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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 13, 2020, and further correction has been made on November 19, 2020.

Supplement to: Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; published online July 20. http://dx.doi.org/10.1016/S0140-6736(20)31604-4.

COV001 ChAdOx1-nCoV19 Vaccine Trial Clinical Study Plan Documents

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ABBREVIATIONS and DEFINITIONS

ABHR	Alcohol based hand rub
Ab	Antibody
ACR	Albumin creatinine ratio
ADL	Activities of Daily living - daily self-care activities usually undertaken by participant
AE	Adverse Event
AESI	Adverse Events of Special Interest
Ag	Antigen
ALT	Alanine transaminase
ALP	Alkaline phosphatase
BMI	Body Mass Index
CRF	Case Report Form (paper version)
CFS	Clinical Frailty Score
CSP	Clinical Study Plan
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRG	Clinical Trials and Research Governance
DHSC	Department of Health and Social Care (UK government)
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form [on RED Cap]
EDTA	Ethylenediaminetetraacetic acid
EMIS	Egton Medical Information Systems, UK electronic patient record system
FFP3	Filtering face piece class 3 respirator
FRSM	Fluid-resistant surgical mask
GMO	Genetically modified organism
GP	General Practitioner
HBV	Hepatitis B virus
HCP	Health Care Professional
HCV	Hepatitis C virus
HCW	Health Care Worker
HIV	Human immunodeficiency virus
ICF	Informed consent form
ID	Identity document
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
Location	Location where clinics will take place
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
OLS	Office of Life Sciences
OPD	Outpatients Department
OVC	Oxford Vaccine Centre
P7	Clinic visit 7 days after positive S0 swab
PI	Principal Investigator
PIS	Participant Information Sheet
PMD	Participant Management Database
PPE	Personal Protective Equipment
PHE	Public Health England
PCR	Polymerase chain reaction
PST	Plasma separator tube
QA	Quality Assurance

RA	Risk Assessment
S0	Swabbing visit 0
S3-5	Swab collected 3-5 days post S0 swab
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
REDCap™	Research Electronic Data Capture – secure database and survey web application
SICP	Standard infection-control precautions
Sites	Trial site listed on IRAS e.g. NHS trust
SOP	Standard Operating Procedure
SST	Serum separator tube
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBP	Transmission-based precaution
TMF	Trial Master File
TOPS	The Over Volunteering Prevention System
VP	Viral particles

1. INTRODUCTION

Susan Jackson, Hazel Morrison, Angela Minassian

The following document contains a collection of the key generalizable clinical study plans and standard operating procedures used in the conduct of the COV001 (phase I/II) COVID-19 vaccine trial, sponsored by the University of Oxford. This trial was designed to assess the safety, immunogenicity and efficacy of the COVID-19 vaccine candidate, ChAdOx1 nCoV-19. Conduct of the trial involves scores of study documents outlining a multitude of processes and study procedures. The collection contained in this document is therefore not exhaustive but is intended to give an overview of the general conduct and administration of the study.

Batches of ChAdOx1 nCoV-19 for COV001 were manufactured by Oxford Clinical BioManufacturing Facility, according to current Good Manufacturing Practice (GMP). ChAdOx1 nCoV-19 was administered as a single or two-dose regimen (4-12 weeks apart). Detailed specifics relating to the investigational medicinal product itself and its preparation and administration are not included in this document.

All documents are current at the time of writing; however, due to the evolving nature of the COVID-19 pandemic, our knowledge of the SARS-CoV-2 virus and subsequent expansion of our clinical trials, amendments to these processes have been needed since their inception. A full version history is not within the scope of this document. Similarly, localisation of the following documents has been undertaken at all study sites. Documents may have been shortened, amalgamated or adapted for this format.

Publication of the following materials is intended to provide a transparent overview of the functioning of the COV001 trial. We hope that the publication of these materials may allow future clinical trials to learn from our processes.

2. STUDY OVERVIEW

Hazel Morrison, Susan Jackson, Pedro Folegatti, Angela Minassian, Andrew Pollard

COV001 Vaccine Trial

Study title:	COV001: A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers
Short title:	A phase I/II study of a candidate COVID-19 vaccine (COV001)
Sponsor:	University of Oxford
Funder:	UK Research and Innovation
Chief Investigator:	Prof A. Pollard
REC reference:	20/SC/0145
IRAS	281259

A multi-centre Phase I/II, single-blinded, placebo controlled, individually randomised study in healthy adults aged 18-55 years recruited in the UK. ChAdOx1 nCoV-19 or the chosen placebo vaccine, licensed MenACWY, are administered as either a single or two-dose schedule via an intramuscular injection into the deltoid. The study aims to assess efficacy, safety and immunogenicity of ChAdOx1 nCoV-19.

There are 4 study groups, with randomisation interventions in each group outlined below. As a phase I study, enrolment is staggered with real time safety assessments undertaken after 1, 4, and 54 participants have received the investigational medical product (IMP). A subset of participants receive paracetamol to assess impact on vaccine reactogenicity. Group 3 is unblinded.

Planned Sample Size	Total number to enrol: Up to 1090 healthy adults aged 18-55 years **Group 1: Intense Follow up group** 1a) Single dose ChAdOx1-nCoV-19 $5x10^{10}$ viral particles (vp), N=44, OR 1b) Single dose MenACWY, N=44 **Group 2**: Overall sample size of up to 412 volunteers, up to 62 (52 IMP and 10 controls) will receive a booster dose at 8 weeks (-7/+14 days). 2a) Single dose ChAdOx1-nCoV-19 $5x10^{10}$vp, N=206, OR 2b) Single dose MenACWY, N=206 2c) Up to 20 volunteers from 2a receive a prime boost of ChAdOx1-nCoV-19 $5x10^{10}$vp after 8 weeks 2d) Up to 32 volunteers from 2a receive a prime boost of ChAdOx1-nCoV-19 $2.5x10^{10}$vp after 8 weeks 2e) Up to N= 10 from 2b receive a prime boost of MenACWY at 8 weeks **Group 3** 3) Two dose ChAdOx1-nCoV-19 $5x10^{10}$vp 4 weeks apart, N=10 **Group 4:** Overall sample size of up to 580 volunteers, up to 112 given Paracetamol at D0 visit. 4a) Single dose ChAdOx1-nCoV-19 $5x10^{10}$vp, N=up to 290 4b) Single dose MenACWY, N= up to 290

3. SCREENING AND ENROLMENT

Hannah Robinson, Yrene Themistocleous, Pedro Folegatti, Simon Kerridge, Marion Watson, Ian Poulton, Maria Moore, Yama Mujadidi, Angela Minassian, Maheshi Ramasamy

3.1 Pre-screening questionnaire, response handling and screening bookings

Recruitment will be processed through an online screening system where potential volunteers can view trial details, including the participant information sheet (PIS) and eligibility criteria, before completing an online pre-screening questionnaire (see *Appendix A and B* for example website text and pre-screening questionnaire). Potential volunteers are directed to this online screening system via adverts posted on email distribution lists, websites, posters, social media and other approved recruitment methods.

Following completion of the pre-screening questionnaire, an invitation for screening will be issued directly for applications deemed likely eligible. Applications that are assessed as possibly eligible will be automatically emailed to the study team for review by a clinician and an invitation for a screening visit will be issued if subsequently deemed eligible. If the volunteer is not eligible, an onscreen message will inform them of this fact.

An online collaborative server [for example Microsoft *Sharepoint* calendar as used by our team] and a participant management database (PMD) [for example Microsoft Access] are used to coordinate, book and track participant bookings.

A screening number is generated by the online screening system and is solely for the use of participant response management. The screening number will not be used for any other purposes.

An invitation for screening will be sent via email containing essential information about the appointment with directions and a request for participants to bring an official form of photo identification, bank details, general practitioner (GP) contact details and their National Insurance number details or passport. Participants will be asked not to attend and to cancel their screening appointment if they are unwell, in particular if they have any symptoms of potential COVID-19 disease.

All volunteers will be sent a reminder text message (SMS) the day prior to their appointment using the university SMS service and global templates that have been set up specifically for this study. These messages will include information about their appointment and instructions to not attend their visit should they have a new onset of fever or continuous cough or shortness of breath.

3.2 Inclusion & Exclusion Criteria

A screening visit will be conducted for all participants in order to assess eligibility and inform the decision to include a volunteer in the study in question. Members of staff from the Oxford Vaccine Group (OVG) and the Jenner Groups working directly on the COVID-19 vaccine trials will not be eligible to take part in the study.

To abide with social distancing measures, the exclusion criteria 'Living in the same household as any vulnerable groups at risk of severe COVID-19 disease' has been included under the specific exclusion criterion of "Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data".

However, where a participant's usual activities represent a greater exposure risk than participation in the study (for example, frontline healthcare professionals), this would not prevent study participation. Clinical judgement will be applied to such cases. The latest Public Health England (PHE)/ NHS guidance on high risk and clinically extremely vulnerable groups and recommendations for these individuals should be followed.

Participants must be able to attend visits by methods other than public transport. If this isn't the case, they would be excluded from the study. This will be covered under the following inclusion criteria: 'Able and willing to comply with all study requirements'.

History of recreational drug use will be assessed using clinical discretion, however, where recreational drug use is recent or current, participants will be asked to discontinue use for the duration of the study to be considered eligible for enrolment.

SARS-CoV-2 serology may be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity. An extra 5mls should be added to cumulative blood volumes if extra COVID-19 serology is required at screening. Where SARS-CoV-2 serology is performed, it will be emphasised that testing will be conducted using a research grade assay, which has not been validated for clinical use and therefore, any results cannot be used to either confirm prior COVID-19 exposure or provide any diagnosis of immune status or protection from future infection

3.2.1 Inclusion Criteria

The volunteer must satisfy all the following inclusion criteria as per the COV001 protocol to be eligible for the study:

- Healthy adults aged 18-55 years.
- Able and willing (in the Investigator's opinion) to comply with all study requirements (participants must not rely on public transport or taxis).
- Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
- For females only, willingness to practice continuous effective contraception during the study and a negative pregnancy test on the day(s) of screening and vaccination.
- Agreement to refrain from blood donation during the course of the study.
- Provide written informed consent.

3.2.2 Exclusion Criteria

Exclusion criteria are followed as per the COV001 protocol as detailed below:

- Prior receipt of any vaccines (licensed or investigational) ≤30 days before enrolment
- Planned receipt of any vaccine other than the study intervention within 30 days before and after each study vaccination, with the exception of the seasonal influenza vaccination. Participants will be encouraged to receive this vaccination at least 7 days before or after their study vaccine
- Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines)
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate
- Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting <14 days)
- Any autoimmune conditions, except mild psoriasis, well-controlled autoimmune thyroid disease, vitiligo or stable coeliac disease not requiring immunosuppressive or immunomodulatory therapy
- History of allergic disease or reactions likely to be exacerbated by any component of the ChAdOx1 nCoV-19 or MenACWY vaccines
- Any history of angioedema
- Any history of anaphylaxis
- Pregnancy, lactation or willingness/intention to become pregnant during the study
- History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
- History of serious psychiatric condition likely to affect participation in the study (e.g. ongoing severe depression, history of admission to an in-patient psychiatric facility, recent suicidal ideation, history of suicide attempt, bipolar disorder, personality disorder, alcohol and drug dependency, severe eating disorder, psychosis, use of mood stabilisers or antipsychotic medication)
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
- Any other serious chronic illness requiring hospital specialist supervision
- Chronic respiratory diseases, including mild asthma (resolved childhood asthma is allowed)
- Participants will be excluded if they have a history of asthma, with the exception of resolved early childhood asthma, which is permissible. Asthma at an older age would constitute an exclusion. History of inhaler use and duration of use will be taken and clearly documented in the electronic case report form (eCRF) to enable clinical judgement
- Chronic cardiovascular disease (including hypertension), gastrointestinal disease, liver disease (except Gilberts Syndrome), renal disease, endocrine disorder (including diabetes) and neurological illness (excluding migraine)
- Seriously overweight (BMI≥40 Kg/m_2) or underweight (BMI≤18 Kg/m_2)

3.3 Screening visit flow

During busy sessions, screening will be conducted in cohorts of up to 6 volunteers, who will view a pre-recorded consent script/presentation (or have a one to one discussion with a suitably qualified health care professional), before signing the informed consent form (ICF). Informed consent will be taken by a clinician or an appropriately trained nurse. A medically qualified member of staff will be available at all times, should participants wish to discuss the study with a clinician before signing the consent form.

