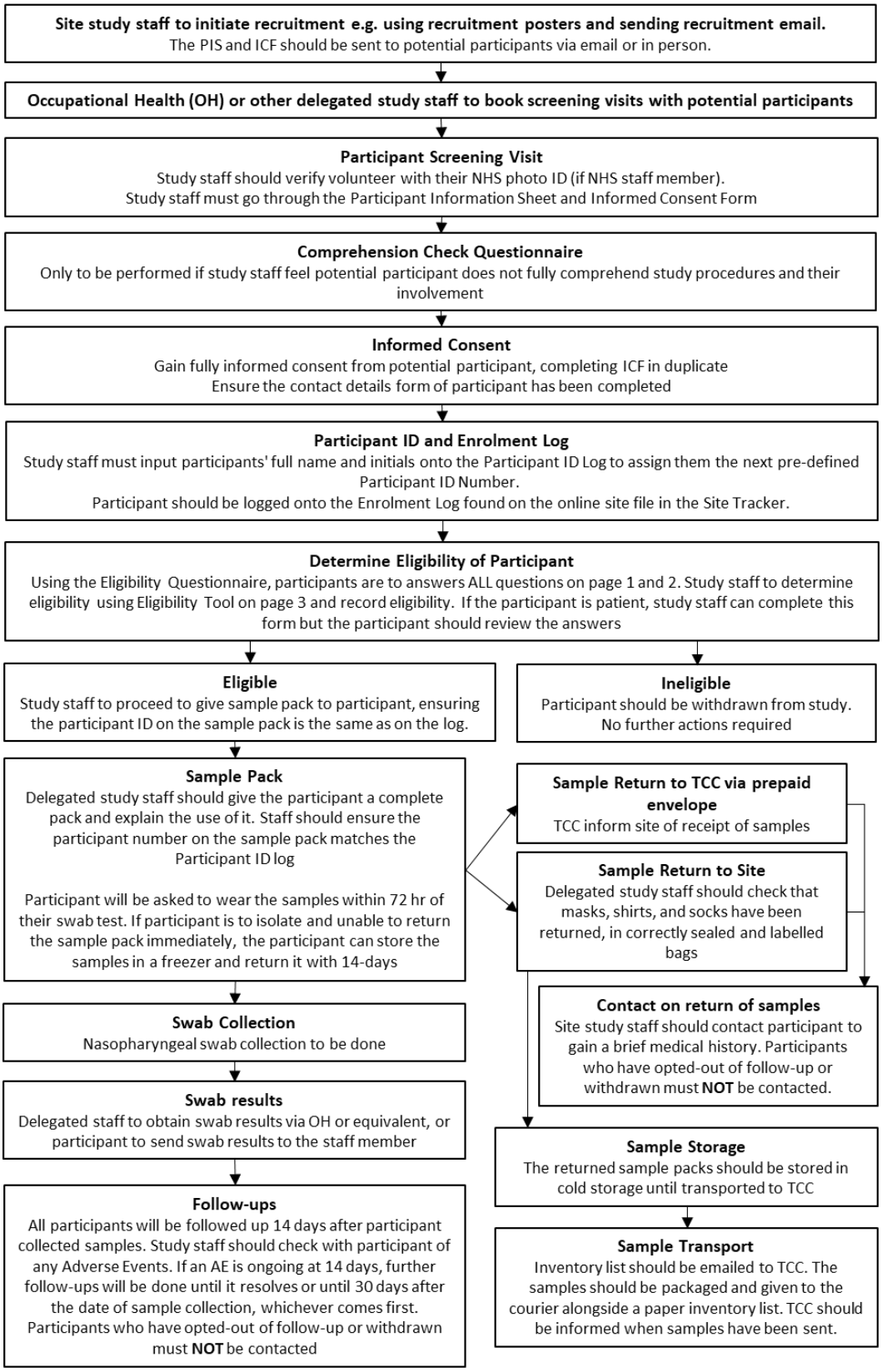
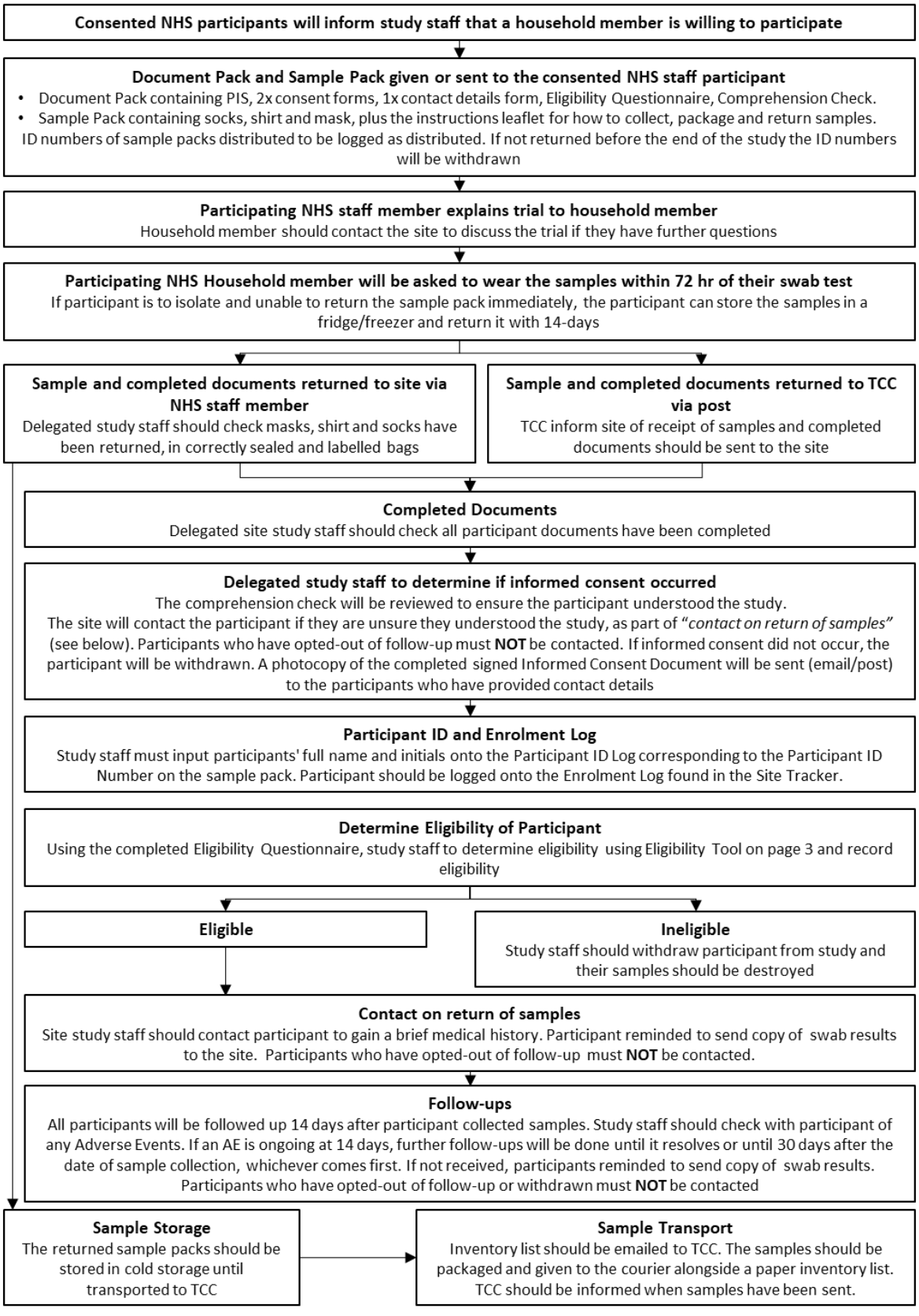
Appendix 1: Flow charts for Recruitment, Enrolment and Follow-ups

