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COVID-19 consortium (COVIDsortium): Healthcare worker Bioresource and preliminary analysis: Immune Protection and Pathogenesis in SARS-CoV-2

A study from the COVID-19 Research Strategy Oversight Group UCLH, plus Barts Hospital and Royal Free London NHS Foundation Trust.

V1.4: 21/09/2020 (current). Previous versions are available at [weblink](#).

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1. Abstract

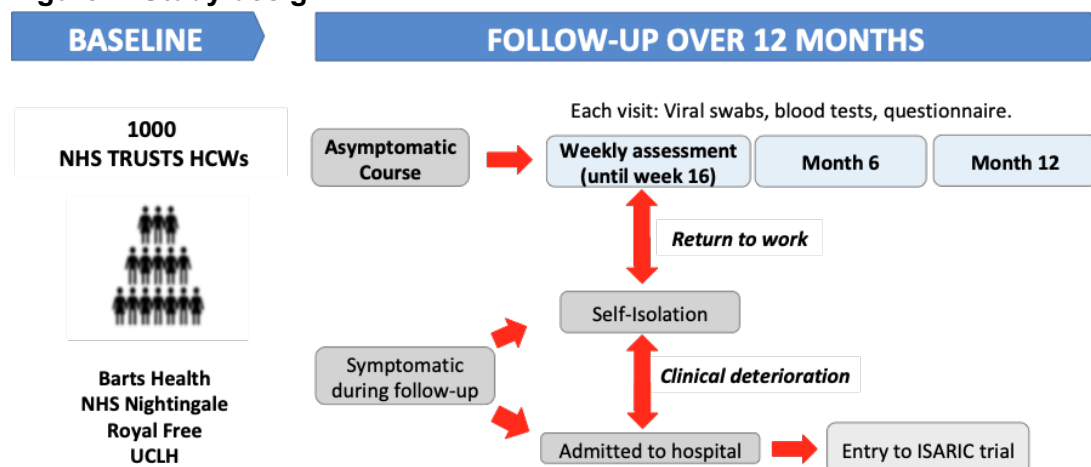
Modelling repurposed from pandemic influenza is currently informing all strategies for SARS-CoV-2 and the disease COVID-19. A customized disease specific understanding will be important to understand subsequent disease waves, vaccine development and therapeutics. For this reason, ISARIC (the International Severe Acute Respiratory and Emerging Infection Consortium) was set up in advance. This focuses on hospitalised and convalescent serum samples to understand severe illness and associated immune response.

However, many subjects are seroconverting with mild or even subclinical disease. Information is needed about subclinical infection, the significance of baseline immune status and the earliest immune changes that may occur in mild disease to compare with those of SARS-CoV-2. There is also a need to understand the vulnerability and response to COVID-19 of the NHS workforce of healthcare workers (HCWs). HCWs present a cohort with likely higher exposure and seroconversion rates than the general population, but who can be followed up with potential for serial testing enabling an insight into early disease and markers of risk for disease severity.

We have set up “**COVID-19: Healthcare worker Bioresource: Immune Protection and Pathogenesis in SARS-CoV-2**” (Figure 1). This urgent fieldwork aims to secure significant (n=1000) sampling of healthcare workers (demographics, swabs, blood sampling) at baseline, and weekly whilst they are well and attending work, with acute sampling (if hospitalised, via ISARIC, if their admission hospital is part of the ISARIC network) and convalescent samples post illness. We will also collect samples at 6 and 12 months from baseline to assess for persistence/ decay of immune protection. These will be used to address specific questions around the impact of baseline immune function, the earliest immune responses to infection, and the biology of those who get non-hospitalized disease for local research and as a national resource. A subset of participants will be invited to undertake in depth analysis of specific subsets of circulating immune cells that contribute to the immune response to the virus.

The proposal links directly with other ongoing ISARIC and community COVID projects sampling in children and the older age population.

Figure 1. Study design



Version 1.4 21/09/2020

2. Aims and Objectives

- To swiftly create the bioresource to understand baseline host factors and early responses that determine protection and pathogenesis in SARS-CoV-2 infection across NHS HCWs.
- to assess genetic influences on disease severity following infection with COVID-19 infection

Hypothesis

- Baseline immune status and early immune responses during subclinical phase of infection and including the pauci-symptomatic and seroconverters will mechanistically determine clinical outcomes in NHS HCWs.

Primary objective

Identify baseline and early immune responses that predict incident disease stratified by time interval to disease in NHS HCWs.

Secondary objectives

Identify immune responses that predict seroconversion in disease free NHS HCWs.

Identify genetic determinants of disease severity following infection with SARS CoV-2.

3. Links to other affiliated projects

This study substantially uses existing infrastructure: Recruits into this study who are subsequently suspected to have COVID-19 can be co-recruited into ISARIC using ISARIC Ethics Ref: 13/SC/0149 (Oxford C Research Ethics Committee, UK CRN /CPMS ID 14152 IRAS ID126600 for acute samples and data collection. Sampling can be delivered via existing research personnel from furloughed projects (CLRN nurses, research fellows, Barts Bioresource). Convalescent sampling will be via an otherwise inactive Clinical Trials unit. It links to 3 additional healthy cohort multi-time point surveillance projects:

- DELPHIC COVID-19 substudy (n=1000 healthy asymptomatic in Camden via the MRC Unit for Lifelong Health and Ageing at UCL): Ethics Ref: 13/SC/0149 (Oxford C Research Ethics Committee), UK CRN /CPMS ID 14152. IRAS ID126600

- SARS-CoV-2 Acquisition in Frontline Health Care Workers– Evaluation to Inform Response (SAFER) Study– submitted to HRA. This study focuses on healthcare worker behavior, risk perception and attitudes, correlating with subclinical virology and serology (monthly) as a seroconversion endpoint, rather than early immune responses)- PI Dr Eleni Nastouli/Dr Catherine Houlihan.