See *Figure 1* below for example staff and location requirements. Roles performed by research nurses may also be performed but suitably trained and supervised medical students.

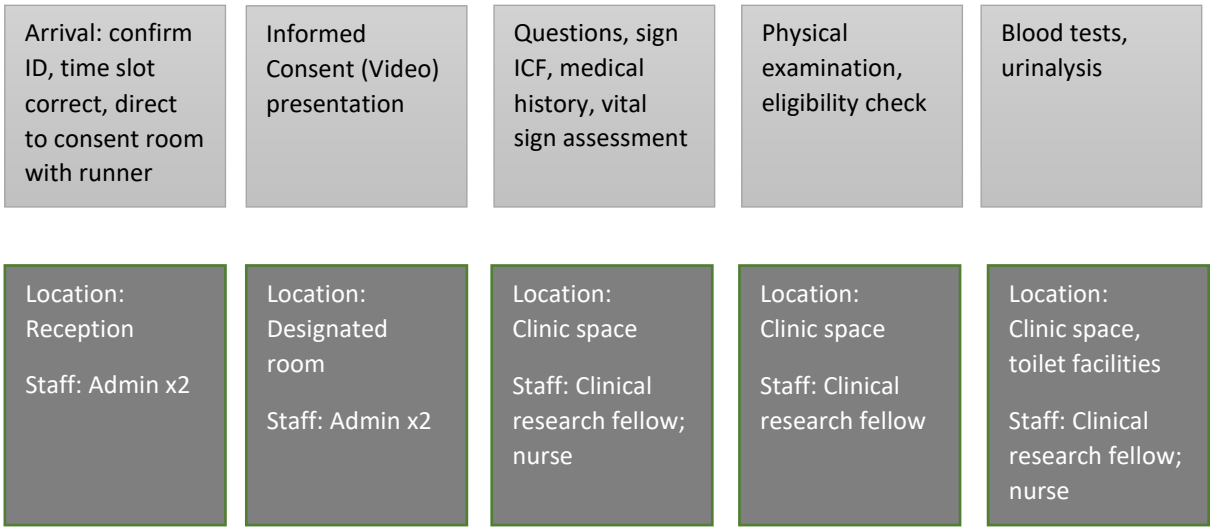


Figure 1. Screening visit staff and location requirements

To maintain a good flow of large numbers, volunteers will be given the following forms to complete ahead of signing the ICF:

- Generic registration form, including contact details and next of kin details
- GP letter release form
- Generic bank detail request form

Any participants who decide they do not want to take part in the study will have their above forms destroyed and no personal data will be kept on volunteers who do not consent to be in the study.

See *Figure 2* for an overview of example screening visit flow.

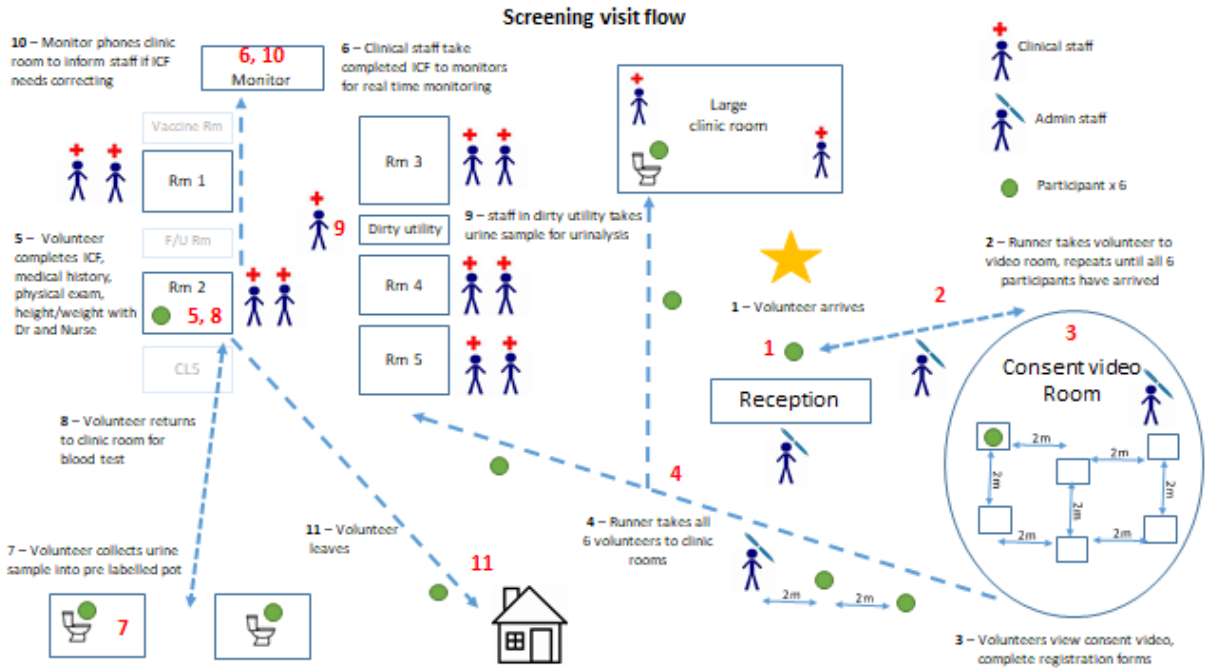


Figure 2. Screening visit flow example, based on the layout of Centre for Clinical Vaccinology and Tropical Medicine, Oxford Site.

3.4 Informed Consent Form

The study specific Participant Information Sheet (PIS) will be made available to all participants prior to consent being obtained. To supplement the written information, participants will either view a pre-recorded video presentation of the information within the PIS or have a one-to-one discussion with a suitably qualified healthcare professional. Where used, the video presentation may be screened to small cohorts of participants or individually at the screening visit. All participants will also have the opportunity for individual discussion with an appropriately trained and delegated researcher, and be able to ask any questions, prior to signing the Informed Consent Form (ICF). A medically qualified member of staff will be available at all times, should participants wish to discuss the study with a clinician before signing the ICF.

After viewing the consent presentation, volunteers will be individually asked if they have any questions and time will be allowed for further discussion as necessary. Key elements to reiterate to the volunteer are:

- Participation in the study is entirely voluntary and the volunteer may withdraw at any time
- Short-lived local and/or systemic side effects are likely following vaccination
- As with any vaccination, although rare, there is also a risk of a serious reaction (e.g. anaphylaxis)
- There is a theoretical risk that the vaccine may increase the severity of disease, if they were to become infected with SARS-CoV-2

- Due to the urgent need for a vaccine against COVID-19, some of the testing usually involved in releasing new vaccines before assessment in clinical trials have been modified. These modifications have been agreed and discussed with regulators in the UK
- Participants should not assume any protection from COVID-19 from the vaccine
- If participants do have symptoms consistent with COVID-19, and if it is appropriate to do so, we will arrange a 'diagnosis' visit where volunteers will be medically assessed and tested for COVID-19.
- Clinical care in the event of diagnosis with COVID-19 is per standard NHS provisions
- Transport to visits must be possible by methods other than public transport or taxi
- Participants may be randomised to receive a control vaccine and not ChAdOx1 nCoV-19. Participants will not know which vaccine they received until we have the results for this study

The research staff must complete the version and date of the participant information sheet before the participant signs.

Consent forms may be monitored in real time to ensure accurate completion of study paperwork. This will be particularly necessary during larger clinics. A member of staff from the clinic room will take the consent form to the monitor while the participant is out of the room e.g. during urine collection. The monitor will review the consent form and request corrections in real time if needed be.

3.5 Participant Trial Identification Numbers

Participants will be allocated unique sequential participant identification numbers at screening, which will be used throughout the study with a screening/enrolment log maintained on a secure server. This unique participant number will be retained throughout the study.

3.6 Clinical Assessment

3.6.1 History & Examination

All screening assessments will be recorded directly into the relevant eCRFs using REDCap database [a secure web-based application for building and storing surveys and databases that is utilised by all sites for data capture and storage during these trials].Screening eCRFs comprise the screening eCRF, the screening urine results eCRF and, where appropriate, the concomitant medications eCRF.

Volunteers will be questioned about their medical history in accordance with the inclusion/exclusion criteria.

The following will be recorded: temperature, pulse, BP, height and weight. Vital signs that meet the grading scale (see *Appendix C* - Vital signs grading table) will be highlighted to a medically qualified doctor.

Participants will have a physical examination conducted or supervised by a medically qualified doctor. The examination, whether abnormal findings were present or not and other medical notes/comments will be detailed in the eCRF.

3.6.2 Screening Blood Tests

Screening blood tests will be taken as per section 3.8. See table in *Appendix E* for grading of clinically significant laboratory abnormalities.

Any blood test result classed as grade 1 and above will deem the participant ineligible, except for the following:

- Grade 1 or 2 hyperbilirubinaemias, where appropriate further history and investigations indicate results are consistent with Gilbert's syndrome (no symptoms or signs of liver disease, all other LFTs are normal
- Grade 1 potassium or sodium
- Grade 1 albumin, where all other LFTs normal
- Grade 1 urea, if isolated

Repeat tests may be arranged for grade 1 abnormalities in neutrophil or white blood cell counts, where the participant would otherwise be considered eligible for enrolment. Abnormalities which are close to normal lab range values may also be considered acceptable, according to clinical judgement, however, any grade 1 lymphopaenia will deem the participant ineligible.

Clinical judgement will be used when assessing any abnormal lab results outside of the local laboratory-specific normal ranges and the advice of a senior clinician may be sought for clinical assessment of any blood test abnormality, with regards to either safety or assessment of eligibility for enrolment. Further testing may be requested at the clinician's discretion.

3.6.3 Urinalysis

Urinalysis will only be carried out at screening in COV001 to determine eligibility of participants. (see details for urinalysis and urine pregnancy testing procedures in *Appendix F*). Eligibility will be assessed according to the criteria in *Figure 3* below.