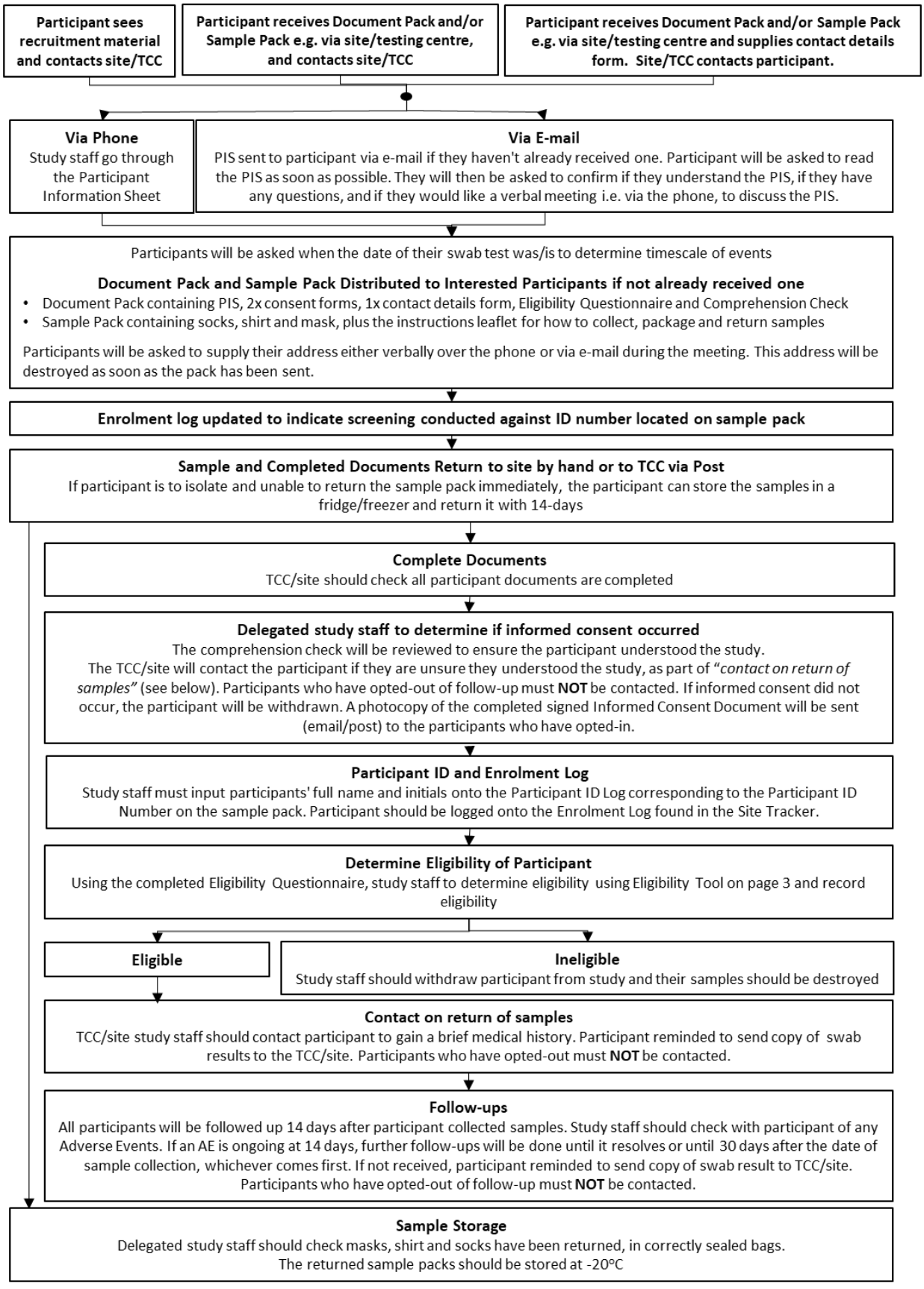
Participants who can attend screening visits i.e. NHS Staff and Patients at NHS sites



Household Members of Participating NHS Staff



Remote Enrolment
e.g. testing centres, home testing, participants who can't attend a screening appointment



Appendix 2: Adverse Event Record Form

Short Study Title: Coronavirus Canine Detection Study IRAS Reference: 284221 Site Ref Code:	Medical Monitor: Dr Anna Last Chief Investigator: Prof James Logan

Adverse Event Record Form

To be completed by Principal Investigator or delegated study staff.

Section 1			Section 2				
Participant ID Number	Date	Brief Description of AE	Related to the study (Yes/No/Unknown)	Action taken	AE or SAE?	AE or SAE Questionnaire completed	Date resolved
		Sign:_____ Date:_____					
		Sign:_____ Date:_____					
		Sign:_____ Date:_____					
		Sign:_____ Date:_____					

Page ___ of ___
Adverse Event Record Form v1.1 19June20

Appendix 3: Adverse Event Monitoring Questionnaire

ADVERSE EVENT MONITORING QUESTIONNAIRE

SECTION 1 – Report of event		
Data to be provided by person who experienced the Adverse Event. Please complete this electronically and return it via email.		
Site 4-digit code	Click or tap here to enter text.	
Today's date	Click or tap to enter a date.	
Participant ID Number *(found on sample pack)*	Click or tap here to enter text.	
Date of onset	Click or tap to enter a date.	
Date of resolution *(if resolved)*	Click or tap to enter a date.	
Stage of participation at onset	Choose an item.	
What kind of adverse event did you experience?	☐ Fever ☐ Cough ☐ Shortness of breath ☐ Joint pain ☐ Loss of taste/smell	☐ Conjunctivitis ☐ Sore throat ☐ Abdominal pain ☐ Headache ☐ Muscle pain
If other, please give details e.g. skin rash, burning sensation, severe allergic reaction,	Click or tap here to enter text.	
How serious was the event?	Choose an item.	
Did you take any action to resolve the event?	Choose an item.	
If yes, please specify	Click or tap here to enter text.	
Was a clinical consultation required?	Choose an item.	
If yes, please specify	Click or tap here to enter text.	
Did you visit A&E?	Choose an item.	
If yes, please specify	Click or tap here to enter text.	
Did you stay in hospital overnight?	Choose an item.	
If yes, please enter details (no. nights/admission/if intensive care was required)	Click or tap here to enter text.	
Outcome	Choose an item.	

Adverse Event Monitoring Questionnaire v3.0 27Aug2020

ADVERSE EVENT MONITORING QUESTIONNAIRE

Would you like to continue to participate in the study?	Choose an item.
Who completed this form?	Choose an item.
How was this form completed	Choose an item.
• ***If completed by the participant*** *- Please email this questionnaire back to the person who sent it to you. Have questions? Contact the researcher on your Participant Information Sheet.*	
• ***If completed by the researcher on behalf of the participant*** *- Please email this questionnaire back to the participant if an email address has been provided.*	
Name of Researcher completing	Click or tap here to enter text.

ADVERSE EVENT MONITORING QUESTIONNAIRE

SECTION 2a – PI assessment of AE	
To be completed by the Principal Investigator or delegated clinician	
Participant ID	Click or tap here to enter text.
Short Study title	**Coronavirus Detection Dogs**
IRAS reference	**284221**
Type of study	**LSHTM Observational Trials**
Were you required to medically intervene? If yes, please give details	Choose an item. Click or tap here to enter text.
Date reported to PI	Click or tap to enter a date.
Was the event serious? If yes, complete section 2b	Choose an item.
	Details of Assessment
Assessor Name	Click or tap here to enter text.
Date Assessed	Click or tap to enter a date.
Date emailed to TCC	Click or tap to enter a date.

GUIDANCE FOR PIs - SUBMITTING YOUR AE REPORT

- If the adverse event is assessed to be **serious**, please also complete **Section 2b** below.
- If the adverse event is non-serious, please save this completed form as a PDF, including **Section 1** and **Section 2a** and send to the Trial Coordinating Centre via email to covidk9@lshtm.ac.uk, copying in James.Logan@lshtm.ac.uk (Chief Investigator) and Anna.last@lshtm.ac.uk (Medical Monitor).