4. Methods

The proposed study is a prospective observational cohort design which will be carried out across three different trusts: Barts Health NHS Trust (St Bartholomew's Hospital, The Royal London Hospital, Whipps Cross Hospital and Newham Hospital and NHS Nightingale), Royal Free London NHS Foundation Trust (Royal Free Hospital) and University College London Hospitals NHS Foundation Trust (UCLH).

Participants will be asymptomatic front-facing HCWs who are involved with delivery of patient care in different areas of the corresponding hospitals above.

a) Study participants

We anticipate 1000 HCWs recruited from NHS trusts. Recruitment will be by hospital email, posters (Appendix 1), staff huddles, training session and participant information leaflets (Appendix 2). We consider "walk-in" centres to assess likelihood of participation. It will be important to ensure there is no coercion/social pressure on staff to participate.

All individuals will be working in the NHS Trusts listed above during the study period will be invited to participate (including nurses, doctors, health care assistants, pharmacists, ward clerk). We will also include participants who are redeployed to the NHS frontline and are working in clinical areas from other sectors due to the Coronavirus pandemic including: army workers, porters, cleaners, ambulance paramedics, etc.

Participation will be voluntary and there will be no remuneration. Members of the research team will attend the above mentioned clinical areas to invite eligible staff to enroll. Verbal and written information will be provided to eligible staff, which includes a study participant information sheet (Appendix 2). The following personal information will be requested: name of the participants, phone number, date of birth, email, home address and NHS number (confirmed from the former). Eligible staff will have an opportunity to discuss any details further with the research team prior to enrolment.

At the time of the original consent, participants were made aware that no clinical results will be available during the study. Since then, virus testing capacity has been expanded and antibody testing has been rolled out across NHS trusts. After consultation with participants, our sponsor (UCL) as well as the clinical and research leadership of our study sites, we would like to disclose all clinically-relevant validated diagnostic virus PCR and SARS-CoV-2 serology results to participants.

On the 22nd of May 2020, we obtained written permission from the Chair of the research ethics committee Oxford A; see appendix) to offer participants the opportunity to receive results available at the time (the first five weeks of the study in the first 400 participants) and to ask if they wished occupational health to be informed (see email in Appendix 6). All participants were contacted on 22nd May 2020. To date >60% of participants requested access to their previous results.

In this substantial amendment (#2; 08/06/2020), we will therefore offer participants the disclosure of results that:

a) have potential specific implications for participant health and well-being (as per initial ethics consent form) based on current knowledge.

b) use validated diagnostic test platforms.

For the sake of clarity, this means disclosure of SARS-CoV-2 antibody testing done with commercial assays in a diagnostically accredited laboratory; virus PCR results. Non-disclosure: assays performed solely in non-clinical / research setting - for example saliva test development results, experimental neutralising antibody results, transcriptomics results, non-approved micronutrient assays, pathogen genome sequencing, B or T cell characterisation results.

All results disclosed will be provided in writing (NHS email) when they become available and accompanied by written clinical advice.

Should we achieve a position where PCR results are anticipated to be available within 8 days of sampling, then participants will be informed at their follow-up visit prior to nasal swab sampling that this is possible, and that any positive results available within 8 days will be disclosed to the participant and occupational health (due to local infection control risks). This is in line with other recent HCW studies during COVID-19 (Rivett et al 2020). If the participant has concerns about potential occupational health involvement they can be offered to withdraw only from the viral PCR swab component of the study.

Should local laboratory workflows and capacity not enable results to be available within 8 days, disclosure to Occupational health will not be made as there will be no public health/ institutional implications.

Signed informed consent (Appendix 3) will be obtained from all participants prior to inclusion. RedCap data collection instruments are in appendix 4.

Inclusion criteria:

- Age at least 18 years AND

- Asymptomatic (meaning healthy enough to attend work according to Trust policy at the time)
AND

- Work in the designated clinical environments for at least 5 hours for at least one day during the study period.

Participants will be free to withdraw from the study at any point, but collection of these data is considered to be in the public interest and will fall under the scope of a 'Public task' by the GDPR definition. Under these conditions rights to erasure and data portability do not apply, and archiving and further processing for scientific research purposes is compatible with the original purpose; no further participant data from medical records will be collected.

The research team may withdraw a participant from the study in the following situations:

- No longer meets the inclusion/exclusion criteria if participants circumstance change

b) Study period

The study period is 12 months, with baseline data collection and subsequent weekly sample and data collection for 16 weeks (until after the predicted peak of the pandemic in London). Data and samples will also be collected at 6 and 12 months (post-baseline) to monitor duration of protective immunity (i.e. decay in immunoprotection).

c) Sample Size

We have designed a primary analysis around a baseline frequency of infection of less than 0.2% average over recruitment period and a seroconversion rate of 30% of which 10% will be hospitalised and potentially enter ISARIC. However, this sample will link to other studies and the responses we are seeking are emergent and unknown. The incidence of SARS-CoV-2 among HCW (either symptomatic or asymptomatic) is not known and thus sample size calculations are challenging. The basic reproduction number (R_0) of this virus is assumed to be between 2 and 3, but one cannot estimate the number of patients admitted and the effectiveness of staff protection measures. The original sample size of $n=400$ was chosen for pragmatic reasons. The lead site (Barts) recruited 400 participants in just over 7 working days. In order to be powered to identify genetic determinants of SARS CoV-2 infection disease severity a larger cohort is required; a sample size of $n=1000$ is considered to have sufficient power for assessing for genetic influences and feasible given the rapid recruitment rates at the Barts site.