Urine Analysis (using Siemens Multistix 10SG reagent strips)
*Results are presented as shown on the original packaging (**chart**) or as printed when using the CLINITEK Status +® analyser (**Status +** (English, conventional units)), any that fall within the greyed areas must be actioned.*

									Units
Protein	**Chart**	**Negative**		0.3	1	3	≥20		g/L
				30	100	300	≥2000		mg/dL
			Trace	+	++	+++	++++		
	Status +		**15**	**30**	**100**	**300**			**mg/dL**

			Non-haemolysed		*Haemolysed*				
Blood	**Chart**	**Negative**	10	80	10	25	80	200	Ery/L
			Trace	++	Trace	+	++	+++	
	Status +		**Trace-intact**	**Moderate**	**Trace-lysed**	**Small**	**Moderate**	**Large**	

Glucose	**Chart**	**Negative**	55	14	28	55	≥111		mmol/L
			1	2.5	5	10	≥20		g/L
			100	250	500	1000	≥2000		mg/dL
			Trace	+	++	+++	++++		
	Status +		**100**	**250**	**500**	**≥1000**			**mg/dL**

Figure 3. COV001 Screening urinalysis actionable results

Actionable results shaded in grey (exclusion applies to pre-enrolment only)

- Proteinuria ≥1+/30mg/dl should be sent for albumin:creatinine ratio (ACR), if the ACR is between 3mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested. (NICE 2014). If the ACR is >70 mg/mmol or an early morning ACR is >3 mg/mmol the volunteer should be excluded from participating in a vaccine trial.

- Haematuria: 'Trace' haematuria on dipstick should be considered negative.

    - Males - All positive results (≥1+) must be repeated ≥3 days later. If repeat is positive, retain sample and send it off for microscopy. Volunteers will be excluded if haematuria is confirmed on microscopy.

    - Females - All positive results (≥1+) – menstruation history to be taken to elicit whether the subject is currently menstruating and if they are, urine dipstick will be repeated after 1 - 2 weeks. Clinical assessment will be required to judge eligibility.

- Glycosuria: exclude volunteer if any actionable result.

3.6.4 SARS-CoV-2 Serological Testing

Where performed, SARS-CoV-2 serological testing results will be reported by the Jenner immunology laboratory team via email. All results received by email will be printed, reviewed and signed by a clinician then filed in the CRF. Results will be reported as either “likely seronegative”, ‘likely low-level seropositive’ or “likely seropositive”. Any result designated “likely seropositive” will deem the participant ineligible for COV001.

3.7 Clinically significant incidental findings identified at screening

A clinically significant incidental finding may be identified either during the screening visit (e.g. physical observations, physical examination or urine dip) or on the basis of investigations conducted as part of the screening procedure (e.g. blood tests or urinary albumin: creatinine ratio).

Where the incidental finding is identified at the screening visit, it is the responsibility of the screening clinician to record the relevant details within the screening eCRF (within “screening notes”), discuss the findings with the participant and to ensure appropriate medical follow up arranged with the permission of the volunteer. Where the incidental finding relates to results of investigations after the screening visit, communication of the result to the volunteer and arrangement of appropriate medical follow-up will be the responsibility of the clinician reviewing the result. Arrangement of appropriate medical care (for example, referral to the GP) should usually be completed on the day that the incidental finding is identified, however, where not possible, this may also be completed at a later date, within a clinically appropriate timeframe.

Exclusion of participants will be recorded as per Section 3.12. A copy of any correspondence relating to arrangement of appropriate medical care (for example, referral letter to GP), should be printed and filed in the participant CRF.

3.8 Sample Collection

Urine analysis for screening, including urinary ßHCG pregnancy test) will be completed using an appropriate automated reader (for example the Clinitec™ Analyser) and printouts attached to investigator comment sheet in CRF for review.

Screening bloods will consist of:

- 1 x 2ml K3 EDTA tube for Full blood count
- 1 x 3ml lithium heparin plasma separator tube (PST) for biochemistry (Sodium, Potassium, Urea, Creatinine, Albumin, ALT, ALP, Bilirubin)
- 1 x 5ml serum separator tube (SST) for serology (HIV Ab/Ag, HCV Ab and HBV surface Ag)
- 1 x 5ml SST for SARS-CoV-2 serology (for some participants only)

3.9 Sample labelling

In each participant screening CRF pack, there is a sheet of labels for adding to sample forms and samples. When adding to sample tubes, fix the label lengthways.

3.10 Infection Control

Participants will be attending screening visits in groups of no more than 6 individuals and may be asked to wait in their transport if they arrive early to minimise the numbers of people in waiting rooms. Waiting areas and consent presentation areas will have extra chairs removed to ensure appropriate social distancing considerations can be followed. Chairs and couches will be wipeable material and will be cleaned with disinfectant wipes between use. Wherever possible and where rotation of staff is necessary to retain rapid flow, participants will remain in situ and the staff will rotate. Appropriate disinfection procedures of medical equipment will take place after consultation as per equipment manufacturer advice. Hand basins and alcohol based hand rub (ABHR) will be widely available. Participants will be given individual pens at each visit to minimise cross infection and clipboards will be cleaned between participants. Participants will be asked to minimise contact with door handles. Once the screening visit has finished participants will be required to exit the building to avoid overcrowding in waiting areas.

Further details on infection prevention and control and use of PPE can be found in **6. PPE and Infection Control Guidance**.

3.11 REDCap

REDCap is a secure online database. All eCRF's will be completed directly into the REDCap database.

Screening blood results will not be entered into the REDCap database until the participant has been enrolled into the study.

3.12 Eligibility assessment during the screening visit

During the screening visit, it may become apparent that the participant is not eligible to take part in the study. This may occur prior to consent procedures or after consent has been obtained. In all cases of exclusion at the screening visit, the exclusion paper document will be completed and the administrative team will update the participant management database, as appropriate.

If a volunteer is identified as ineligible after providing written consent, the reason for exclusion will be clearly documented in the "screening notes" of the screening eCRF (for example clinically significant incidental finding such as hypertension). If the participant is identified as ineligible prior to providing consent (for example, through unsolicited information volunteered by participant), a volunteer number will not be issued, an eCRF will not be started and the reason for exclusion will be documented on the exclusion paper document only.

3.13 Final Eligibility sign off

3.13.1 GP letters & medical records

For all volunteers assessed as potentially eligible during the screening visit, a letter will be sent to their GP by a member of the admin team, requesting information about the volunteer's past medical history. The below template email (*Figure 4*) will be sent to the named GP using the study secure NHS email account ensuring the subject heading includes the participant ID. A copy of the GP letter release consent must be included in the email.

Dear Dr XXXX

Please find enclosed an urgent request for a copy of the named individual's medical records (an EMIS brief summary would be ideal) with patient's consent on page 2. They have attended a screening appointment to assess eligibility to participate in a COVID-19 vaccine trial. Further information and a copy of their consent is included.

If you have any queries, please do not hesitate to contact one of the clinical trial team members on Insert local contact details.

Figure 4. GP letter request template email.

GP summaries will come into the study NHS inbox. This will be monitored by the administration team who will print a copy of the GP summary when received and put a participant label on the print out. Once printed the team will record receipt of GP summary on the PMD and file email in the NHS inbox into the "GP summaries received" folder. Once GP letter and all results have been received for a participant, the CRF pack will be moved to "screened and ready for eligibility review" file.

3.13.2 TOPS

All participants will be registered on TOPS (The Over-Volunteering Prevention System – a UK based database that aims to prevent participants from taking part too frequently in trials of new medicines) on the day of the screening visit. Once completed, this will be recorded on the PMD and the paper generic registration form.

3.13.3 Blood Results

Each day a named clinician will be tasked with reviewing and assessing all outstanding blood results. Normal ranges can be found in *Appendix E*. Abnormal results will be assessed as described in section 3.6.2. The advice of a senior clinician may be sought for clinical assessment of any blood test abnormality, with regards to either safety or assessment of eligibility for enrolment. Further testing may be requested at the clinician's discretion.

If any results are phoned through as urgent due to results being out of the normal range, this call will go to the on call telephone held by a study clinician 24 hours a day.

3.13.4 Final Inclusion

The screening results query on the study PMD will be used to generate a list of participants who have attended screening visits and any outstanding results. This should be checked daily by the lead nurse/administrator supporting the eligibility assessment pathway.

A paper checklist will also be completed by a named research nurse or admin support as evidence that the below are complete before final eligibility assessment:

Blood results reviewed
GP summary received
TOPS registration complete
Urine result reviewed

Eligibility to participate in the trial will be reviewed by an appropriately delegated medically qualified doctor. All results, GP medical summary and eCRF will be reviewed to make final eligibility assessment. For urinalysis and pregnancy tests, this will involve review of the original paper-based result to avoid assessment being made on the basis of results which have been incorrectly entered into the relevant results eCRF and may not have yet been reviewed during the monitoring process.

The clinician's review of the GP medical summary and any other results which have not already been reviewed, will be documented by a clinician's signature and date. If any new information is evident from the GP letter, which may be relevant to eligibility assessment, and which was not captured at the screening visit, the clinician will enter this new information into the screening eCRF, for example past medical history, allergies, medications.

The eligibility assessment against the trial inclusion and exclusion criteria will be made on REDCap eligibility eCRF. If the participant is excluded, the reason for exclusion should be clearly documented in "screening notes" in the screening eCRF. If there are queries regarding a participant's potential eligibility, a senior clinician will be available daily, as designated by a rota, and should be consulted before eligibility sign-off. Any participant found to be ineligible will be informed by a trial clinician (by telephone or email). Following eligibility assessment, the assessing clinician will update the PMD and complete the paper exclusion document, documenting here if the participant has been informed.

CRFs of participants assessed as eligible will be filed in the "eligible to book", or "excluded" section of the lockable study cupboard, as appropriate. A named individual (as per the administrative team rota) will invite the participant to the vaccination visit and provide them with their study schedule of visits based on the group allocation.

3.14 Enrolment

Participants will only be considered enrolled following administration of the first vaccination (Day 0).

4. VACCINATIONS & ROUTINE FOLLOW UP VISITS

Yrene Themistocleous, Mimi Hou, Susanne Hodgson, Susan Jackson, Hazel Morrison, Mathew Snape, Maheshi Ramasamy, Angela Minassian

4.1 Study Enrolment

Volunteers will be considered enrolled in to the trial at the point of vaccination. At the vaccination visit, before enrolment, the ongoing eligibility of the volunteer will be reviewed including checking for any new symptoms arising since the screening visit. Prior to vaccination, temperature and pre-vaccination blood tests will be taken. A urine pregnancy test will be performed on female participants of childbearing potential. If a volunteer has an acute respiratory illness (moderate or severe illness) and or a fever (oral temperature ≥37.8°C), the volunteer will be withdrawn from the study. If the participant is well the 'Pre-vaccination' eCRF will be completed on REDCap, including informed consent check. A clinician will confirm that the participant is fit to proceed to vaccination by completing the appropriate trial Vaccine Authorisation form. Randomisation of the participant will then occur on REDCap.

4.2 Randomisation

Participants will be randomised according to allocated group randomisation schedule, as detailed in the appropriate trial protocol. Randomisation will occur directly within REDCap. Only study staff delegated to randomisation and preparing vaccines for administration will have access to the relevant eCRFs within REDCap. To randomise, select the 'Randomisation' form. Select 'electronic' randomisation method, date/time, appropriate study site then press the 'Randomize' button. REDCap will then display which vaccine the participant has been assigned to receive (either ChAdOx1-nCoV-19 or MenACWY).