ADVERSE EVENT MONITORING QUESTIONNAIRE

SECTION 2b – PI assessment of SAE/SUSARs		
To be completed by the Principal Investigator or delegated clinician if adverse event is considered serious or unexpected.		
Date adverse event become serious		Click or tap to enter a date.
Seriousness criteria (please select all that apply)		
☐	Life threatening	
☐	Required hospitalisation	
☐	Prolonged hospitalisation	
☐	Congenital anomaly	
☐	Disabling/incapacitating	
☐	Important medical event	
☐	Required intervention to prevent impairment or damage	
☐	Fatal	
SAE Status		Choose an item.
Expectedness i.e. was the SAE a recognised undesirable effect of intervention		Choose an item.
Admitted to Intensive Care Unit?		Choose an item.
If fatal, date of death		Click or tap to enter a date.
Primary cause of death		Click or tap here to enter text.
Was a post-mortem performed?		Choose an item.
Possible contributing factors to SAE other than study participation or underlying disease being studied. Please tick and give details		
☐	Non-apparent	Click or tap here to enter text.
☐	Concurrent illness, disease, or other external factors	Click or tap here to enter text.
☐	Concurrent medication	Click or tap here to enter text.
☐	Study procedure	Click or tap here to enter text.
☐	Accident, trauma, or other external factors	Click or tap here to enter text.
☐	Other, please specify	Click or tap here to enter text.
Relevant concomitant medication at time of SAE? If yes, please provide details		Choose an item. Click or tap here to enter text.
Treatments/procedures for SAE? If yes, please provide details		Choose an item. Click or tap here to enter text.
Relevant medical history (include only relevant past or concurrent medical disorder, surgeries, etc that might help explain the SAE) If yes, please provide details		Choose an item. Click or tap here to enter text.
Relevant laboratory testing If yes, please provide details		Choose an item. Click or tap here to enter text.
If relationship to study participation was unrelated, provide causality Please give specific details		
☐	Discontinuation of study participation	

Adverse Event Monitoring Questionnaire v3.0 27Aug2020

ADVERSE EVENT MONITORING QUESTIONNAIRE

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE
ARCTEC

☐	**Concurrent disorder**
☐	**Concomitant medications**
☐	**Other, please specify** Click or tap here to enter text.
If action taken was during study participation, was study interrupted or discontinued? If yes, please provide date of interruption.	Choose an item. Click or tap to enter a date.
Did SAE abate after study was stopped?	Choose an item.
Did SAE reoccur after reintroduction of study participation?	Choose an item.
Narrative/Comments Please describe the SAE including a chronological clinical presentation and evolution of the SAE and associated signs/symptoms	Click or tap here to enter text.
Details of Assessment	
Assessor Name:	Click or tap here to enter text.
Date Assessed:	Click or tap to enter a date.
Date emailed to TCC:	Click or tap to enter a date.
Confirm that the SAE has also been reported to the TCC on the AE hotline (0207 927 2877)	
☐ **I confirm that I have reported the SAE using the SAE hotline.**	

SUBMITTING YOUR SAE REPORT

1) Please save this completed form as a PDF, including **Section 1, 2a and 2b** and send to the Trial Coordinating Centre via email to covidk9@lshtm.ac.uk, copying in James.Logan@lshtm.ac.uk (Chief Investigator) and Anna.last@lshtm.ac.uk (Medical Monitor)
2) Additionally you must also notify the TCC immediately using the SAE hotline.

Serious Adverse Event hotline: 0207 927 2877

Adverse Event Monitoring Questionnaire v3.0 27Aug2020

SECTION 3 – Receipt by TCC	
To be completed by Chief Investigator or Clinical Trial Manager ONLY	
Date received by TCC	Click or tap to enter a date.
Date questionnaire sent to Medical Monitor	Click or tap to enter a date.
Date entered in Central AE Record	Click or tap to enter a date.
AE reference	Click or tap here to enter text.
Name of receiving person	Click or tap here to enter text.

SECTION 4 - Decision of Medical Monitor	
To be completed by delegated study Medical Monitor ONLY	
Likelihood of Adverse Event being related to study	Choose an item.
Do you agree with the PI's classification?	Choose an item.
If no, please specify the classification	Choose an item.
Recommended course of action:	Choose an item.
Medical Monitor Name:	Click or tap here to enter text.
Date Reviewed:	Click or tap to enter a date.
Date sent to TCC (covidk9@lshtm.ac.uk)	Click or tap to enter a date.
Please send this assessment to the TCC via email to covidk9@lshtm.ac.uk. SAEs that are confirmed by the Medical Monitor as being both related and unexpected must be reported promptly to the TCC.	

SECTION 5 – Receipt of Decision by TCC	
To be completed by Chief Investigator or Clinical Trial Manager ONLY	
Date received by TCC	Click or tap to enter a date.
What are the implications (if any) for the safety of other trial participants, and how will these be addressed?	Click or tap here to enter text.
Date questionnaire sent to site PI	Click or tap to enter a date.
Name of actioning person	Click or tap here to enter text.

SECTION 6 – Participant follow up	
To be completed by the Principal Investigator or delegated clinician	
Follow up required?	Choose an item.
Date of follow up	Click or tap to enter a date.
Outcome	Choose an item.
Progression	Choose an item.
Date resolved	Click or tap to enter a date.
Name of Assessor	Click or tap here to enter text.

INSTRUCTIONS FOR SITE

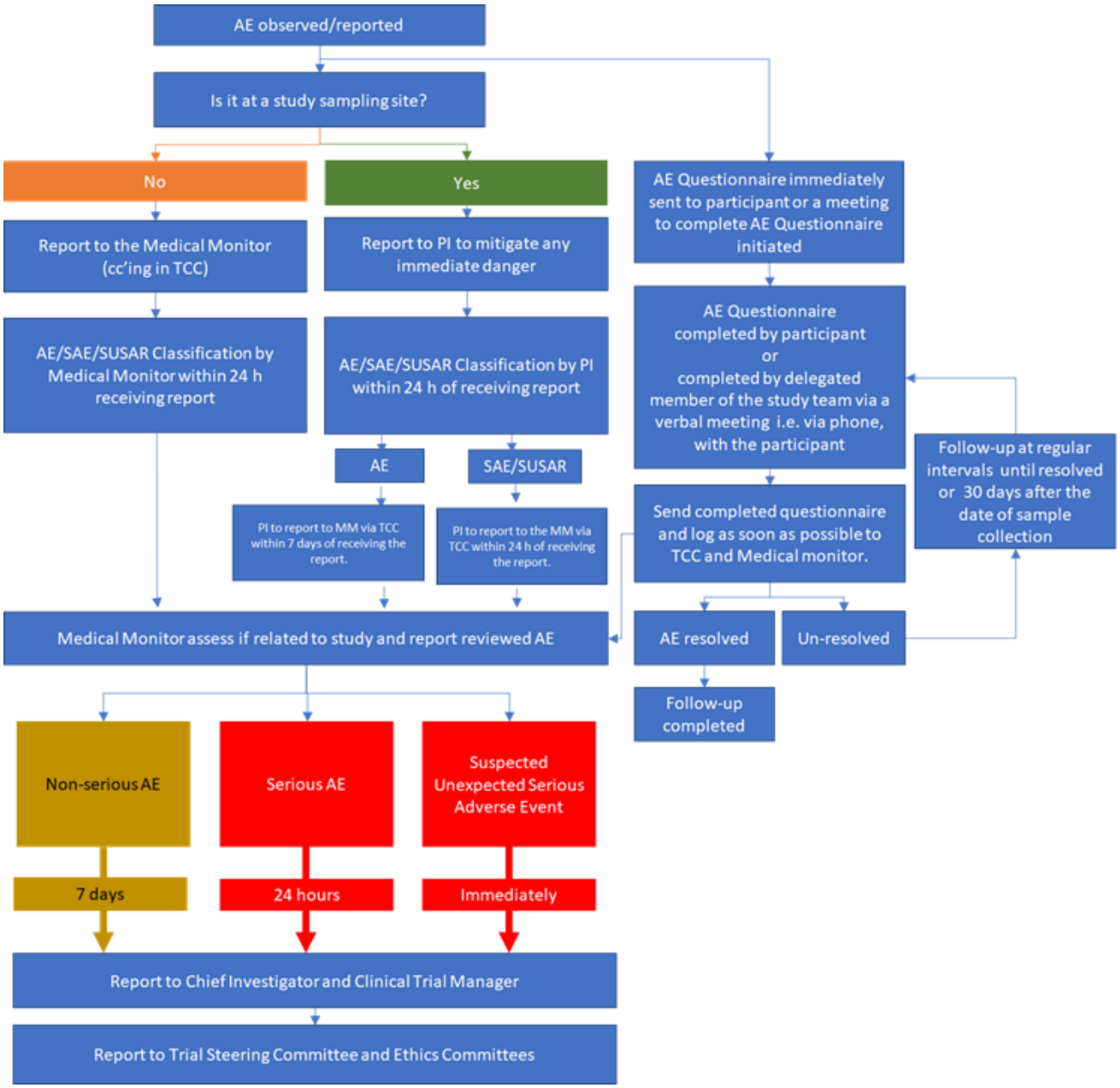
Please complete the AE log including any required actions stipulated by the Medical Monitor in section 4