We anticipate using multiple sites to secure staff participation to 1000, subject to local site approval. Should it be possible with sufficient interest, staff and consumables, this number will be expanded. Furthermore, if there is sufficient interest in study participation, recruitment will be stratified by sampling by sex, age and ethnicity. Currently age categories proposed are between 25-40, >40-55, >55.

d) Study design

A baseline questionnaire and sample collection will be performed, followed by weekly resampling (Figure 1) for 16 weeks, and two additional visits at 6 and 12 months time.

1 Baseline questionnaire

Consented study participants will complete a brief baseline questionnaire which collects standard variables related to demographics (including household size and details), anthropometry, past medical history including drug and vaccination history and SARS-CoV-2 symptoms, exposure and prior testing, and contact history including details of work-based exposure and personal protective equipment used. See Appendix 4 (RedCap eCRF) for details.

2 Baseline sample collection

We aim to capture pre-infection levels of several markers (and how they evolve), including but not restricted to immune cell population (e.g., pre-infection antibody levels against other coronaviruses might influence host response to SARS-CoV-2), genomic and transcriptomic profiles. Sample collection will include:

a. Nose swabs: Nose swabs will be performed at baseline and weekly for the duration of the study. Participants will self-swab to minimise the risk of potential contamination or aerosolisation. Swab samples will be collected from a designated collection point by the research staff and submitted to the designated laboratory at each site within 48 hours of collection. Only staff who are asymptomatic and not currently self-isolating at home will be recruited for baseline sample collection.

b. Blood samples (summarized in Table 1):

- Blood samples collected at baseline will consist of 1 x blue PAXgene RNA (2.5ml), 2 x yellow biochemistry gel tube (6ml), 2 purple EDTA plasma (5ml) and 1 purple EDTA DNA (5ml) totalling 29.5mL. Research staff will arrange blood sample collection in the hospital at a conveniently accessible location and at a suitable time for the participant. Blood samples will be stored at -20, 40 or 80°F for the first week until delivery to secure -80C. Processing, aliquoting and analysis will be handled outside this fieldwork application.
- In the case of blood sample failure (vacuum partially gone, iv access only partial success, processing failure) we will ask the participant for a second sample (re-bleed request) if this is practically possible (e.g. immediately or at next scheduled follow-up; total <30mL).

c. Saliva sample (summarized in Table 1):

- We will ask participants to pool 2-3mL of saliva into commercially used saliva collection tube (see diagram on the right). This system is designed to prevent leak/ spillage and consists of the tube with an attached funnel and flip-top lid.
- Saliva contains most of the same antibodies, proteins and nucleic acid markers that can be found in blood. We will use an ultrasensitive measurement technology, with single molecule sensitivity which enables even very low levels of molecular marker to be quantified. Only small quantities of saliva are needed for each test; the aim is to validate this test on COVID-19 and deliver High Throughput assay technology that can be used for the detection of IgM, IgG and IgA in saliva against SARS-CoV-2 with high reliability and precision.

3 Interval questionnaire and sampling

Following recruitment all participants will undertake weekly swabs, blood sampling and health questionnaire assessments. Additional questions that may be asked at this point include questions related to new symptoms, coronavirus test results (where relevant), new exposures, sense of smell (detailed validated smell questionnaire in collaboration with Mr Matt Lechner, Associate Professor ENT Surgery and Head and Neck Cancer Research, UCL) and other potential influences on disease severity (exercise, hormone status, micronutrients).

Depending on the participant's status progression (see Figure 1) such follow-up will take place in either of 3 places: at the workplace i.e. Barts (if well and attending work), in the ward/intensive care unit (if SARS-CoV-2 positive and admitted to hospital) or at home (if SARS-CoV-2 positive and self-isolating at home).

Four types of status progression are predicted for enrolled participants:

3.1) Asymptomatic course without exposure to SARS-CoV-2 positive cases necessitating isolation– samples will continue to be collected while at work in-hospital, by research staff.

Participants will be serially screened for any symptoms consistent with SARS-CoV-2 , e.g. fever, continuous cough, shortness of breath. *If COVID-19 prevalence in the community and among HCW is low, the study team may reduce the sampling frequency to alternate weeks. Participants will be informed about this change in the weekly appointment message (email / text / whatsapp depending on preference).*

3.1a) Nasal Swab: A nasal swab will be taken on each weekly follow-up.

3.1b) Follow-up blood sampling: Blood samples collected at weekly intervals (8.5mL - 1 x blue PAXgene RNA [2.5ml] + 1 x yellow biochemistry gel tube [6ml]).

- **Week 4,8,12,16:** We will take an additional 1x EDTA for PBMCs at month 1,2,3,4 (+5mls).
- At 6 months and 12 months follow-up, 50mL of blood will be taken: Serum (6mL), plasma (6mL), RNA pax (2.5mL), peripheral blood mononuclear cells (PBMC) for T cell response and neutralisation (35mL).

3.1c) A saliva sample will also be taken at the first possible time point after ethics approval for baseline (baseline or week 4-6). In participants that are PCR or antibody positive (after disclosure), we would like to invite participants to increase frequency of saliva sampling to weekly to understand test performance over time. Consumables and a research nurse to cover this additional work are already in place. Saliva samples will also be collected at 6 months and 12 months.