4.3 Processes for Unblinding of Participants

The Lead Statistician has responsibility for creating and maintaining the master randomisation list. Randomisation of participants will be done via REDCap as described in Section 4.2. Participants will be blinded to the arm they have been allocated to, whether investigational vaccine or MenACWY. All study research nurses involved in vaccine administration will have access to the unblinded vaccination CRF on REDCap.

If a member of the study team feels that the clinical condition of a participant requires unblinding, this must be escalated to the site PI in the first instance. The site PI will then discuss directly with the CI or one of the Oxford senior clinicians. For queries out of hours, there is an Oxford senior clinician available 24 hours on the on-call rota who can be contacted via the Oxford COVID on-call doctor. Once the decision to unblind has been confirmed, this can be done by:

- accessing the unblinded vaccination CRF for the participant on REDCap or
- opening the sealed envelope containing the participant's individual vaccine record in their paper CRF

The site senior research nurse on duty for the day can assist with accessing the REDCap vaccination CRF during normal office hours. After hours, it will be necessary to contact one of the senior research nurses to access REDCap remotely.

All decisions and processes regrading unblinding will be documented on the Investigator Comments CRF of REDCap.

4.4 Vaccination

Vaccine administration will be recorded on REDCap under the 'Vaccination' eCRF and on the appropriate trial Vaccine Record. Vaccinations will be administered intramuscularly according to site specific SOPs. After vaccination, the injection site will be covered with a sterile dressing. Participants will wait in the clinical area for at least 15 minutes to observe them for any immediate adverse reactions. The sterile dressing will then be removed and the injection site inspected.

Fever is an expected post vaccine side effect. Participants should be advised that if they develop an isolated fever at any point in the first 48 hours post-vaccination they and their household contacts should self-isolate. The participant and household contacts may end self-isolation without a SARS-CoV-2 test once afebrile for 24 hours as long as it resolves within the 48-hour post-vaccination period. Participants and their household contacts who are HCW should preferentially follow advice given by their occupational health department if this differs.

4.5 Participant e-diaries and post-vaccination take home packs

All participants will be provided with a medic alert card with their participant ID and contact details for the study on-call team.

All participants will be required to complete electronic symptom diaries (e-diaries) for 28 days post vaccination. Participants will be provided with an oral digital thermometer and tape measure. Participant e-diaries are set up for each participant through REDCap.

4.6 Routine study visit procedures

Visit procedures and blood draws for each routine visit are specified as per the schedule of attendances in the protocol. At the start of each routine visit, check the identification of the participant and ongoing consent. Take the temperature and ascertain if the participant has been unwell and if they have had any symptoms consistent with COVID-19 infection. If the participant has had any of the following symptoms, they require testing for COVID-19 as per the Symptomatic Participant Pathway (see **5. Management of Adult Participants with Suspected or Confirmed COVID-19 Infection)**:

- fever ≥37.8C OR
- new persistent cough OR
- shortness of breath OR
- anosmia (loss of smell) AND/OR
- ageusia (loss of/ or altered taste)

If the participant is unwell with non-Covid symptoms, following medical history and examination by a clinician and safety bloods and immunology bloods if possible, the ongoing clinical management of the participant should be discussed with the on call lead study clinician.

If the participant is well, at routine visits study staff will:

- Ascertain any solicited and unsolicited adverse events and record and grade
- Check participant's e-diary if applicable
- Take blood tests as per visit schedule
- Remind volunteer of next appointment and counsel regarding on call trial phone

If a participant is due to attend for a routine visit but they are self-isolating as per current PHE guidelines (e.g. due to symptomatic household contacts or due to being symptomatic themselves), then this visit may be performed as a telephone and/or video consultation instead.

4.7 Sample collection at vaccination & routine study visits

Bloods samples should be collected according the trial laboratory manual and labelled with the pre-printed labels in each participant's CRF pack. Specimens are to be processed at local site laboratories as specified in the laboratory manual.

4.8 Infection Control

Participants will be attending study visits in small groups and may be asked to wait in their transport if they arrive early to minimise the number of people in waiting areas. Seating should be arranged to ensure appropriate social distancing. Wherever possible and where rotation of staff is necessary, participants will remain in situ and the staff will rotate. Appropriate disinfection procedures of participant chairs, high touch surfaces and medical equipment will take place after consultation.

4.9 Participant e-diaries on REDCap

For all participants, e-diaries will be kept for 28 days from vaccination on REDCap. Participants will be contacted by automated email every day to remind them to complete their e-Diary for the required duration after vaccination. Participants should be asked to complete their e-diaries by 10pm at night to facilitate review by study staff the next day. Any diary adverse events (AEs) of Grade 3 or higher will automatically trigger an email to the Lead Study Doctor and a delegated cohort of the Clinical Study Team. This team will be responsible for reviewing participants' e-diary responses and following up any actions arising from these. Any uncertainties regarding a participant's condition or otherwise, should be discussed with the on-call study doctor and with the CI or senior clinician as appropriate.

An overview of participants' e-diary responses can be generated within REDCap by performing a data extract on participants' diary responses. This access on REDCap will be granted to 1 or 2 lead clinicians at each site.

4.10 Household questionnaire

Participants will be asked to complete a weekly questionnaire to monitor their exposure to COVID-19 in the community. This will not be required of healthcare workers or other staff at high risk of COVID-19 exposure as their main exposure will be at work rather than in their households.

4.11 Unscheduled visits

In the event of an unexpected or serious adverse event, a participant may need to have unscheduled clinic visits. During these visits, a clinician will review the participant and safety bloods may be sent, at the discretion of the investigator. Unscheduled reviews may also take the form of a telephone and/or video consultation.

All communication regarding an unscheduled visit (including phone calls and emails preceding the visit) should be clearly documented in the eCRF on REDCap under 'Investigator Comments' and 'Extra Blood Results'. Participants should be encouraged to contact their GP with all medical concerns as they usually would, if it cannot be dealt with appropriately by the study team. All adverse events should be added to the REDCap adverse events line listing.

4.12 Reporting to the Data & Safety Monitoring Committee

For definitions of Adverse Events, Adverse Events of Special Interest (AESI), Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reactions (SUSAR) refer to the protocol. All SAEs must be entered as new line listing on the 'Adverse Event' form on REDCap. Of note all grade 4 laboratory AEs should be reported as SAEs and under the category of outcome of an important medical event. The exception to this is eosinophilia of ≥ 1.5 x10^9/L, which is a grade 2 laboratory AE but should be reported as an SAE because it is an AESI.

SAE reporting forms will be provided to the sites and should be stored in the investigator site files or electronically. SAEs are required to be discussed with the local site PI in the first instance, and can then be discussed with an allocated Oxford senior clinician by phone, as needed. They must be reported to the Chief Investigator at Oxford within 24 hours of becoming aware of the event. If the SAE is deemed to be at least possibly related to the IMP, it will be classified as a SUSAR (as there are no expected SARs to the IMP). The CI will then decide on whether to unblind and will forward to the DSMB within 24 hours of becoming aware. If stopping rules are triggered, immunisations will be halted pending further assessment by the DSMB. See *Figure 5* for further details on the process:

For all urgent clinical queries, these should also be escalated to the site PI in the first instance. The site PI will then have a central point of contact at Oxford as needed for advice (an Oxford Vaccine Centre (OVC) senior clinician is available 24 hours by phone).

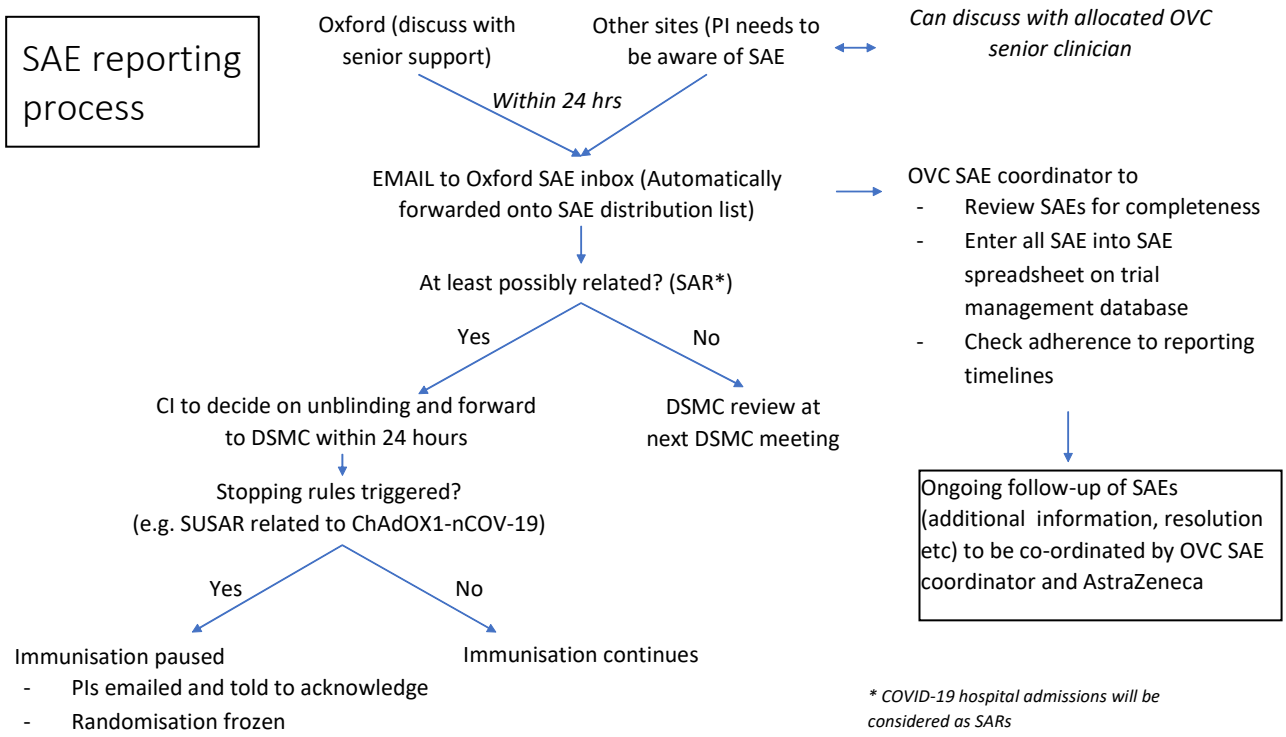


*Figure 5. Serious Adverse Event (*SAE) Reporting process.

4.13 Pregnancy

If a volunteer becomes pregnant at any point in the study they will not receive any further doses of the IMP but will remain in the study for safety follow-up (and will enter the symptomatic pathway if they develop symptoms of COVID-19; refer to **5. Management of Adult Participants with Suspected or Confirmed COVID-19 Infection**). They will be followed up until pregnancy outcome, and both mother and baby for 3 months post-partum. They will not have any further venepunctures, other than for safety reasons/ clinical need. No participant should be withdrawn because of pregnancy, unless this is specifically requested by the participant.

There should be a very low threshold for discussion of any symptomatic, pregnant participants with the on call senior clinician.

In the event that a participant becomes pregnant, complete the pregnancy eCRF in REDCap. This will generate an automatic notification to the coordinating centre in Oxford.

5. MANAGEMENT OF ADULT PARTICIPANTS WITH SUSPECTED OR CONFIRMED COVID-19 INFECTION (Symptomatic Pathway)

Hazel Morrison, Susan Jackson, Katherine Emary, Brama Hanumunthadu, Maria Moore, Paola Cicconi, Brian Angus, Angela Minassian, Maheshi Ramasamy, Susanne Hodgson.