Adverse Event Assessment & Reporting v1.0 27Aug2020

SECTION 7 – SAE/SUSAR EC Notification	
For SAEs and SUSARs only - Acknowledgement of Document Receipt by Ethics Committees and Data Monitoring Committee	
Date ethics committees notified	Click or tap to enter a date.
The LSHTM Research Ethics Committee Acknowledges Receipt of the Above Questionnaire	
Date	Click or tap to enter a date.
Name	Click or tap here to enter text.
Position on the REC	Click or tap here to enter text.
The Biosciences Ethics Committee, Durham University Acknowledges Receipt of the Above Questionnaire	
Date	Click or tap to enter a date.
Name	Click or tap here to enter text.
Position on the REC	Click or tap here to enter text.
The NHS Trust Ethics Committee Acknowledges Receipt of the Above Questionnaire	
Date	Click or tap to enter a date.
Name	Click or tap here to enter text.
Position on the REC	Click or tap here to enter text.

TCC to PDF form on completion.

Appendix 4: Flowchart for Safety Reporting



Appendix 5: Risk Register

Study Title: Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.

Study ID: LSH1285

RISK ASSESSMENT (RA1285-001): SAMPLE COLLECTION

Assessors	Vanessa Chen-Hussey, Robert Jones, Sarah Dewhirst, Chelci Squires
Date	29th June 2020
Procedure	Collection of breath and skin odour samples from participants following screening for SARS-CoV-2
Location	On-site sampling stations within hospitals; during transport; LSHTM

Hazard Description	**Risk Rating**			**Controls**	**PPE Required**
	Consequence	Likelihood	Rating		
Biological: Bodily Fluid & Virus/Disease Used masks may be contaminated with saliva and sputum from the wearer. Sputum may contain SARS-CoV-2 as well as other infectious agents. Both socks, shirts and masks may also be contaminated with other infectious agents.	Infection or Fatality	Highly Unlikely	Medium-High	The samples will be removed by the participants who have to wash their hands before they remove the samples. Masks will be wrapped in tin foil and will be sealed within a Category B UN3373 Biobag- 1 bag (tested to meet a pressure of 95kpa) by the wearer. Shirts and socks will be packaged in tin foil and placed into two separate sealed bags by the wearer. The biobag containing masks and the press	Gloves Mask/ faceshield Coverall

				sealed bags containing the socks and shirt will then be placed into another sealed bag by the wearer. The exterior of the bags will be wiped down with an alcohol wipe by the wearer. The sample drop-off will be designed to allow 2m space between participants dropping off, and researchers receiving samples Study researchers receiving the samples and/or taking participant information face-to-face will wear gloves, mask/ face shield, and coveralls.	
Facilities: Hospital collection sites	Unknown	Unknown	Unknown	Separate risk assessments will be required of the worksite for study researchers before onsite sampling stations are set up.	Unknown
People: Hospital Staff, Patients, General Public Study researchers will be based inside hospitals whilst collecting samples. There is a risk of physical and verbal abuse from other NHS users or staff	Minor injuries	Unlikely	Medium	Times for distribution and collection of samples will be planned around shift changes to minimise time spent in hospital, if possible Locations of sampling stations will ideally be somewhere without access by general public.	None

RISK ASSESSMENT (RA1285-002): SAMPLE STORAGE AND TRANSPORT

Assessors	Vanessa Chen-Hussey, Robert Jones, Sarah Dewhirst, Chelci Squires
Date	21st August 2020
Procedure	Transport of biological samples from participants homes or hospital sites to LSHTM, from LSHTM to Medical Detection Dogs, and from Medical Detection Dogs to LSHTM. Masks will be sealed within a Category B UN3373 Biobag- 1 bag. Socks and shirts will be sealed in separate press-sealed bags. All bags will then be sealed in a secondary press-sealed bags and placed in an envelope. The exterior of the bags and the envelope will be wiped down with an alcohol wipe. This will be done by wearer before drop-off or postage Samples will be transported as UN3373 Category B. Samples could be stored at hospital sites, participant homes, LSHTM and Medical Detection Dogs
Location	Multiple

Hazard Description	**Risk Rating**			**Controls**	**PPE Required**
	Consequence	Likelihood	Rating		
Biological: Bodily Fluid & Virus/Disease Socks, shirts and masks may be contaminated with bodily fluids from the wearer. There is potential for these to be contaminated with infectious agents including SARS-CoV-2.	Fatality	Highly Unlikely	Medium	Study participants will not be displaying severe Covid-19 symptoms. Some participants will be of higher risk of having been infected by virtue of their occupation (Health Care Workers), but they must not be displaying severe symptoms at the	Gloves, Eye protection and Aprons

				time of the study. An exclusion criteria questionnaire has been developed to ensure this. The risk of viral shedding is therefore limited, but not impossible. Items should not worn in areas where Covid-19 patients are being treated, unless they are a patient. With regards to the sock and shirt samples, there is no evidence that the virus is shed through the skin and therefore none should be shed directly onto the socks and shirt, even if the participant was infected. The participant will be asked to avoid contact between the shirt and the face when changing in and out of the shirt. Any virus on the mask will be immobilized on	

				the filter material and it is improbable to see how this could be re-aerosolised. Participants will wrap their own masks, shirts and socks in foil and place into separate bags (mask in a biobag-1). These bags will then be placed into a separate large bag and then into a mailing bag. All bags will be sealed and cleaned with alcohol. The participant is asked to adhere to strict hand hygiene is practiced, before and after removing the items No direct handling of samples will occur by any delegated member of staff, postal staff or other household member during	

				transport and storage. Delegated staff must wear gloves, aprons and eye protection when checking the contents of the envelope. Staff should not open the large sealed bag unless one of the sample bags is unsealed.	
Environment: Asphyxiation and extreme cold from dry ice	Major injuries	Unlikely	Medium	Dry ice must only be handled by staff members trained to do so. Only use dry ice in a suitable ventilated area, and if necessary a carbon dioxide monitor should be used. Transport of the box containing dry ice should be in a vehicle where the drivers' cab is sealed from the load compartment.	Eye protection Insulated gloves

RISK ASSESSMENT (RA1285-003): SAMPLE PROCESSING

Assessors	Vanessa Chen-Hussey, Robert Jones, Sarah Dewhirst, Chelci Squires
Date	29th June 2020
Procedure	In a microbiological safety cabinet in a Containment Level 2 lab the samples will be cut into smaller pieces. Some of these will be placed into a glass vials and a clean nylon sock will be placed over the vial, with two elastic bands securing the clean nylon sock in place. The open end of the nylon sock will be tied, and a metal screw cap will be secured on top. The vial will then be sealed into a press-sealed bag. Theses vials will be used for later presentation to the dogs. The remaining pieces of the samples will be stored in sealed bags in a secure -20C freezer at CL2. Volatile organic compounds (VOCs) will be extracted from some of the remaining pieces by with either isopropyl alcohol or ethanol, and by air entrainment of samples using a porous polymer such as Porapak eluted with a solvent.
Location	London School of Hygiene & Tropical Medicine

Hazard Description	**Risk Rating**			**Controls**	**PPE Required**
	Consequence	Likelihood	Rating		
Biological: Bodily Fluid & Virus/Disease Socks, shirts and masks may be contaminated with bodily fluids from the wearer. There is potential for these to be contaminated with infectious agents including SARS-CoV-2.	Infection or Fatality	Unlikely	Medium - high	There is no evidence that the virus is shed through the skin and therefore none should be shed directly onto the socks or shirts, even if the participant was infected. Any virus on the mask will be immobilized on the filter material and it is improbable to see how this could be re-aerosilised. The following precautions are therefore based on the risks associated with direct contact with the mask.	Eye protection Gloves Lab gown

				The only direct handling of the samples will be undertaken at LSHTM by trained staff wearing gloves and lab gown in a microbiological safety cabinet in a Containment Level 2 laboratory. Handling of samples will occur 72 hours after collection. Scissors will be used to cut the samples and all equipment and surfaces sprayed with 70% ethanol after use. The outer surface of the vials/sock will be sprayed with 70% ethanol before removing from the safety cabinet and will be placed in the packaging for transport using clean gloves and outside of the cabinet in a clean part of the lab.	
Environment: Asphyxiation and extreme cold from dry ice	Major injuries including burns	Unlikely	Medium	Dry ice must only be handled by staff members trained to do so. Only use dry ice in a suitable ventilated area, and if necessary a carbon dioxide monitor should be used.	Eye protection Insulated gloves
Equipment: Sharps	Cut or prick injuries	Unlikely	Low	Staff handling sharps will be trained where necessary. All cutting equipment will be examined for damage before use.	None

				Sharps waste should be available with the biosafety cabinet.	