Table 1: List of laboratory samples to be taken during the study: Baseline and Follow-up

	Volume (in mL)	Baseline	Week 2+3	Week 4	Week 5-7	Week 8	Week 9-11	Week 12	Week 13-15	Week 16	Month 6	Month 12	*Convalescence (replacing scheduled collection)	Optional Home Visit
Nasal Swab		1	1	1	1	1	1	1	1	1	1	1	1	1
Saliva				1	0	0	0	0	0	0	1	1	1	1
Purple DNA	5	1	0	0	0	0	0	0	0	0	0	0	0	0
Purple PBMC/Plasma	5	2	0	1	0	1	0	1	0	1	7	7	1	0
Blue Pax RNA	2.5	1	1	1	1	1	1	1	1	1	1	1	1	0
Yellow Serum	6	2	1	1	1	1	1	1	1	1	2	2	2	0
Volumes/visit		29.5	8.5	13.5	8.5	13.5	8.5	13.5	8.5	13.5	49.5	49.5	19.5	0
Total over 6 months	287													
*Convalescence visit = first visit after self-isolation with symptoms														

Table 2. List of key samples to be collected and planned laboratory procedures.

Biosample type [Time points]	Processing [Volume]	Key analyte [Analysis laboratory]
Nasal swab [Baseline & F/U]	Freeze -80°C	Molecular testing for SARS-CoV-2 ± other pathogens [UCLH virology lab]
Saliva sample [Week 4, convalescent, 2x at months 6 and 12]	Freeze -80°C	Molecular testing for SARS-CoV-2 ± other pathogens
Serum tube [Baseline, all follow ups, convalescent]	Analyse	SARS-CoV-2 antibody testing i.e. IgG, IgM

PAX RNA gene tube [Baseline, all follow ups, convalescent]	Freeze -80°C	Transcriptomics
PAX DNA gene tube [Baseline only]	Freeze -80°C	Genetics

F/U = follow-up. Other abbreviations see main text.

3.2) Symptomatic course or suspected (not-confirmed) SARS-CoV-2 infection

necessitating self-isolation at home– we will record the number of days participants remain away from work, any treatment received, and whether they receive a formal SARS-CoV-2 diagnosis as the result of routine clinical testing. During their illness, they will be advised to follow Public Health England national guidance and will be assessed and treated by routine clinical services, as required. We will offer the participants to opt-in to have a swab and saliva collection tube sent to their home address for self-sampling.

On the first return after a symptomatic course of suspected (not-confirmed) SARS-CoV-2 infection necessitating self-isolation at home, they rejoin the sampling scheme as detailed in 3.1. On this visit we will take an additional 11mL blood (1 x biochemistry; 1 x EDTA for PBMCs = total 19.5mL) and a saliva sample.

3.3) SARS-CoV-2 positive participants admitted to hospital– participants with a confirmed SARS-CoV-2 positivity diagnosis (on the basis of research or clinically mediated testing) will be asked to report this to the study team. At the point of hospital admission, such participants automatically enter the ISARIC trial for subsequent sample collection and analysis.

3.4) Target blood donation in selected participants: A specific objective of the bioresource is to provide the opportunity to undertake further in depth analysis of immune responses to SARS-CoV-2 in selected participants on the basis of demographic, clinical and laboratory characteristics during the follow up period. We will invite individuals to attend an additional study visit to give one extra blood sample of up to 120 mL. This volume of blood is equivalent to one quarter of the volume donated to routine blood bank service in the UK. This volume is necessary to undertake in depth analysis of specific subsets of circulating immune cells that contribute to the immune response to the virus. Requests for participant recall by investigators will be made in writing to the bioresource steering group, who will be responsible for ensuring that the request is within the scope of the aims of the bioresource, and responsible for inviting the participants for the additional sample. Participants will be free to decline this additional sample without giving a reason and without affecting their participation in the remainder of the study.

3.5) Cardiovascular Substudy:

As the vast majority of infected participants have been pauci- or asymptomatic, this data will be important to contrast the cardiovascular effects of COVID-19 in hospitalised patients requiring simple oxygen or critical care treatment. This data will be compiled as part of the European CARTESIAN Consortium (Covid-19 effects on **ARTE**rial **Stiffness** and vascular **AgeiNg** Study). These adverse vascular effects of COVID-19 are likely to result in lasting damage to the vasculature and accelerated vascular aging. These vascular effects can be assessed using simple non-invasive tests. Identifying the presence, the causes and progression of early vascular ageing in COVID-19 patients will improve cardiovascular risk assessment and patient management. If participants agree to take part, they will undergo non-invasive measurement of pulse wave velocity, central and peripheral blood pressure (15 minutes) at the three or six and twelve months visits:

- Resting clinic brachial BP and pulse readings will be taken using a Sphygmocor device. Central blood pressure will be estimated by pulse wave analysis (PWA).
- Vascular stiffness will be assessed by carotid-femoral Pulse Wave Velocity (PWV) measurement using a Vicorder device.

Safety measures related to staff, research team members, recruited participants are detailed in section 6 (“Duty of care”).

4 Sample and data collection

After sample collection all vials/tubes will be consolidated in a transport bag. Only the EDTA tube for PBMCs (peripheral blood mononuclear cells) will be spun (by Professor Aine Mcknight, QMUL) to reduce the risk to staff processing samples. All other tubes and nasal swabs will be frozen in the same gel separator tube used for sample collection immediately at -80 degrees on site. Table 2 details the sampling strategy.

Data collection instruments are in RedCap and based on those of ISARIC. Specific questions related to immune status and home/work exposure are included in the eCRF. (appendix 4).