5.1 Introduction to Symptomatic Participant Pathway

Volunteers participating in the COV001 vaccine trial may be exposed to, and become infected with SARS-CoV-2. Given that the vaccine trial seeks to assess efficacy as well as safety and immunogenicity, swabbing symptomatic vaccinees to test for confirmed SARS-CoV-2 infection is a critical endpoint. It is anticipated the majority of infected vaccinees would have mild disease. However, a minority may require review or admission to secondary care.

This section sets out the review process and collection of clinical samples in adult vaccinees in the COV001 clinical trial with suspected or confirmed SARS-CoV-2 infection/COVID-19 disease

5.2 Indications for Symptomatic Swabbing for COVID-19 Infection

There are two criteria for clinic-administered COVID-19 swab collection, dependent on participant time-point during trial: AT D3 or POST D3 following any vaccination. These criteria are symptom-based and refer to new, acute symptoms. These criteria apply regardless of any recent swab results from any other external source of testing.

For all time points, clinic-administered swabs should only be taken at least 24 hours after the onset of symptoms and should still be booked even if symptoms have resolved (e.g. single fever)**.**

1. The criteria for COVID-19 swab collection **AT D3** visit*:
    - Fever ≥37.8C for >48 hours (i.e. 2 fevers ≥37.8C separated by greater than 48 hours)** OR
    - Persistent cough (with or without sputum) OR
    - Shortness of breath OR
    - New onset complete anosmia (inability to smell) OR
    - New onset ageusia (change in taste sensation)
2. The criteria for COVID-19 swab collection **POST D3** visit+:
    - Fever ≥37.8C (single reading) OR
    - Persistent cough (with or without sputum) OR
    - Shortness of breath OR
    - New onset complete anosmia (inability to smell) OR
    - New onset ageusia (change in taste sensation)

**The only difference between the two criteria is in relation to Fever –> 48 hours or Single Reading. The rationale for this is the diagnostic difficulty of expected vaccine induced reactions compared to symptoms of COVID-19.*

Persistent cough is defined by NHS England as: coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if the participant usually has a cough, it may be worse than usual).

Of note, at the time of writing isolated shortness of breath has ceased to be one of the key case definition symptoms for community-based COVID-19 according to PHE. It remains part of the broader inpatient definition. Despite this, isolated shortness of breath will remain part of the trial definition, so as not to alter the primary endpoint definition of symptomatic COVID-19 disease (see section 5.19 for isolation advice in this circumstance).

Participants who do not clearly fit these indications for swabbing should not have a clinic-administered swab for COVID-19 sent as part of the trial.

If a participant is asymptomatic on contact but discloses previous case-definition symptoms, these must have been present in the last 7 days to justify a swab visit. If the participant has ongoing symptoms, the case definition symptoms must have started within the last 14 days. Further information regarding the management of COVID-19 positive swab results from other sources is covered in section 5.18.

5.3 Identification of Participants Meeting Criteria for Swabbing

On study enrolment, participants will be given details of a 24/7 on-call number to contact the study team. Participants will be encouraged to contact the study team via this number if they meet the criteria for COVID-19 swab collection or are clinically concerned (as previously highlighted, they should continue to call 999 as normal if they are concerned they are seriously unwell and should not delay this in order to contact the trial phone). Occasionally participants may be found to meet the criteria for swab collection during a routine study visit or review of vaccine ediary.

If a participant is found to potentially meet the case definition for a COVID-19 swab on review of the vaccine ediary and has not already made contact with the study team, a member of the study team should contact the participant, complete an “Initial contact with new suspected COVID case“ eCRF and book an S0 visit (clinic-administered swab) if indicated.

Participants who meet the case definition for swab collection should attend an S0 visit even if they have been tested elsewhere (e.g. test & trace system, occupational health). This ensures a nasopharyngeal sample is sent but is also a necessity for safety review and collection of exploratory immunology

5.4 Overview of Symptomatic Participant Pathway

Participants are defined as being on the "Symptomatic Pathway" from the time their S0 visit is booked (i.e. the time the study team becomes aware they have symptoms that meet the COVID19 case definition) until:

- If any swab PCR positive, for a minimum of 14 days from start of diary and until their symptoms have fully resolved
- Two swabs PCR negative (at S0 and S3-S5 time-point)
- Participant has a negative S0 swab and:
    - Participant presented with isolated shortness of breath as their key symptom for swabbing. In this instance, as long as there are no objective signs of respiratory distress (e.g. desaturation, tachypnoea) clinical discretion may be used if the S0 swab is negative with regards for need to obtain a second PCR result at S3-S5.
    - Participant has had a validated second swab elsewhere after the S3 time point (for example, government test & trace system, occupational health swab).
    - The S3-S5 swab result was 'indeterminate' or 'unclear.' In this instance, if clinical suspicion for COVID-19 infection is low then the study team may decide not to repeat the swab for a third time. For example, if clear alternate cause for symptoms has been found/ symptoms have fully resolved.

See *Figure 6* and *Table 1* for overview of Symptomatic Pathway flow and schedule of visits.

Figure 6. Symptomatic Participant Overview Diagram

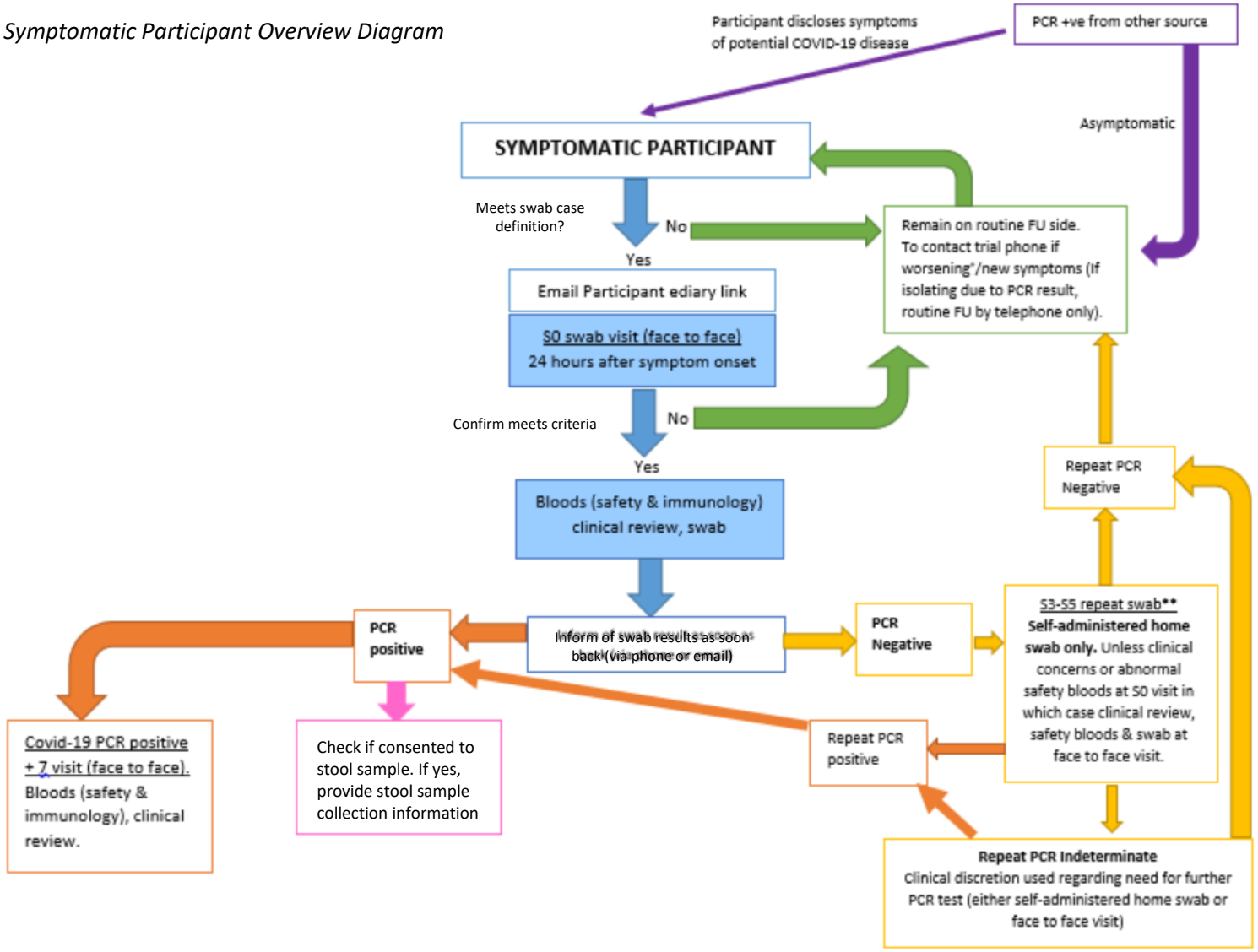


Table 1. Schedule of attendances for Symptomatic Pathway

Attendance Name	**Initial Contact**	**S0**	S3-5	COVID 19 PCR Positive +7 (P7)
Timeline	NA	0	3-5 days Only if S0 negative	7 days following date positive PCR taken
Window period	NA	Minimum 24 hours* after onset of symptoms meeting criteria for swabbing Maximum 7 days post COVID criteria symptom onset if symptoms have resolved OR Maximum 14 days onset of symptoms if ongoing symptoms	+/- 2 days	+/- 2 days
Appropriate eCRF	X	X	(X)	X
Clinical History	X	X	(X)	X
Vital signs	(X)	X	(X)	X
Physical examination	(X)	(X)	(X)	(X)
Safety bloods		X	(X)	X
Immunology bloods		X		X
SARS COV 2 PCR swab		X	X	

**S0 swabs should be booked in for as soon as practicable after the 24 hours has elapsed to maximise chance of capturing a true positive result*

5.5 Routine Post-Vaccination Reviews for Self-isolating Participants

Participants self-isolating either due to their own symptoms/PCR results or symptoms/PCR results of their household or other contacts (e.g. if informed to isolate by test and trace system) should not attend clinic for routine post-vaccination visits.

Participants on the Symptomatic Pathway

- If a routine post-vaccination review is due, this can be performed at the S0 or COVID 19 PCR Positive +7 (P7) clinic review provided the S0/ P7 falls within the window period for the routine visit. In this circumstance, blood should be drawn according to the S0/P7 requirements but labelled with both visits (e.g. S0 + D28).
- To avoid unnecessary extra visits/ blood draws, any planned visits in the week following any P7 visit (i.e. whilst the participant remains on the symptomatic pathway) should be reviewed and combined with the P7 visit if in-window

If an upcoming routine post-vaccination clinic review cannot be performed at the S0 or P7 visit as it does not fall within window and the participant is still self-isolating then the review should take place by telephone. If the participant is no longer required to self-isolate they can attend the visit in person.

Participant isolating due to an asymptomatic positive PCR result or Household Contact's Symptoms/ positive PCR (i.e. not on the Symptomatic Pathway)

- All planned visits that cannot be moved and remain within window should be conducted by telephone.