RISK ASSESSMENT (RA1285-004): SAMPLE HANDLING DURING DOG TRAINING AND TESTING

Assessors	Vanessa Chen-Hussey, Robert Jones, Sarah Dewhirst, Chelci Squires
Date	29th June 2020
Procedure	Handling of vials containing progeny samples during training and testing of dogs
Location	Medical Detection Dogs

Hazard Description	**Risk Rating**			**Controls**	**PPE Required**
	Consequence	Likelihood	Rating		
Biological: Bodily Fluid & Virus/Disease	Infection or Negligible Injury	Unlikely	Low	The sample vials are robust and can only be opened deliberately. The samples will not be able to fall out of the vial nor be able to touch the grille, due to the vial being housed within the sock. In the unlikely event the vial will break, the nylon sock will minimize the risk of the contents being dispersed. No staff member or dog will be able to touch the contents unless deliberately removing the lid and the clean nylon sock. Staff at the Medical Detection Dog Facility are	Gloves Safety glasses coverall

				instructed to practice frequent hand hygiene and will be required to wash their hands thoroughly immediately after handling the vials. In the extremely unlikely event of a vial opening and the sample falling out at the Medical Detection dog Facility, or of the vial breaking, the dog will be removed immediately from the area and the handler will spray the sample and area with 70% ethanol before using gloves and forceps to place the sample and any other waste back in the vial and then into the transport packaging for return to LSHTM. The time between collection and samples being received by Medical Detection Dogs Facility will be greater than 72 hours. Without any direct touching of the samples by either the dogs or the handlers at any stage, the chances of exposure to any virus on the samples is negligible. Once used, the samples will be returned to LSHTM by courier as UN3373 Category B for autoclaving and final disposal.	

RISK ASSESSMENT (RA1285-005): GAS CHROMATOGRAPHY COUPLED MASS SPECTROMETRY

Assessors	Vanessa Chen-Hussey, Robert Jones, Sarah Dewhirst, Chelci Squires
Date	29th June 2020
Procedure	Analysis of volatiles from breath and skin odour samples by gas chromatography coupled mass spectrometry
Location	London School of Hygiene & Tropical Medicine; Cardiff University

Hazard Description	**Risk Rating**			**Controls**	**PPE Required**
	Consequence	Likelihood	Rating		
Biological: Bodily Fluid & Virus/Disease Inactivated alcohol extracted biological sample.	Negligible injury	Unlikely	Low	Samples will be inactivated in alcohol and will not present any infection risk to researchers handling for the purposes of chromatography. The vials containing the solvent extracts can also be cleaned with alcohol to disinfect	Gloves Coveralls/ laboratory coat
Chemical: Hazardous chemicals and solvents Risk of eye irritation or skin irritation	Minor injury	Unlikely	Medium	Chemicals to be kept in appropriate cabinet and sealed when not in use. Disposed of through LSHTM/Cardiff University chemical waste process	Laboratory coats Goggles Gloves
Sharps: Risk of cuts	Minor injury	Unlikely	Medium	Syringes to be handled with care and kept in secure containers when not in use. Disposed in a sharps bin.	Gloves

Electricity: Risk of electric shock	Major injury	Unlikely	Medium	Equipment PAT tested routinely.	None
Pressurised Containers: Risk of injury if gas builds up and seal breaks. Risk of injury if cylinder falls	Major injury	Unlikely	Medium	Gas flowing through the equipment to be turned off at the regulator when not in use. The equipment is outfitted with alarms, which sound if there is a build-up of gas within the machine. All external fittings will be regularly checked for leaks. Gas cylinders to be transferred by two people. Cylinders strapped in place to prevent toppling.	Goggles
Machinery: Hot interior and inlets of the GC machine could cause burns	Minor injury	Unlikely	Medium	All users trained in safety procedures such as not opening the equipment to expose hot interior. Signs on GC machine indicating which parts can be hot. No unauthorised persons allowed to use the GC machine.	Gloves

Appendix 6: Participant Information Sheet and Informed Consent Form

Recruiting Hospital Site or TCC: [To be pre-populated for each site]
Principal Investigator at site or TCC: [To be pre-populated for each site]

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Version 4.0, 12Oct2020

Study Title:	Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.
Chief Investigator:	Professor James Logan, London School of Hygiene & Tropical Medicine
Protocol version:	Version 4.0, 12th Oct 2020
IRAS Number:	284221

What is informed consent?

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research study is being done and what it will involve. Please take time to read the following information carefully, or have the information explained to you in a language you are comfortable with. If you have any questions or would like anything to be explained further, please do ask. You should not join this research study until all your questions are answered. You may also wish to consult your spouse, family, friends or others before deciding to take part. If you do decide to take part, you will be required to sign two copies of a consent form, one for you to keep and one for the research team to keep.

What is the purpose of this study?

The purpose of this study is to determine whether trained medical detection dogs are able to detect the presence of Coronavirus (also known as SARS-CoV-2 or COVID-19) in adults who are not currently showing any symptoms or have mild to moderate symptoms, due to a change in odour. If this is possible, it will help to identify cases in situations where there is a high number of people such as airports and help to prevent further spread of infection in the population. The results of this study will be made available to your community.

Do I have to take part?

It is up to you to decide whether or not to take part in this study. If you do decide to take part, you will be given this information sheet to keep and be asked to sign two copies of an informed consent form and provide your contact details. One consent form should be returned to the study researcher for approval, and will be kept and stored in the confidential study documentation. The study researcher will either complete the other copy and return to you or a photocopy of the complete form will be set to you via email or post for your own records. If you decide to take part, you are still free to withdraw at any time without giving a reason.

Why do you need my contact details?

To enable us to contact you during the trial, we (the recruiting hospital or Trial Coordinating Centre) ask that you provide your contact details. We will only contact you for the following reasons:

1. To ensure informed consent occurred (if enrolling remotely)
2. To follow up on your participation to check for any adverse events and symptoms (wellbeing check)
3. To inform you of the results of the trial
4. To arrange collection of samples if self-isolating and unable to store or post your samples.

If you would prefer not to provide your contact details or would not like to be contacted, you can still take part. However, this would mean that we are unable to follow up with you to check your wellbeing, inform you of the results of the trial or, if applicable, arrange collection of samples from you if you are self-isolating and

unable to store or post your samples. This does not affect your ability or right to contact a study researcher at your recruiting hospital or the Trial Coordinating Centre (TCC) in order for informed consent to occur or report an adverse event. If you have any questions or concerns during your participation, please get in touch with a trial researcher using the details in this Participant Information Sheet.

What will happen to me if I take part/what does the study involve?

If you decide to take part, following informed consent we (the recruiting hospital or TCC study staff) will need to assess your eligibility to be included in the study. To be enrolled in this study you must be:

- Due to have a coronavirus swab test or have had a swab test conducted in the previous 72 hours;
- Have suspected mild or moderate COVID-19 symptoms, or have been exposed to COVID-19, or have received results of a positive COVID-19 swab test conducted in the previous 72 hours, or are a current NHS staff member, or currently living with an NHS staff member;
- Aged 16 years old or older;
- Not receiving palliative care;
- willing and able to wear a face mask for at least 3 hours*;
- willing and able to wear nylon socks for at least 12 hours;
- willing and able to wear a shirt for at least 12 hours*
- willing and able to provide access to or a copy of your coronavirus swab test result

*Participants unwilling or unable to wear a face mask and/or shirt for medical reasons will still be eligible to participate.