5 Biosample procedures (as per Trust policy and PPE guidance)

Obtaining baseline nasal swab samples

- Wear designated aprons, surgical masks and visors.
- Apply alcohol gel to hands and then apply fresh gloves.
- Explain procedure clearly to HCW.
- Label the sample tube with the appropriate participant number.
- Ask participants to open their mouths and say “ahhh”.
- Swab nostril and/or posterior pharynx (for the latter avoid saliva and tongue, rotating swab covering left and right faucial pillars).
- Place COPAN swab immediately into a sterile tube containing 2-3 ml of viral transport media.
- Follow the instructions in section below for transport of samples.

Obtaining baseline blood samples

- No sharp should be exposed/unsheathed without the necessary sharps container available in which to discard it.
- Label the blood tube with the appropriate participant number.
- Identify the vein and clean the overlying skin with a chlorhexidine skin swab. Discard in a clinical waste bag.
- Using the BD vacutainer push button blood collection set with pre-attached holder, insert needle into identified vein. Then attach to the vacutainer system:
 - o 5ml yellow topped serum blood collection tube x 2
 - o 5ml purple topped EDTA blood collection tube x 2
 - o 2.5ml PAXgeneRNA blood collection tube
- Once the blood tubes are full, remove the tube from the collection system, place in 2 leak proof bags with absorbent material (Safety gel granules) and seal.
 - Press the push button on the blood collection system and the needle will retract from the vein into the plastic receptacle, ensuring a completely sharp safe system.
 - Discard the used blood collection system into the sharps container.
 - Discard any gauze used to stop bleeding into the clinical waste bag.
 - Follow the instructions in section below for containment of samples for transport.

Post-sampling

All samples at the point of sampling should have been placed in a leak proof bag with absorbent material (safety gel granules) and sealed. Following this:

- Ensure the specimen bag is tightly sealed and wipes the outside of the bag with a Medical high level disinfectant wipe. They then discard the wipe in a clinical waste bag.
- Once sample collection is complete and samples are contained within their respective transport packs, personal protective equipment can be removed.
- Ensure a heavy duty clinical waste bag is available for disposal of waste.
- Clean gloves with alcohol gel.
- Tear apron ties and remove apron by folding in on itself, discard in waste bag
- Remove mask and visor by snapping ties and pulling forwards, then discard in a clinical waste bag.
- Remove gloves inside out without skin touching the outer aspect of the glove. Discard in the waste bag.
- Clean hands with alcohol gel.

All waste to be disposed of at recruiting hospitals according to PHE recommendations.

6 Follow-up: Subjects will be assessed weekly until 16 weeks, with a further visit at 6 months and 12 months from baseline visit. Follow-up sampling will consist of one nasal swab, blood and saliva sample collection as per Table 1.

In the event of participants being unable to attend for a follow-up visit (reasons might include being re-deployed to work at a different site, shifts preventing visits, self-isolation due to household symptoms, self-isolation due to infection), that visit will be omitted and the participant will attend the next scheduled visit.

If home-self isolation occurs due to symptoms, and subjects have consented to opt-in to self-collection of nasal swabs and saliva, participants will be couriered the appropriate means to collect these samples. These samples will be collected by the study team and returned to the study laboratory using appropriate infection control procedures.

When participants return to work following self-isolation due to symptoms, sample collection will include additional samples to capture convalescent serology including sputum collection.

6. Duty of Care

Usually for a study like this, all participants will receive clinical advice on managing any symptoms through the Chief Investigator as well as any clinically actionable results from FBC, U&E, CRP. Here however, with a rapidly evolving situation, recruited staff will use the same advice channels as all other staff in line with NHS/ Public Health England recommendations.

e) Safety: Potential Harm and Risks

Study participants: This is a study recruiting HCW who are well and attending work. They are therefore self-declaring as asymptomatic, and are attending a “dirty” healthcare environment. Swabs are the standard COPAN nasal flu swabs and are not considered a coughing risk with training. Blood sample collection may cause slight bruising at the venepuncture site, but weekly sampling is not an unusual sampling periodicity. The total blood volume at baseline is estimated at ~30mL. As with all staff recruitment projects, there is concern about coercion to enrol. To mitigate against this we are following the Barts “Guidance on obtaining and using human blood and tissue from healthy volunteers for research purposes”.

Research staff: At enrolment study participants will consist of well and asymptomatic HCWs attending work, but during subsequent follow-up HCWs may well develop symptoms or a formal SARS-CoV-2 diagnosis. No participants should be attending if symptomatic as they should not be working. Protection of research staff collecting samples will consist of surgical masks, visor, gloves and apron implying minimal consumption of PPE as the visor and surgical mask can be reused by one nurse for multiple encounters whilst gloves will be changed each time. This will be as per Trust policy. Staff will train participants to obtain their own nasal swabs to minimise the risk of staff exposure and maximise yield. Saliva collection is via commercially-available kits to minimise potential for spillage.

Sampling strategy: This has been designed to be as safe as possible for maximum scientific yield, and to minimise burden on stretched infrastructure. This means: no sampling of symptomatic subjects or of HCWs once they begin self-isolation or after confirmation of SARS-CoV-2 positivity. No complex sample processing (no opening of tubes – no aliquoting, no lymphocyte isolation, no use of staff needed by PHE or NHS labs). Spinning is routine for multiple epidemiological studies and done in a sample preparation room, not category 2 lab. All samples can be batch spun (e.g. morning and evening). We note also that for coronavirus, blood is substantially virus free. Appropriate practice will be implemented in case of blood spills.