5.6 Telephone Assessment of Participants with Possible or Confirmed COVID infection

Following contact from a participant with symptoms consistent with suspected COVID-19 infection, the on call clinician should:

1. Identify the participant and ask for their study number.
2. Open REDCap and complete the CRF titled; *'Initial contact with new suspected COVID case*.'
3. Determine if any clinical concern / red flag symptoms (Section 5.10) and action accordingly.
4. Determine if criteria for COVID-19 swab collection have been met. If so, arrange an S0 appointment time. To minimise the risk of false negative swab results, all S0 swab visits should be booked for a MINUMUM of 24 hours POST ONSET OF SYMPTOMS that meet swabbing criteria **(**ideally between 24-48 hours after symptom onset**).**
   N.B. If there are clinical concerns and it is felt that a face-to-face review prior to 24 hours of symptoms is warranted, then an earlier appointment can be booked but a swab should not be taken until COVID-19 swabbing criteria symptoms have been present for at least 24 hours.
5. Set up the participant on the COVID-19 symptom e-diary. Advise the participant that this needs to be completed daily until the study team inform them they can stop (see section 5.9 for further information) If they are still completing a vaccine e-diary both need to be completed.
6. Provide pre-swabbing clinic instructions including:
   a. **Self-isolation:** Need for self-isolation of participant and household members as per PHE guidelines (or occupational health if a HCW).
   b. **Safety Netting Advice:** Emphasis need for participants to seek medical advice (call the trial phone or 999 if acutely unwell) if any worsening in symptoms or concerns.

5.7 Swab collection clinic process

Swab collection clinic should be available 7 days a week.

Summary of symptomatic clinic visit processes (see *Table 2*):

Participants will be reviewed in clinic for a swab 24 hours after symptom onset. The S0 swab visit should be booked in for as soon as practicable after the 24-hour period has elapsed. If at any point symptoms are disclosed that have been present for longer than 24 hours, an S0 swab visit should still be booked in provided the symptom onset was in the last 7 days (if symptoms have resolved) or last 14 days (if symptoms are ongoing).

If participants are coughing significantly during the clinic visit, they may be asked to wear a disposable, fluid resistant surgical facemask at the discretion of the swabbing staff.

At the S0 visit, a home self-swab kit should be given to the participant so that they can perform a second home swab in the S3-S5 window if their S0 swab is negative and the study team have no clinical concerns.

If there are any clinical concerns and a repeat clinical review or repeat safety bloods are indicated, then the S3-5 visit may be conducted face to face.

Table 2 S0, S3-S5 (if face to face visit) and P7 visit overview process

Confirm Identification of Participant

Review Participant Trial Documentation (Consider completing task prior to participant arrival)

- *eCRF: Initial contact with new suspected COVID case, any ad hoc contact eCRFs that have been filled since the last visit*
- *Need to undertake any routine post-vaccination visit documentation*
- *Medical History and Medication*
- *Safety Blood Tests (+ any other relevant tests).*

NB: 'Swabbing team' should be blinded to group allocation and so should not view details of vaccination.
IF S3-5 or P7: REVIEW PREVIOUS COVID-19 SWAB RESULT/ S0 SAFETY BLOODS

Medical History Review and ?need for COVID swab: – *Must be reviewed by Doctor*

1. S0:
   Confirm criteria swabbing has been met. NB if swabbing criteria have not been met then perform observations but do not proceed with swabbing or venepuncture and discharge participant from clinic with advice to call trial phone if concerned.

   S3-5:
   Visit only occurs if S0 negative AND clinical indication for face to face review
   Send repeat COVID-19 PCR swab
   P7:
   No COVID-19 PCR swab needed

2. Review Symptoms/ediary
3. Assess participant severity of disease

Observations:

- Oral Temp
- Respiratory Rate (RR)
- Heart Rate (HR)
- Blood Pressure (BP)
- Oxygen Saturations (Sats)
- (Review vaccine site if indicated as part of a concurrent routine post-vaccination follow-up)

Venepuncture:
S0, P7, optional S3-5 Safety bloods: FBC, U&E, CRP, LFTs
S0, P7 visits only Exploratory Immunogenicity

- REDCap eCRF will indicate which blood tubes are to be taken
- Refer to site specific lab analytical plan for further details

Clinical review: *Doctor*

- General Inspection
- +/- Respiratory
- +/- Cardiovascular
- +/- Abdominal
- +/- Abbreviated Neurological Examination
- +/- further examination as required

Clinical Safety Decision: *Doctor* 1. Is the participant safe to be discharged into the community? 2. Should an alternative diagnosis be considered?
Communicate with the Participant: • Follow-up instructions to participant • Need to self-isolate according to government guidelines • Any routine post-vaccination visits due to take place when they are self-isolating will be combined with swabbing visits where possible or converted to telephone reviews. • Need to complete COVID-19 symptoms ediary daily until either two negative swab results or if swab positive, for a minimum of 14 days from start and until resolution of all symptoms. (Set up ediary if not already done). Continue vaccine ediary concurrently if applicable. • That they will be informed of PCR result as soon as available • For S0 visit, if PCR result is negative, they will need a second swab at S3-S5. This can be done using a home swab kit as long as there are no clinical concerns or significant safety blood abnormalities in which case the S3-S5 swab may be conducted as a face to face visit • All participants should be given a home swab kit at this visit. • Safety netting – if become seriously unwell or feel symptoms are deteriorating to call 999 as standard, otherwise if stable but clinical concerns to contact trial phone (NHS 111 as backup)
Collection of Swab for COVID testing if applicable

5.8 Swab Collection Method

Using a single swab: sample from throat (touching each tonsil) then nose (swabbing nasopharynx via single nostril) as below.

1st: Collection of Oral Swab

1. Ask participant to open mouth as wide as comfortable.
2. Insert swab into the posterior pharynx and tonsillar areas. Rub swab over both tonsillar pillars and posterior oropharynx for at least 5 seconds and avoid touching the tongue, teeth, and gums (see diagram).

2nd: Collection of Nasopharyngeal Sample (using SAME swab as above): From one side only

1. Remind participant where the nasopharyngeal space is located and how far the swab will go into the nasal passage (same distance as from nostrils to external opening of ear).
2. Ask participant to tilt head backwards (lean head back against couch) - it is easier to insert the swab horizontally along the floor of the nose and you will meet less resistance reaching the nasopharyngeal space.
3. Gently insert the swab into the nasal passage and push backwards horizontally along the floor of the nose until resistance is felt and rotate 180° several times before removing.
4. Place the swab in the media tube, ensuring it is fully immersed in the transport medium. Cut the swab using scissors. Recap tube.
5. Provide participant with a tissue if required.

5.9 eDiary for COVID Symptoms

After the initial contact with a participant with suspected or confirmed COVID-19 the on call doctor should set the participant up on the COVID-19 symptom ediary. This is done via REDCap. Participants should complete this ediary daily whilst on the symptomatic pathway.

Participants will receive a daily email after starting the ediary. This will contain a link to the ediary as well as the instructional video. It will also request completion of the ediary daily. If a participant has failed to complete an ediary they should be prompted to complete it the next day.

The total duration of e-diary entries depends on PCR results and symptom length. E-diaries can be stopped if:

- Participant has two negative swabs (S0 and S3-5) and therefore is no longer on the symptomatic pathway
- Participant has a negative S0 swab, but is no longer on the symptomatic pathway because either:
    - Participant is not having a S3-S5 swab as their presenting symptom was isolated shortness of breath without objective signs of respiratory distress and the study team feel it is not clinically necessary.
    - Participant has had a validated second swab elsewhere after the S3 time point (for example, government test & trace system, occupational health swab).
    - The S3-S5 swab result was indeterminate and the study team have decided a third swab is not clinically necessary (clear alternate cause for symptoms or symptoms fully resolved).
- Participant has a positive swab but has completed a minimum of 14 days of diary entries and their symptoms have fully resolved.

The study team will need to instruct REDCap to stop sending daily ediary reminder emails for each participant when it is appropriate to do so.

If a participant attends for a S0 visit and is found to not meet the criteria for swabbing, the participant does not need to continue completing the COVID symptom ediary.

Participants may meet the criteria for swabbing multiple times during the study follow-up (See section 5.21). Participants should complete the ediary for each episode.

5.10 Assessment of participant for disease severity by telephone

It is important when speaking to symptomatic volunteers remotely that clinical fellows perform a thorough systems review to exclude alternate causes for symptoms (and therefore appropriate signposting to necessary medical care). The eCRF form on REDCap should be completed in real time for all phone calls.

If able, when assessing symptomatic patients remotely a video app to enable assessment of additional parameters (detailed below).

If symptoms are in keeping with suspected COVID-19 infection then severity assessment should cover the following points:

History:

- Presence of SOB
- Presence of chest tightness
- Ability to perform ADLs

Remote Examination:

- Respiratory Rate (RR) via video call (without informing volunteer RR being counted to allow a more accurate result)
- Ability to speak in full sentences
- Additional evidence of high work of breathing/ poor oxygenation e.g. obvious dyspnoea, cyanosis, lethargy, confusion

Table 3. Remote risk stratification if suspected/confirmed COVID-19 infection

Illness severity	Features	Advice to participant	COVID19 SWAB/ Follow up
MILD	- Completing full sentences - No SOB (grade 0) - No chest tightness (grade 0) - Able to do ADLs (grade 0-1) - RR 12-20 - No other red flags/ concerning features from history & remote examination	TREAT: - Paracetamol for fever SELF ISOLATE: - Follow guidance in Section 5.19 SAFETY NET: - Re-contact via trial phone (or 999 if an emergency) if develops SOB, chest tightness or inability to do ADLs. - EDIARY: - Remind to complete daily until instructed otherwise	- Safe to attend for COVID-19 swab collection. Proceed with appointment booking.

Illness severity	Features	Advice to participant	COVID19 SWAB/ Follow up
MODERATE A	- Completing full sentences - Able to do ADLS but lethargic (grade 1-2) - Mild chest tightness (grade 1) - Mild SOB on exertion only (grade 1) - RR 12-20 - Any symptoms from other systems considered to be moderate and not requiring medical review - No other red flag features from history & remote examination *i.e. Subjective symptoms but no objective evidence of respiratory compromise or other red flags*	TREAT: - Paracetamol for fever. SELF ISOLATE: - Follow guidance in Section 5.19. SAFETY NET: - Seek medical advice (trial phone or 999 in an emergency) if worsening symptoms - EDIARY: - Remind to complete daily until instructed otherwise	- Safe to attend for COVID-19 swab collection. Proceed with appointment confirmation
MODERATE B	- Completing full sentences - Able to do ADLS but lethargic (grade 1-2) - Mild chest tightness (grade 1-2) - Mild SOB on exertion (grade 1-2) - RR 20-24 - Any symptoms from other systems considered to be moderate and requiring medical review i*.e. Subjective symptoms and objective measures of mild respiratory compromise with need for clinical assessment*	For Medical review. SELF ISOLATE: - Follow guidance in Section 5.19. SAFETY NET: - Seek medical advice (trial phone or 999 if an emergency) if worsening symptoms. - EDIARY: - Remind to complete daily until instructed otherwise	- Advise participant to contact 111 (likely to have to wait for call back from nurse). - Only to attend for S0 COVID 19 swab if not clinically reviewed and swabbed by NHS services. - Senior on call clinician to be informed.