You will be unable to take part in the study if you are younger than 16, and if you have previously been infected with Coronavirus (either clinically diagnosed or laboratory confirmed), if you receiving palliative care, or are currently presenting with any severe associated symptoms which require mechanical ventilation.

During the collection of foot, body and breath odours, we ask you not to apply any cosmetics associated with a strong scent e.g. perfume, or make-up that will rub onto the provided mask, shirt or socks. We also ask you to avoid getting the mask, socks and shirt dirty or wet and to avoid areas with strong odours whilst wearing them i.e. when cooking. Socks and shirt should be in contact with bare skin therefore we ask you not to wear them over other clothing, although bras can be worn. Clothing and shoes can be worn over the socks and shirt.

How will I take part via an NHS recruiting hospital?

If you are eligible to take part, you will be asked to provide consent for us to access the result of your nasopharyngeal swab test. A screening appointment will occur at the hospital where informed consent may be given, and your eligibility to participate assessed. If you are living with a NHS worker participating in the trial, the hospital will contact you after receipt of the samples to determine if informed consent occurred.

You will be asked to provide samples of breath and skin odour immediately after the swab test and preferably within 72 hours of your test. To collect these samples, you will be asked to wear a facemask for 3 hours and a pair of nylon socks and a shirt or T-shirt for 12 hours on the day of your swab test. The facemask will collect a sample of your breath as you breathe naturally, and the socks and shirt will collect skin odours from your feet and body as you go about your day normally. When you change in and out of the shirt or T-shirt please try to avoid the shirt or T-shirt touching your face. You should also continue to wear these overnight if needed to

wear these for a minimum of 12 hours. You can wear them for longer. It is important to note that these items are not a suitable replacement for frontline PPE and should not be worn in a healthcare setting.

How will I take part from home?

If you are eligible to take part, you have/will be provided with a package containing:

- this Participant Information Sheet,
- two copies of the informed consent form,
- a participant contact details form,
- an eligibility questionnaire,
- a comprehension check questionnaire
- an instruction leaflet for how to collect, package and return your samples
- and everything you need to collect your samples.

You will be able to participate from your home. Please read this information sheet and call or e-mail the TCC or site, as soon as possible, if you do not understand any of the process or you have some questions.

You will be required to provide samples of breath and skin odour immediately after the swab test and consent, preferably within 72 hours of your test. If your sample package arrives after 72 hours of your test, please proceed to collect your samples as soon as possible after receipt. To collect these samples, you will be asked to wear a provided a facemask for 3 hours and a provided pair of nylon socks and shirt or T-shirt for 12 hours straight after doing the swab. If required, you should wear these overnight to ensure they are worn or a minimum of 12 hours. You can wear them for longer. The facemask will collect a sample of your breath as you breathe naturally and the nylon socks and shirt will collect skin odours from your feet and body as you go about your social distancing normally. When changing in and out of the shirt or T-shirt please try to avoid the shirt or T-shirt touching your face.

If you are taking part from home, it is important that you provide the study team with a copy of your swab test result. To do this, forward a copy of the email (or screenshot of the text) showing your result to the study team email address or include a printout in the sample pack on return. Please include your participant ID, and the date on which your swab test occurred.

How do I return my samples?

Please package you items as guided in the home test form, ensuring the you have written the **start date of collection on the labels**.

Please return your samples and completed documents (if applicable) within 24 hours of collection to the recruiting NHS hospital (if enrolled via an NHS recruitment site or an NHS staff member) or via the post. If you are unable to, please either ask a friend or relative to post your samples or store your samples in a fridge/freezer. If storing in a fridge/freezer, please inform the NHS site and/or TCC if possible and return the samples within 14 days.

Please send a copy of your coronavirus swab test result, as soon as possible after you have received it, to the NHS recruitment site or TCC using the information at the end of this document. This will allow for the Site or TCC to determine whether you have a Coronavirus infection. If you are an NHS staff member and the swab was done on site, Occupational Health or equivalent may access your swab test results.

The NHS recruitment site or TCC will contact you on receipt of your samples in order to check your wellbeing. If you consented remotely, your consent form will be checked, and your eligibility to participate assessed.

If you have any questions or would like to talk to a member of the study team before you consent or during your participation you can contact the dedicated study member using the information at the end of this document.

What will I need to do after I send my samples?

After you have sent your samples you may continue as normal. You may be contacted three times by a researcher to follow up on your wellbeing. Details are listed later in this document.

How will I find out if I have Coronavirus?

If you are swab tested and found to be positive for Coronavirus, you will be notified by a representative of the test facility through their standard notification procedure. Results can take up to 3-4 days, and if found to have a coronavirus infection, you are advised to follow the government's current guidelines for self-isolation. This includes NHS workers.

Please send a copy of your coronavirus swab test result, as soon as possible after you have received it, to the NHS recruitment site or TCC, along with the date of your test. Please either forward the email with your result, or share a screen shot of the text message containing your result.

If at any time the research study must end, you will be informed if you have provided your contact details. Recruitment and sampling will stop and you will be followed up to check your well-being, as planned.

What will happen to the samples taken in this study?

Firstly, your infection status will be confirmed by validated laboratory diagnostics at the time of the study. The results of this test will be made available to you. This study does not offer additional swab testing for those who are not currently eligible for screening.

The face mask, shirt and sock samples will need to be returned to your recruiting hospital or TCC (instructions will be provided). At the point of return, the face mask, shirt and nylon socks you have worn for the allocated time will need to be packaged in separate labelled polythene bags which you will be provided with, and returned. These samples will be stored frozen and confirmation of your consent will be checked. The samples will then be processed to extract and preserve the volatile organic compounds responsible for smell, but in a way which ensures that the dogs and the researchers in the subsequent study are not at risk of infection. Samples will be grouped into either positive or negative infection status based on the result of laboratory diagnostic testing when available. Inconclusive results may be repeated where possible or, if not possible, may be deemed ineligible and withdrawn from the study.

Firstly, we (TCC and Medical Detection Dogs) will use the samples to see if dogs can be trained to distinguish between odour samples from coronavirus infected and uninfected individuals. If this is successful, another study will be run using your samples to determine the dogs' diagnostic accuracy. Further research looking into the odours of Coronavirus may also be conducted using these samples by the TCC and Cardiff University.

How will we use information about you?

We (the recruiting hospital and the TCC at LSHTM) will need to use information from you for this research project.

This information will include your name, age, biological sex, ethnicity, details of any recent symptoms and medication treating COVID-19 symptoms, contact details (if provided) and result of your NHS screening for coronavirus. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

The sponsor, recruiting hospital and TCC will keep all information about you safe and secure. Some of your information may be sent to the trial Medical Monitor and TCC for the purpose of checking your safety if an adverse event is reported or checking that consent and eligibility has been assessed correctly. They must follow the Sponsors rules about keeping your information safe.

Your personal details will be kept in a different safe place to the other study data and will be destroyed at the end of the study once the trial results have been communicated to you. The other non-identifiable study data will be archived by the London School of Hygiene & Tropical Medicine for 10 years after the end of the study. The data will be made available to other researchers worldwide for research and to improve medical knowledge and patient care. Your personal information will not be included and there is no way that you can be identified.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we (the recruiting hospital and the TCC at LSHTM) will keep information about you that we already have. If you choose to stop taking part in the study, we would like to follow up with you to collect information about your health from you. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to consent to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?

You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients/ or www.hra.nhs.uk/patientdataandresearch and by asking one of the research team, by sending an email to coviddogs@lshtm.ac.uk, or by ringing the TCC on +44 (0) 20 7927 2777.

What will happen to information collected about me?

All information collected about you will be kept private. Only the study staff and authorities who check that the study is being carried out properly will be allowed to look at information about you. Data may be sent to other study staff, but this will be anonymised. This means that any information about you which leaves the hospital or recruitment team within the TCC, will have your name and address removed so that you cannot be recognised.

The responsible Investigator at the hospital will send some details about you to the TCC at the London School of Hygiene & Tropical Medicine which may also be shared with medical detection dogs to aid with training. All data will be store securely. Your identifiable information will be kept until the trial results are published and then destroyed. Until then it will be stored in a different safe place to the other non-identifiable study information, which will be destroyed 10 years after the end of the study.