Hospital infrastructure: Staffing will be stretched. For this project we anticipate around 10 staff being used. At Barts, this will be 6 staff. This compares to an employee base of 15,500 (ie

assuming one third at work clinically, this study consumes 0.1% of staff time. The attendance for bloods is estimated at 15 minutes. The space needed is 2 rooms for blood tests and 1 sample prep room per site for 50 subjects/day. At BHC for example, this would be the ante rooms of the MRI scanners (2 of which will be mothballed so the space is not otherwise used and has sinks and reclining chairs for blood sampling). We identify a clean route for travel to the site. We have multiple sites with centrifuges and local -40 or -80 freezers for interim sample storage.

Contingency: Staff from UCL Lifelong health and aging are available to help recruitment/ follow-up should other staff not be available. Funding redundancy has been requested.

f) Dissemination of results

At completion of the study, findings will be disseminated to all participants, to the hospital management and relevant groups (for example, infection control), and to all hospital staff at arranged open meetings. It is anticipated that the samples will be analysed at the end of the project, so it will not be possible for individual staff members to be identified as having tested positive (or negative) for SARS-CoV-2 or immune response during this project. Individual staff members who are interested in their personal results will be able to access these via the study nurse or PI at the end of the study.

g) Ethics: Ethical approval for the study is in place from the NHS Health Research Authority Research Ethics Committee and University College London Ethics board.

h) Sample access: Samples will be coordinated by Professor Madhad Noursadeghi locally. We expect to make these nationally available subject to a process that maximises yield for society.

i) Review process: Approvals are documented in appendix 7: Local review has been at Barts (Peer review group Riyaz Patel, Andrew Wragg), UCL (Professor Pier Lambiase and Alun Hughes), and JRMO (Professor Steffen Petersen)

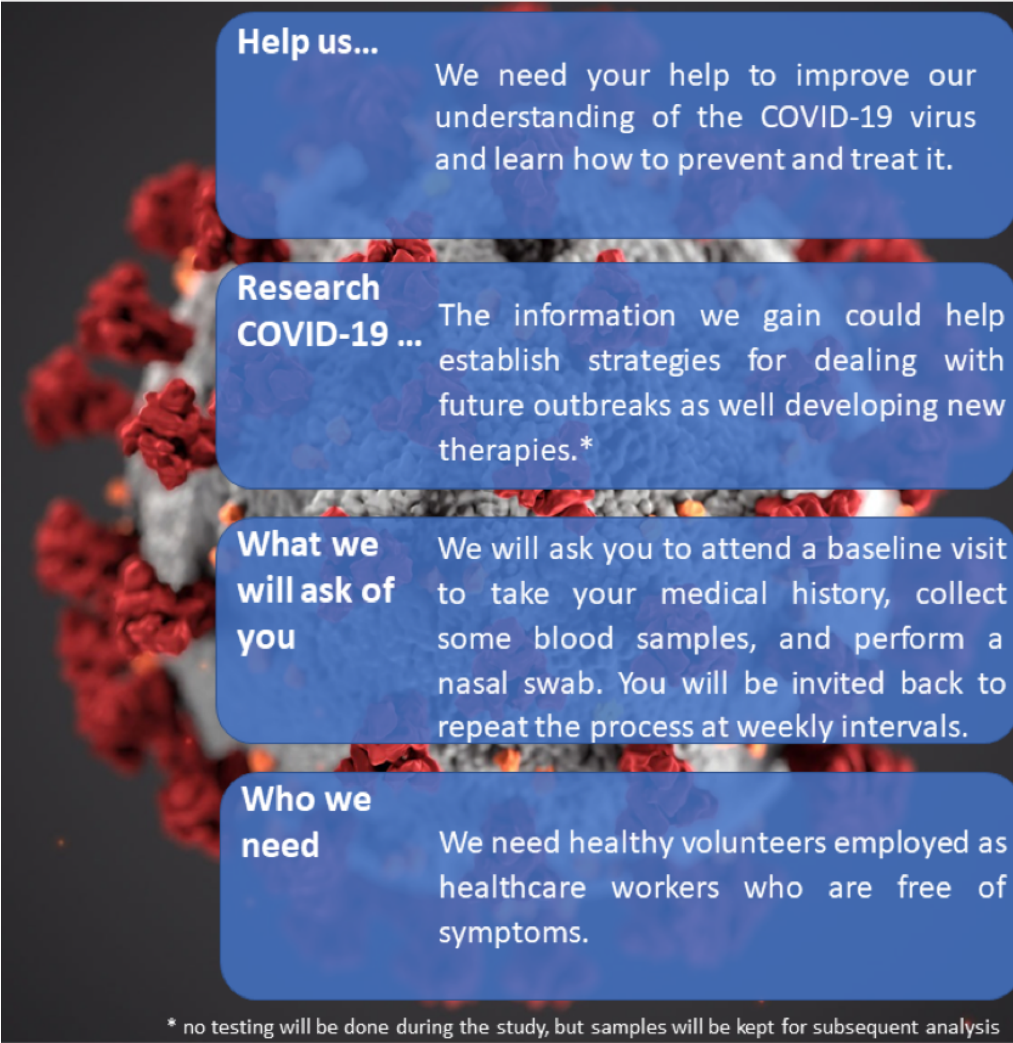
There has been additional review and approval by the Barts COVID-19 Research Committee (chair Professor Rupert Pearse) in conjunction with Barts JRMO - contact Mays Jawad, Governance operations manager JRMO M.jawad@qmul.ac.uk

References

1. ISARIC documentation, downloaded here https://www.dropbox.com/sh/2risg0y9tImakit/AAAxXJ21kAjDMwLCpAD_kmvUa/branches/England/v8.2?dl=0&subfolder_nav_tracking=1
2. Barts and QMUL Guidance on obtaining and using human blood and tissue from healthy volunteers for research purposes v1.0. Created 14/1/2020, author Amy Shou, available from the authors.