Illness severity	Features	Advice to participant	COVID19 SWAB/ Follow up
SEVERE	Any **one** of the following: - Inability to complete full sentences - Unable to do any ADLs/ get out of bed (grade 3) - RR>25 - Any other clinical concerns for severe disease in any system e.g. cyanosis/ confusion	**Urgent** medical review	- **Urgent** medical review needed for this patient. - Advise to call 999. (Trial clinician should only call 999 if participant is unable to do so themselves) - Senior on call clinician to be informed - Not to attend for COVID 19 swab.

Of note, this is not an all-encompassing guide and individual clinical judgement by reviewing clinician should always be taken into account. Should the reviewing clinician have any concerns regardless of risk stratification then they can contact the on-call senior clinician for further advice. Please be aware referral pathways may change dependent upon available NHS resources.

Participants will be encouraged to contact the study team by calling the 24 hours emergency phone at any time if clinically concerned. N.B. Participants should always be advised to call 999 if they are concerned they are seriously unwell and should not delay this to call the trial phone

At each telephone contact, remind the participant of the importance of continuing to complete the COVID symptoms ediary daily until instructed and if indicated remind them to send their S3-S5 swab.

5.11 Assessment of Participant for Disease Severity in Person

Participants should be stratified into the following groups as per *Table 4*.

Table 4. Risk stratification if suspected COVID-19 infection following clinical review

Illness Severity	Features	Advice to participant	Discharge
MILD	- Completing full sentences - No SOB (grade 0) - No chest tightness (grade 0) - Able to do ADLs (grade 0-1) - No other red flags/ concerning features from history & examination Observations: - RR 12-20 - HR 50-100 - $SpO_2 \geq 95\%$	TREAT: - Paracetamol for fever SELF ISOLATE: - Follow guidance in Section 5.19. SAFETY NET: - Re-contact via trial phone (or 999 if an emergency) if develops SOB, chest tightness or inability to do ADLs. - EDIARY: - Remind to complete daily until instructed otherwise	- Proceed with COVID-19 swab. - Safe to go home with advice and safety netting.
MODERATE A	- Completing full sentences - Able to do ADLS but lethargic (grade 1-2) - <u>Mild chest tightness (grade 1)</u> - <u>Mild SOB on exertion only (grade 1)</u> - No other red flags/ concerning features from history & examination - Any symptoms from other systems considered to be moderate and not requiring medical review Observations: - RR 12-20 - HR 50-100 - $SpO_2 \geq 95\%$	TREAT: - Paracetamol for fever SELF ISOLATE: - Follow guidance in Section 5.19. SAFETY NET: - Seek medical advice (trial phone or 999) if worsening symptoms EDIARY: - Remind to complete daily until instructed otherwise	- Proceed with COVID-19 swab - Safe to go home with advice and safety netting.

Illness Severity	Features	Advice to participant	Discharge
MODERATE B	- Completing full sentences - Able to do ADLS but lethargic (grade 1-2) - Mild chest tightness (grade 1-2) - Mild SOB on exertion (grade 1-2) - Any symptoms from other systems considered to be moderate and requiring medical review Observations (any **one** of the following automatically classifies as Moderate B): - RR 20-24 - HR persistently 100-130 - SpO_2 93-94%	**For Medical review.** SELF ISOLATE: - Follow guidance in Section 5.19 SAFETY NET: - Seek medical advice (trial phone or 999) if worsening symptoms. EDIARY: - Remind to complete daily until instructed otherwise	- Discussion with admitting medical registrar to arrange review in hospital. - Senior on call clinician to be informed - COVID-19 swab should be taken by study staff prior to transfer if this does not delay referral.
SEVERE	Any **one** of the following: - Inability to complete full sentences - Unable to do any ADLs/ get out of bed (grade 3/4) - Any other clinical concerns for severe disease in any system e.g. cyanosis/ confusion Observations: - RR>25 - HR >130 - SpO_2 ≤92%	Urgent medical review	- **Urgent** inpatient medical admission needed for this patient. - Trial clinician to call 999. - Senior on call clinician to be informed - COVID-19 swab can be taken by study staff prior to transfer if this does not delay referral. - Oxygen may be administered

5.12 Symptomatic Pregnant Patients

Any pregnant study participant who develops symptoms consistent with the COVID-19 case definition should enter the symptomatic pathway as normal. They should be reviewed and swabbed as per this CSP and should have safety bloods taken at S0 (and S3-5/ P7 if indicated). They should not have samples taken for exploratory immunology to minimise volumes of blood being drawn.

There should be a low threshold for discussion of any symptomatic, pregnant participant with the local PI or on call senior clinician.

5.13 Stool sampling in confirmed PCR positive participants

Participants who have a positive PCR for SARS-CoV-2 (either as part of the symptomatic pathway or via an external validated swab e.g. via occupational health) may be asked to provide an optional stool sample at approximately day 7 post symptom onset (or initial PCR positive date if asymptomatic) to look for virus shedding in the stool.

Once a positive PCR result has been received for a participant, a stool-collection instruction leaflet should be posted to the participant's home address or emailed to the participant. The participant will be asked to contact the specialist courier service (as detailed in their instruction leaflet) to request a stool collection pack, which will be delivered to their home within 48 hours. Once the participant has collected a stool sample and packaged it (as per written instruction sheet), they will need to contact the courier service to arrange collection. Samples will collected between 7am-7pm from the participant's home address.

If the participant is willing, a further sample may be requested at approximately 14 days post-symptom onset (or initial PCR positive date if asymptomatic). Stool PCR results will be batched for processing and results fed back to Oxford. These results will not be available in real time and will therefore not be used for decisions around clinical care or self-isolation. Participants will not be informed of the results of tests from stool samples.

5.14 Participants requiring review in Secondary care

All trial participants who meet the criteria for 'Moderate B' during assessment of severity of disease by telephone will be advised to contact 111 and follow the procedure as per NHS standard of care. They may be advised to attend secondary care for a review if appropriate. Trial participants who meet the criteria for 'Moderate B' during the clinical review in person should have a hospital review arranged. 999 should be called for participants who meet the criteria for 'Severe' disease.

5.15 Follow-up Post- S0 Swabbing Visit

5.15.1 Remote Review of eDiary Entries

eDiary entries of participants on the symptomatic pathway should be reviewed remotely on a daily basis by the study team. If any concerning symptoms are noted in terms of duration or severity, the study team should contact the participant, conduct an *ad hoc* telephone assessment and advise accordingly.

If a participant discloses a review in hospital or admission, the study team should arrange completion of the Admission survey as per Section 5.16.

5.15.2 Follow up after S0 safety bloods and PCR result received

At their S0 visit, all participants should be given a home swabbing kit. Once the S0 safety blood results and swab PCR results have been received, the swabbing doctor will contact the participant to disclose results and discuss the ongoing follow up plan with the participant as per *Table 5*.

All positive PCR results will require a COVID PCR-positive +7 visit (P7), at 7 days from the date the swab was taken. This allows the study team to review the participant for safety purposes both due to the risk of later deterioration with COVID-19 disease and importantly to assess for evidence of vaccine-enhanced disease.

Table 5: Follow up after S0 safety bloods/ PCR result received

S0 PCR result	Follow up	Other important points
Positive	*Book a COVID PCR positive +7 visit (P7),* at 7 days from the date the swab was taken. This will consist of clinical review, observations and collection of safety & exploratory immunology bloods *No need for repeat swabs.*	- **E-diary:** continue for minimum of 14 days and until all symptoms have resolved. - **Consented to stool sample**? If yes, send stool sample instruction leaflet - **Self-isolation advice** as per section 5.19 - **Safety net:** medical advice (trial phone or 999) if worsening symptoms.
Negative	*S3-S5 swab required* – instruct participant to send home swab unless clinical concerns about the patient or there are any significant abnormalities on their S0 safety bloods. If so, this swab can instead be done as part of a face-to-face S3-S5 visit (clinical review, observations, safety bloods only and swab collection).*	- **E-diary:** continue whilst awaiting S3-S5 swab result. - **If undertaking home swab:** participant must contact study team with swab result. - **Self-isolation advice** as per section 5.19 - **Safety net:** medical advice (trial phone or 999) if worsening symptoms.
Negative result and isolated SOB	*May be exempt from an S3-S5 swab* at the clinical discretion of the study team if they have no objective signs of respiratory distress.	- **E-diary:** if not repeating swab, can stop. - **Safety net:** medical advice (trial phone or 999) if worsening symptoms. - **Medical follow up**: If any ongoing clinical concerns or abnormal bloods at S0 visit may need ongoing follow up with study team +/- referral to GP or secondary care.

**Examples of when a face-to-face S3-S5 visit should be conducted include: ongoing symptoms where a clinical review may assist assessment or concerns about blood abnormalities (all grade 3 and above results should be seen in addition to any grade 2 and above eosinophilias). Clinical discretion can be used regarding further review for other grade 1 and 2 abnormalities.*

5.15.3 Follow up after S3-S5 swab result

For those participants who have an S3-S5 swab sent (either in clinic or home swab) the result will need to be chased. Extraction of data from the National Pathology Exchange (for home swabs) does not occur in a timely fashion. Therefore, participants will be asked to contact the study team once they have received their swab results. Further follow up will then be communicated as per *Table 6*.

Of note, an indeterminate or unclear PCR result can occasionally occur in the home self-swab testing. These are either due to an error with labelling of samples or due to a lab processing complication.

Table 6: Follow up after S3-S5 swab result

S3-S5 PCR	Follow up	Other important points
Positive	*Book a COVID PCR positive +7 visit (P7),* at 7 days from the date the swab was sent. This will consist of clinical review, observations and collection of safety & exploratory immunology bloods *No need for repeat swabs.*	- **E-diary:** continue for minimum of 14 days and until all symptoms resolved. - **Consented to stool sample**? If yes, send stool sample instruction leaflet **Self-isolation advice** as per section 5.19 - **Safety net:** medical advice (trial phone or 999) if worsening symptoms.
Negative	*End symptomatic pathway* -2 x negative swabs have been received.	- **E-diary:** can stop. - **Self-isolation advice** as per section 5.19 - **Safety net:** medical advice (trial phone or 999) if worsening symptoms. - **Medical follow up**: If any ongoing clinical concerns or abnormal bloods may need ongoing follow up with study team +/- referral to GP or secondary care.
Indeterminate	Consider repeat PCR – either self-swab using home swab kit or face-to-face visit (depending on participant preference, clinical concerns). If clinical suspicion for COVID-19 infection is low, then the study team may decide not to repeat the swab for a third time. For example, in cases where a clear alternate cause for symptoms has been found or participants symptoms have fully resolved.	**If further repeat swab being sent:** - **E-diary:** continue whilst awaiting repeat swab result. - **If undertaking home swab:** participant must contact study team with swab result. Study team to ensure adequate supply of home swabs (may need to post/ arrange pick up of further swab packs). **If NO further swab being sent:** *End symptomatic pathway* - **E-diary:** can stop - **Self-isolation advice** per section 5.19 - **Safety net:** medical advice (trial phone or 999) if worsening symptoms. - **Medical follow up**: If any ongoing clinical concerns or abnormal bloods may need ongoing follow up with study team +/- referral to GP or secondary care.

5.15.4 Ad hoc Telephone Reviews

Participants will be encouraged to contact the study team by calling the 24-hour emergency phone at any time after S0 if clinically concerned. In this case, an ad hoc telephone assessment '*Ad hoc telephone contact For Swabbing Pathway'* eCRF should be completed.