At the end of the project, the study data will be archived at the London School of Hygiene &Tropical Medicine. The data will be made available to other researchers worldwide for research and to improve medical knowledge and patient care. Your personal information will not be included and there is no way that you can be identified.

Will I benefit from my participation in the study?

There is no monetary benefit to you for participating in this study. However, the results of this study may be useful in the fight against Coronavirus.

What happens if I choose to withdraw from the study?

You are free to withdraw from the study at any time, without giving a reason. Information already generated from the samples until the time of withdrawal will be used and samples already collected, for which you have given consent, will also be analysed and data used.

What are the risks or side effects of participating?

Some people may experience distress if found to have a positive coronavirus result, but the research staff will be available to support those during this time. It is not expected that there will be any clinical side effects of participating in this study, though you may experience mild discomfort whilst wearing the facemask. If you have any questions or concerns, or would like to report and adverse event you can contact the following people:

The Research Nurse or Principal Investigator at your recruiting hospital:

Insert PI / RN / other contact information here

The Trial Coordinating Centre (TCC) for the study:

ARCTEC Clinical Trials
Address: Room LG38, LSHTM, Keppel St, London WC1E 7HT
Tel: +44 (0) 20 7927 2777
Email: coviddogs@lshtm.ac.uk

What is an Adverse Event and how to report it?

An adverse event is any untoward medical occurrence that occurs whilst you are recruited in the trial. This could be, for example, a cold/flu, a reaction to the facemask or socks or something seemingly unrelated to the study such as nausea or injuries. All enrolled participants and research staff will be able to report adverse events throughout the duration of the study to study staff. If an adverse event occurs during any part of the trial, please contact the Principal Investigator or Research Nurse at your recruiting hospital or the TCC (details above). The adverse event will then be assessed by the doctor delegated to this trial (Medical Monitor) to assess if the event is related to the trial or not. If an adverse event occurs during sampling, for your safety and well-being you should stop collecting the samples by removing the facemask and socks. If an adverse event occurs before or after sampling, you may be asked to withdraw from the study depending on the severity and risk determined by the medical clinician.

Will I be followed up to check I am well?

If you consent to take part, you will be enrolled into the study. If you have opted to provide your contact details, you will be contacted on receipt of your samples where a brief medical history will be taken. You will be followed up 14 days after sample collection, by the Principal Investigator or Research Nurse at your recruiting hospital or a member of the TCC to check for any adverse events or the development of symptoms. This will be repeated up to 30 days after sample collection if there is an ongoing AE at 14 days after sample collection. If you have opted to not to provide your contact details, you will be opting out of follow up and will

not be able to be contacted by a member of the study team. Adverse events will be tabulated and reportec the TCC, Trial Steering Committee and relevant authorities for the purposes of participant safety. Adverse events occurring after the end of your participation (day 30) but before the end of the study will be listed separately.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will d their best to answer your questions (detailed above). If you remain unhappy and wish to complain formally you can do this by contacting the Research Governance and Integrity Officer, Patricia Henley at rgio@lshtm.ac.uk or +44 (0) 20 7927 2626

The London School of Hygiene and Tropical Medicine holds insurance policies which apply to this study. If y experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation

Who has reviewed this study?

ARCTEC (TCC) have obtained approval for this study from the National Institute for Health Research, the He and Safety Executive, LSHTM Ethics Committee and Animal Welfare and Ethics Review Board, Department Biosciences Ethics Committee at Durham University, the Health Regulatory Authority and the NHS Trust Research Ethics Committees for the participating hospitals. ARCTEC (TCC) will require a copy of the ethics approval letters before accepting participants into the study. The study will be conducted in accordance wi the recommendations for physicians involved in research on human participants adopted by the 18th Worl Medical Assembly, Helsinki 1964 and later revisions.

Recruiting Hospital Site or TCC: [To be pre-populated for each site]
Principal Investigator at site or TCC: [To be pre-populated for each site]

INFORMED CONSENT FORM

Full Name of Participant:	
Study Title:	Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.
Chief Investigator:	Professor James Logan, ARCTEC, London School of Hygiene & Tropical Medicine

	Please initial or tick box	
1. I confirm that I have read and understood the information on the Participant Information Sheet version 4.0 dated 12th October 2020 for this study. I have had the opportunity to consider the information, ask questions and have had these answered to my satisfaction.		
2. I understand fully the study process, nature and purpose of the samples to be collected and what is to be done.		
3. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason.		
4. I understand that sections of my data collected during the study will be shared with responsible individuals from the NHS, London School of Hygiene & Tropical Medicine, Durham University Medical Detection Dogs, Cardiff University and regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to access the data collected from me.		
5. I give my consent, where necessary, for the NHS to share the result of my coronavirus test with the Trial Coordinating Centre for the purposes of this study.		
6. I agree to follow all study guidance as detailed, for the safety of myself and others, and inform the Trial Coordinating Centre if I was unable to follow these instructions.		
7. I agree to take part in the above study.		
8. Did you have sufficient time to consider your options before consenting to participate?	YES	NO
9. OPTIONAL - I consent to my anonymised data being uploaded to a data repository for future research and I understand that the information/sample collected from me will be used to support other research in the future, and may be shared anonymously with other researchers, for their ethically-approved projects.		

Signature of Participant:		Date signed:	
Signature of consenting Researcher:		Date signed:	
Name of consenting Researcher			

********** **PARTICIPANT COPY** **********

Recruiting Hospital Site or TCC: [To be pre-populated for each site]
Principal Investigator at site or TCC: [To be pre-populated for each site]

INFORMED CONSENT FORM

Full Name of Participant:	
Study Title:	Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.
Chief Investigator:	Professor James Logan, ARCTEC, London School of Hygiene & Tropical Medicine

	Please initial or tick box	
1. I confirm that I have read and understood the information on the Participant Information Sheet version 4.0 dated 12th October 2020 for this study. I have had the opportunity to consider the information, ask questions and have had these answered to my satisfaction.		
2. I understand fully the study process, nature and purpose of the samples to be collected and what is to be done.		
3. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason.		
4. I understand that sections of my data collected during the study will be shared with responsible individuals from the NHS, London School of Hygiene & Tropical Medicine, Durham University, Medical Detection Dogs, Cardiff University and regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to access the data collected from me.		
5. I give my consent, where necessary, for the NHS to share the result of my coronavirus test with the Trial Coordinating Centre for the purposes of this study.		
6. I agree to follow all study guidance as detailed, for the safety of myself and others, and inform the Trial Coordinating Centre if I was unable to follow these instructions.		
7. I agree to take part in the above study.		
8. Did you have sufficient time to consider your options before consenting to participate?	YES	NO
9. OPTIONAL - I consent to my anonymised data being uploaded to a data repository for future research and I understand that the information/sample collected from me will be used to support other research in the future, and may be shared anonymously with other researchers, for their ethically-approved projects.		

Signature of Participant:		Date signed:	
Signature of consenting Researcher:		Date signed:	
Name of consenting Researcher			

********** **RESEARCHER COPY** **********

Recruiting Hospital Site or TCC: [To be pre-populated for each site]
Principal Investigator at site or TCC: [To be pre-populated for each site]

PARTICIPANT CONTACT DETAILS FORM

Full Name of Participant:	
Study Title:	Using medical-detection dogs to identify people with SARS-CoV-2. Phase I. Proof-of-concept studies.
Chief Investigator:	Professor James Logan, ARCTEC, London School of Hygiene & Tropical Medicine

Why do you need my contact details?

To enable us to contact you during the trial, we (the recruiting hospital or Trial Coordination Centre) ask that you provide your contact details. We will only contact you for the following reasons:

1. To ensure informed consent occurred (if consenting remotely) and all documentation/samples have been completed and received.
2. To follow up on your participation to check for any adverse events and symptoms (wellbeing check)
3. To inform you of the results of the trial
4. To arrange collection of samples if self-isolating and unable to store or post your samples.

If you would prefer not to provide your contact details, or would not like to be contacted, this would mean that we are unable to follow up with you to check your wellbeing, inform you of the results of the trial or arrange collection of your samples from you if you are self-isolating. If you received this pack from a walk-in test centre, or via the post, it may mean we are unable to access your test result or rectify any documentation issues.