Healthy volunteers
needed

for research into COVID-19



Help us... We need your help to improve our understanding of the COVID-19 virus and learn how to prevent and treat it.

Research COVID-19 ... The information we gain could help establish strategies for dealing with future outbreaks as well developing new therapies.*

What we will ask of you We will ask you to attend a baseline visit to take your medical history, collect some blood samples, and perform a nasal swab. You will be invited back to repeat the process at weekly intervals.

Who we need We need healthy volunteers employed as healthcare workers who are free of symptoms.

* no testing will be done during the study, but samples will be kept for subsequent analysis

To volunteer, or for further information, please contact XXXX (XXX@nhs.net) or visit the cardiac imaging department, 2nd floor King George V building, St Bartholomew's Hospital



ADD PIS AND CONSENT AS APPENDIX 3 & 4

Appendix 4. RedCap data Collection

See document with highlighted changes attached

Appendix 5. Biosample procedures

1. Obtaining nasal swab samples

- Apply alcohol gel to hands and then apply fresh gloves.
- Explain procedure clearly to participants and explain that they will be collecting their own swabs and need to swab each nostril for 15 seconds etc.
- Label the sample tube with the appropriate participant number.
- Ask the participants to collect their own samples
- Place COPAN swabs immediately into sterile tubes containing 2-3 ml of viral transport media.
- Then follow the instructions in the section below for transport of samples.

2. Obtaining blood samples

- NO sharp should be exposed/unsheathed without the necessary sharps container available in which to discard it.
- Label the blood tube with the appropriate participant number.
- Identify the vein and clean the overlying skin with a chlorhexidine skin swab. Discard in a clinical waste bag.
- Using the BD vacutainer push button blood collection set with pre-attached holder, insert needle into identified vein. Then attach to the vacutainer system and collect the blood bottles outlined in Table 1
- Once the blood tubes are full, remove the tube from the collection system, place in 2 leak proof bags with absorbent material (Safety gel granules) and seal.
- Press the push button on the blood collection system and the needle will retract from the vein into the plastic receptacle, ensuring a completely sharp safe system.
- Discard the used blood collection system into the sharps container.
- Discard any gauze used to stop bleeding into the clinical waste bag.
- Follow the instructions in the section below for containment of samples for transport.

3. Obtain saliva sample: collection kit including OmniGene 505 collection tube; a biohazard bag.

Donation should typically take less than 5 minutes:

- I. Do NOT remove the plastic film from the funnel lid.
- II. Allow saliva to pool under the tongue.

- III. With the head tilted forwards, gently guide saliva from the mouth into the collection tube. This way, a clear, non-foaming liquid is produced.
- IV. Spit into funnel until the amount of liquid (not bubbles) reaches the fill line shown in the picture below.
- V. Do not close the funnel lid. Hold the tube upright. Unscrew the funnel from the tube.
- VI. Use the small cap to close the tube tightly. Discard the funnel.
- VII. Place the tube into the biohazard bag and seal it closed. Place the biohazard bag into the fridge until collection.

4. Post-sampling

- All samples at the point of sampling should have been placed in a leak proof bag and sealed.

Following this:

- Once sample collection is complete and samples are contained within their respective transport packs, personal protective equipment can be removed.
- Ensure a heavy duty clinical waste bag is available for disposal of waste.
- Clean gloves with alcohol gel.
- Tear apron ties and remove apron by folding in on itself, discard in waste bag
- Clean gloves with alcohol gel.
- Remove mask and visor by snapping ties and pulling forwards, then discard in a clinical waste bag.
- Remove gloves inside out without skin touching the outer aspect of the glove. Discard in the waste bag.
- Clean hands with alcohol gel.

Sample storage at source

- After all home visits have been conducted, samples may be consolidated in the transport bag.
- Samples of direct clinical relevance will be sent to UCLH NHS laboratory and actioned clinically within 48 hours.
- COPAN oropharyngeal swabs in symptomatic patients (c/o Dr Eleni Nastouli, Consultant Virologist, UCLH) for SARS-CoV-2 and other routine respiratory virus testing.
- Full blood count (FBC), urea and electrolytes (U&E), C reactive protein (CRP) (serum tube no. 1, EDTA tube no. 1.)
- Research samples will be transferred to Imperial College Infectious Diseases research laboratory (c/o Professor Michael Levin, Imperial College).
 - Samples will be delivered at the end of each working day.