This does not affect your ability or right to contact a study researcher at your recruiting hospital or the Trial Coordinating Centre. If you have any questions or concerns during your participation, please get in touch with a trial researcher using the details in the Participant Information Sheet.

Please choose **one** option below:

OPTION 1 - If you would like us to be able to contact you, please provide at least one of the details below.

I am happy to be contacted by a member of the study team by the following methods:				
	Tick	**Contact details**		
Telephone		Telephone number:		
Email		Email address:		
Post		Postal address: Postcode:		
Participant Signature			Date signed	

OPTION 2 - If you would not like us to be able to contact you, please opt out of participant follow up below.

	Tick	**Participant Signature**	**Date signed**
I do not wish to be contacted with regards to this study			

This form and all records of your contact details will be destroyed at the end of the trial and will not be stored with the trial data.

Appendix 7: Eligibility Questionnaire

ELIGIBILITY QUESTIONNAIRE
[To be completed by Participant]

Please answer the questions below to the best of your ability. Please do not leave any questions blank
Please use a blue or black pen and write clearly.

If participant is a patient, the form can be completed by the study researcher and reviewed by the participant.

1	**Date completed eligibility questionnaire** *(DD/MM/YYYY)*	D D	M M	Y Y Y Y	
2	**Participant Identification (PI) number** *(copy from label on sample pack)*				
3	**Biological sex** *(please circle one)*	Male	Female	Intersex	
4	**Date of birth** *(DD/MM/YYYY)*	D D	M M	Y Y Y Y	
5	**Ethnicity** *(please circle one)*	White	Black	Asian	Mixed/Other
6	**Please state the date of your coronavirus swab test.** *(DD/MM/YYYY)*	D D	M M	Y Y Y Y	
7	**Have you received the results of your swab test?** *(please circle one). Please provide a copy of your result to the site or TCC via e-mail or in the sample mailing bag when received.*	Positive	Negative	Inconclusive	No
8	**Swab test conducted via a** *(please circle one)*	Hospital Site	NHS Testing Centre	Other Testing Centre (please provide details)	
		NHS Home Test		Other Home Test (please provide details)	
9	**Who conducted the swab?** *(please circle one)*	Not yet done	Medical staff	Yourself, Family or Friend	
10	**Are you having/had a swab test because you:** *(please circle)*	have been exposed to COVID-19	have suspected COVID-19 symptoms	None of these reasons	
		are an NHS Staff member	are a household member of NHS staff		
11	**Do you currently have or had in the last 72 hours any of the following symptoms:** *(please circle)*				
A	A fever (37.8°C or higher at any point)	Yes	No		
B	A persistent cough	Yes	No		
C	Shortness of breath	Yes	No		
D	Muscle pain	Yes	No		
E	Joint pain	Yes	No		
F	Loss of or altered smell	Yes	No		
G	Loss of or altered taste	Yes	No		
H	Conjunctivitis	Yes	No		

ELIGIBILITY QUESTIONNAIRE
[To be completed by Participant]

I	Sore throat	Yes		No	
J	Abdominal pain	Yes		No	
K	Headache	Yes		No	
12	**Please state which medical treatments you have received for COVID-19 symptoms or none?** *(please circle)*	Paracetamol	Remdesavir	Dexamethasone	None
		Other (please state):			
13	**Are you currently on mechanical ventilation due to COVID-19 symptoms?** *(please circle)*	Yes		No	
14	**Are you receiving palliative care?** *(please circle)*	Yes		No	
15	**Are you an inpatient?** *(please circle one)*	Yes		No	
	Please state reason for admission:				
16	**Have you previously been diagnosed by a clinician as having COVID-19, prior to the swab test reported in question 6?** *(please circle)*	Yes		No	
17	**Have you previously been diagnosed by a laboratory test as being positive for Coronavirus, prior to the swab test reported in question 6?** *(please circle)*	Yes		No	
18	**Have you provided fully informed consent to participate?** *(please circle)*	Yes		No	
19	**Are you able and willing to wear a facemask for at least 3 hours?** *(please circle)*	Yes	No due to medical reasons	No	
20	**Are you able and willing to wear a shirt for at least 12 hours?** *(please circle)*	Yes	No due to medical reasons	No	
21	**Are you able and willing to wear a pair of nylon socks for at least 12 hours?** *(please circle)*	Yes		No	
22	**Are you able and willing to provide a copy of your coronavirus swab test result?** *(please circle)*	Yes		No	

ELIGIBILITY QUESTIONNAIRE
[To be completed by Study Researcher]

Eligibility Assessment				
	To be completed by delegated study staff			
1.	**Is this participant eligible to take part?** *(please circle)* Refer to eligibility tool below	Yes		No
If the participant is ineligible, please withdraw them from the study. If the eligibility is indeterminate, clarification from the participant may be sought.				
2.	***Who completed the eligibility questionnaire?*** *(please circle)*	Participant		Study Researcher
3.	***If the study researcher completed the questionnaire, did the participant review the form and confirmed accuracy?*** *(please circle)*	Yes	No	Not applicable
4	***If the participant is a patient, please confirm answer given to question 12 is accurate.*** *(please circle)*	No (please state why):		
		Yes		Not applicable
Study Researchers Name:				
Date of Eligibility Assessment:				

Eligibility Assessment Tool

Question	Eligible Answers	Ineligible/Indeterminate Answers
1	Date within recruitment range	Date not complete, date outside recruitment range
2	Participant ID fully completed	Participant ID not completed Reason: unable to identify participant accurately, if participant and their consent form is present, this can be completed.
3	Male, Female, Intersex	None Reason: This study is open to male, female and intersex individuals. The study population will be stratified for differences in male, female and intersex associated odours
4	Fully completed and aged 16 years or older	Incomplete or aged < 16 years Reason: Study is only open to those aged 16 years and older who are deemed be at to risk of COVID-19
5	White, Black, Asian, Mixed/Other	None Reason: This study is open to all ethnic groups. The study population will be stratified for differences in ethnic associated odours
6	Date is after date specified to question 1. Date is less than 72 hours before date specified to question 1. Date is greater than 72 hours before date specified to question 1 and participant received sample pack via the post.	Incomplete or date is more than 72 hours after the date specified to question 1 and didn't receive sample pack via the post. Reason: Participants must be due to have a swab test or have had a swab test conducted in the previous 72 hours. For remote recruitment additional time is allowed to factor in delivery of sample packs.
7	Positive, Negative, Inconclusive, No	Inclusive Reason: This study is open to positive and negative results.

8	Hospital site Testing Centre Home Test	None Reason: This study is open to all test types. Results may be stratified by means test was taken.
9	Not yet done Medical staff Yourself/Family/Friend	None Reason: This study is open to all methods of conducting the test. Results may be stratified by means test was conducted.
10	Been exposed to COVID-19, Suspected COVID-19 symptoms, An NHS staff Member, A Household member of NHS staff None of these reasons if answer to question 7 is positive	None of these reasons if answer to question 7 is negative or not received Reason: Not in a high-risk group of having COVID-19
11 (A-K)	Yes, No	None Reason: To determine if the participant has COVID-19 symptoms
12	All	Reason: The study population will be stratified for medical treatment for COVID-19 symptoms.
13	No	Yes Reason: Considered severe illness and therefore ineligible.
14	No	Yes Reason: Patients receiving palliative care are considered too ill to participate in this study
15	Yes, No	None Reason: This study is open to inpatients. The study population will be stratified for conditions leading to hospital admission.
16	No	Yes Reason: Prior COVID-19/Coronavirus infection is not being investigated in this study.
17	No	Yes Reason: Prior COVID-19/Coronavirus infection may have a different odour profile that is not being investigated in this study.
18	Yes	No Reason: All participants must provide written fully informed consent before participating
19	Yes, No due to medical reasons	No Reason: All participants must ideally be able to provide a breath odour sample during participation but those not able for medical reasons are still eligible to participate
20	Yes, No due to medical reasons	No Reason: All participants must ideally be able to provide a shirt odour sample during participation but those not able for medical reasons are still eligible to participate
21	Yes	No Reason: All participants must be able to provide a foot/skin odour sample during participation
22	Yes	No Reason: All participants must be able to provide a copy of their swab test results