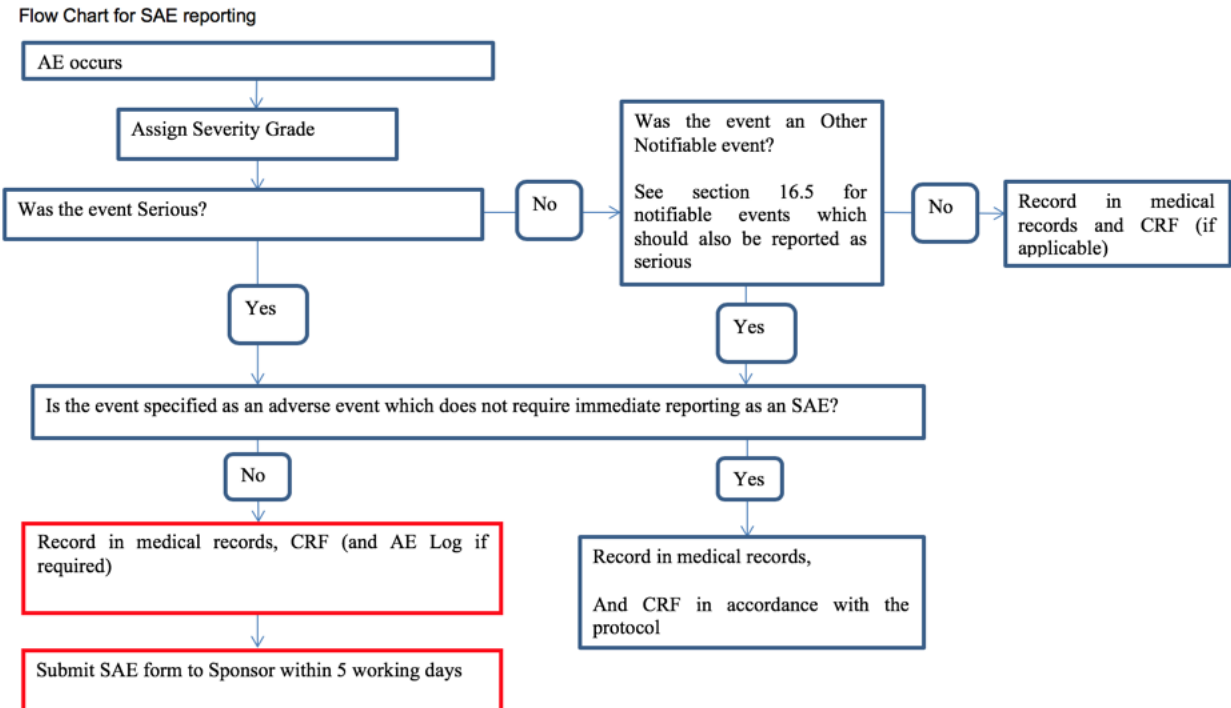
Hospitalisation

In the event a participant is hospitalised, we ask that the team is informed, and that they tell the admitting hospital highlight that they are in this project, and request that they be recruited to the main ISARIC protocol where appropriate. Local ISARIC teams and this project will liaise re collection of convalescent samples.

Data management and sharing

All data will continue to be collected using existing RedCap infrastructure used at UCL and QMUL (AIMES hosted). All data is pseudoanonymised with no personal identifiable information available, with a participant identification number assigned to each participant for identification purposes on REDCAP. The key linking participant identification number with participant identifiable data will be stored on the research drive on the relevant NHS Trust Server.

Appendix 6. Flow Chart for SAE reporting



Appendix 7: Endorsements and approvals

From: Hugh Davies <hughtdavies@gmail.com>

Sent: 22 May 2020 19:32

To: MOON, James (BARTS HEALTH NHS TRUST)

Subject: Re: Fw: COVID19- Healthcare worker Bioresource: Immune Protection and Pathogenesis in SARS-CoV-2 Study

Dear James

Thank you for your email.

You ask

"Please may I be permitted to inform participants and their employers of the historic results?"

As chair of the Oxford A REC, acting urgently, I would agree that the participants should be asked if they wish to be told their historic results now they are available and also asked if they wish occupational health to be informed. They should also be told that if they wish to seek advice on these results then they should contact the Employee Well being service (number provided).

This I think is a proportionate approach.

I hope this helps and that this important study can continue.

With best wishes

Hugh Davies
Chair Oxford A REC

Professor Alun Hughes

12:39 PM (28 minutes ago)

Hughes, Alun via@liveuclac.onmicrosoft.com

Sorry forgot to say that the MRC unit for Lifelong Health and Aging will be happy to assist through re-deployment of their clinic staff if required.

I've discussed it with Nish

BW Professor Alun Hughes

Professor Pier Lambiase

Re: COVID-19: Healthcare worker Bioresource and preliminary analysis: Immu

Lambiase, Pier via@liveuclac.onmicrosoft.com
to james@moonmail.co.uk, Steffen

Dear Professor Moon,

I fully approve this important and timely project and submit that I can provide the research nurse and team resource:

BW

Professor Pier Lambiase PhD FRCP FHRM
Professor of Cardiology, UCL & Barts Heart Centre
Co-Director of Cardiovascular Research Barts NHS Trust
Inherited Arrhythmia Clinical Lead
UCL MRC DTP Theme Lead
BHRS Committee Research Lead
Institute of Cardiovascular Science, UCL
Dept of Cardiology, Barts Heart Centre

From: James Moon <james@moonmail.co.uk>
Sent: 16 March 2020 13:28
To: Lambiase, Pier <p.lambiase@ucl.ac.uk>
Subject: urgent review.

here is document
here is ISARIC. <https://isaric.tohn.org/>
do please send comments and write to me saying I approve (in your role)
submission at 4-m
Professor James Moon
Lead, CMR, Barts Heart Centre and UCL
Tel [+447801283812](tel:+447801283812)



On Mon, Mar 16, 2020 at 4:02 PM Steffen Petersen <s.e.petersen@qmul.ac.uk> wrote:

Dear James, I am supportive of this research proposal of the COVIDsortium.

This is a low risk study, this is very important from a research point of view. It has been peer reviewed at Barts Heart Centre (Dr Patel).

If you have any further questions, please do let me know.

Good luck with your submission to HRA. Barts Joint Research Management Office (JRMO) are aware and will look into site approval once we hear back from HRA.

Best wishes, Steffen

Steffen E. Petersen, MSc MPH MD DPhil SFHEA FRCP FSCMR FEACVI FESC FACC
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Honorary Consultant Cardiologist,
Co-Director for Research, Cardiovascular Clinical Board, Barts Health NHS Trust

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European Association of Cardiovascular Imaging (EACVI)

European Society of Cardiology (ESC)

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