5.15.5 Uncontactable Participant

If the study team is unable to contact a participant by telephone for a routine assessment or a participant does not attend for a planned clinic review, the participant's documented next of kin should be contacted.

5.16 Participants admitted to hospital

How will the study team become aware of participants admission to hospital?

1. Notified by the participant directly via the 24-hour trial phone.
2. Notified by the admitting NHS medical doctor (after the participant presents their study card) either by phone call to the 24-hour trial phone or by completion of the admission survey (see below).
3. After referral to hospital by study doctor post-telephone or face to face assessment
4. By a participant's nominated next of kin, whom the study team may contact if a participant fails to attend clinic or respond to telephone calls.

What to do when notified that a study participant has been admitted?

1. **SAE Report:** An SAE report should be generated if a participant is admitted to hospital, but not necessarily if a participant simply has a clinical review at hospital and is subsequently allowed home. If there is any uncertainty as to whether an SAE should be reported, discuss with the PI. SAEs should be reported using the COV001 trial specific SAE form. These should be completed and forwarded to the SAE email account within 24 hours of awareness. There are no expected SAEs, therefore any SAEs deemed related to a vaccine will be reported as SUSARs. [See section 4.12]

2. **Contact the NHS Medical team:** Inform them of the patient's participation in the study, give them the **How will data be captured?**

There are 2 online surveys to be completed for all participants admitted to hospital;

1. **Admission Survey:** To be completed as close to admission as possible reflecting information available at point of completion (e.g. if completed 2 days after admission, the information entered should reflect that available 2 days after admission and not simply that available at time of admission).
2. **Discharge Survey:** To be completed once a participant has been discharged from hospital.

The purpose of these surveys are to capture information regarding the severity of participants' COVID-19 disease to enable the assessment of potential vaccine enhanced disease. The discharge survey repeats the admission survey questions, with some added questions, in order to capture data on the entire admission. This is to maximise the likelihood that all relevant data is captured.

The forms are further split into:

- **Part 1 (core information)** – This asks about relatively easy to find information that should be able to be completed quickly.
- **Part 2 (detailed information)** – This more detailed information will capture disease severity information with much greater resolution but will necessarily take longer to fill in.

The admission and discharge surveys may either be completed by:

- **NHS medical team caring for the participant during their admission:** either spontaneously through accessing the URL on the participants study card or on the instruction of the study team, who can also send the link.
- **Study team directly:** In this situation, allocation blinded study team members that have honorary contracts with the local trust and access to medical records will access this information directly if local permissions allow this. The study team will be able to access the REDCap CRF version of these surveys.

5.17 Results Handling

5.17.1 Safety Bloods

Safety blood results are AE graded based on the modified FDA criteria (*Appendix E*).

Safety blood results can be reviewed by either a research nurse or doctor. However, all abnormal blood results and laboratory AEs must be flagged for review by a doctor. Results should be uploaded to the appropriate eCRF in real-time

All **Grade 1- 2** Laboratory Adverse Events:

- Must be reviewed by the doctor to determine clinical significance and whether further action (e.g. repeat blood sampling) required. If clinical concern discuss with senior study clinician.
- ****Grade 2 or above eosinophilia must be reported as an SAE****

All **Grade 3-4** Laboratory Adverse Events:

- Discussion with senior study clinician +/- PI and prompt action including possible medical referral.
- **Grade 3**: Consider whether needs to be reported as a Serious Adverse Event (SAE).
- **Grade 4**: Report as Serious Adverse Event (SAE).

All clinically significant discussions and actions taken must be documented in the participant eCRF.

All SAEs must be entered as new line listing on the Adverse Event page on Redcap.

5.17.2 COVID-19 PCR Swab Results – S0/S3-5

Results require review by a doctor. Swab results for S0 & 3-57 should be added to the swab PCR result eCRF REDCap in real time by the local study team.

Extraction of data from the National Pathology Exchange (for home self-performed swabs) does not occur in a timely fashion. Therefore, participants will be asked to contact the study team once they have received their S3-S5 swab results. Swab result should be confirmed by asking the participant to forward a copy of the email or text on to the study team.

The DHSC laboratory will automatically notify PHE of any positive results. Participants will be directed to PHE self-isolation guidance on receipt of results however, may seek clarification on communication with the study team.

COVID-19 disease and SARS-COV2 are a PHE notifiable disease and causative agent respectively and so all positive cases identified must be notified to PHE.

5.18 PCR Tests Conducted Outside the Study

As PCR testing expands into the community, it is possible that participants will have testing performed outside of the study (including but not limited to other COVID-19 surveillance studies, community testing, work place testing, self-bought swab or saliva tests). Participants should be encouraged to contact the study team with any external positive PCR results. These should be recorded in the COVID Swab PCR eCRF on REDCap detailing (if known) name of the testing centre/lab (and whether this is UKAS-accredited) and type of assay used (and whether this is CE-marked or MHRA derogated).

Participants should be advised to self-isolate as per latest government advice following any new SARS-CoV-2 PCR positive result and any routine follow-up visits that cannot be moved should be conducted via telephone.

Any participant with case definition symptoms should enter the symptomatic pathway for an S0 visit regardless of results from other tests performed outside the study.

5.19 Isolation Advice for Participants

Isolation advice given to participants is based on current government advice, which is subject to change. Current advice combines symptoms and swab results. The latest advice can be found at https://www.gov.uk/coronavirus. The duration of self-isolation will be determined by this latest government advice. See *Appendix H* for tabular version of study specific advice. For any participant (or household contact of any participant) who is a HCW, they will be advised to discuss isolation advice with their occupational health department and any occupational health advice supersedes study team advice where there are any discrepancies.

At all points, where advice recommends a participant self-isolates, household contacts should also be advised to self-isolate and follow latest government advice.

All participants who display new symptoms consistent with COVID-19 (and their household contacts) will be asked to self-isolate, regardless of any recent self-swab or external swab results. Self-isolation can end following a negative S0 swab result, provided the participant has been afebrile for 48 hours.

Any participants who subsequently have their first positive swab at the S3-S5 time point will be advised to restart isolation from the date of this swab result, even if their symptoms have resolved. Their household contacts would be advised to isolate from the date of this swab. The duration of the isolation will be as per latest government advice for self-isolation following a positive test.

If the S0 swab result is positive, participants should self-isolate for from the day their symptoms meeting the swabbing criteria started. Participants can end self-isolation after completing the currently recommended duration of isolation, provided they have been afebrile for 48 hours and are feeling better. Anosmia and cough may continue for some time after resolution of active infection.

Of note, at the time of writing isolated shortness of breath has ceased to be one of the key case definition symptoms for community-based COVID-19 according to PHE. It remains part of the broader inpatient definition. Despite this, isolated shortness of breath will remain part of the case definition, so as not to alter the primary endpoint definition of symptomatic COVID-19 disease. If a participant contacts the trial team with isolated shortness of breath, they should continue to be booked for an S0 swab visit and advised to self-isolate until this visit. If at the S0 visit, the participant is afebrile with no tachypnoea, normal oxygen saturations and no other symptoms, the pre-test probability for COVID-19 is low. In this circumstance, it may be appropriate for the participant to stop isolation (and contact isolation) without needing to wait for the result of the swab. This will be based on individual clinical discretion and should be discussed with the PI or appropriate other if there are any concerns.

Asymptomatic participants who disclose positive PCR results from other sources (for example, asymptomatic staff surveillance) should be advised to self-isolate from the date of their first positive test. This result should be documented on Redcap.

Some participants are expected to experience a fever post-vaccination. If febrile at any point in the first 48 hours post-vaccination the participant (even if a HCW) and house hold contacts should self-isolate. The participant and household contacts may end self-isolation once participant has been afebrile for 24 hours. Participants and their household contacts should preferentially follow advice given by their NHS Occupational health department if this differs.

5.20 Re-Swabbing of Participants

Participants may have symptoms that meet the swabbing criteria at multiple times in the follow-up period post-vaccination. In such cases, ***Error! Reference source not found.****7* shows when clinic-administered PCR sampling should be performed. Of note, once criteria for a new S0 swab is met, an ediary should be commenced and follow-up telephone consultations and clinic reviews performed as per Section 5.4. Note these criteria are irrespective of any external swab results.

Table 7. Timing of repeat clinic PCR sampling in participants meeting the swabbing criteria

		S0 PCR	
		Positive	**Negative**
S3-5 PCR	**Positive**	> 28 days from S0, symptoms resolved for at least 7 days*	> 28 days from S0, symptoms resolved for at least 7 days*
	Negative	> 28 days from S0, symptoms resolved for at least 7 days*	> 48 hours after S3-5 swab

**excluding cough and anosmia*

5.21 Participant Handover, Tracking of Clinical Status & Planned Visits

It is essential that careful documentation is in place locally to clearly indicate:

- Which participants have met criteria for swabbing to trigger planned follow-up reviews.
- Which participants have been hospitalised – to ensure timely completion of SAE forms and admission surveys.
- Dates of S0 and P7 visits – to ensure timely review of safety bloods and PCR results.
- Dates home S3-S5 swabs have been sent & results communicated to study team – to ensure timely completion by participants and planning of further follow up visits.
- Outstanding PCR results
- Which routine post-vaccination reviews will be performed by telephone rather than in clinic.

6. PPE AND INFECTION CONTROL GUIDANCE

Angela Minassian, Maria Moore, Parvinder Aley

6.1 Introduction to PPE/ Infection control guidance

COVID-19 virus is expelled as droplets from the respiratory tract of an infected individual (for example, during coughing and sneezing) directly onto a mucosal surface or conjunctiva of a susceptible individual(s) or environmental surface(s). Droplets travel only short distances through the air; a distance of at least 1 metre has been used for deploying droplet precautions. However, this distance should be considered as the minimum rather than an absolute. Live virus can persist on hard surfaces (such as metal/plastic) for up to 72 hours.

Volunteers participating in SAR-CoV-2 vaccine trials may be exposed to and become infected with SARS-CoV-2 infection in the community, at any stage of the trial. This means that clinical staff will need to review and may need to perform limited procedures (such as swabbing) on these volunteers that might pose a risk of transmission of infection. Staff themselves may also become infected (in the community, in the hospital, or on the trial premises), and could unknowingly pass on infection to volunteers if they are asymptomatic (there is now clear evidence for transmission from asymptomatic carriers). It is therefore crucial that a risk assessment is made for each potential clinical scenario involving volunteer contact and the appropriate personal protective equipment (PPE) worn.

This section outlines the PPE that should be worn for various scenarios and clinical procedures during the review of trial volunteers in the COV001 trial. It also covers the wearing of PPE by non-clinical (office) staff.

6.2 Procedure

Before undertaking any procedure, staff should assess any likely exposure and ensure PPE is worn that provides adequate protection against the risks associated with the procedure or task being undertaken. All staff should be trained in the proper use of all PPE that they may be required to wear.

All PPE should be:

- compliant with the relevant BS/EN standards (European technical standards as adopted in the UK);
- located close to the point of use; stored to prevent contamination in a clean/dry area until required for use (expiry dates must be adhered to);
- single-use only;
- changed immediately after each patient and/or following completion of a procedure or task; and
- disposed of after use into the correct waste stream i.e. healthcare/clinical waste (yellow bag waste)

6.3 Types of PPE explained

6.3.1 Standard Infection Control Precautions

Hand hygiene

Hand hygiene is essential to reduce the transmission of infection in health and other care settings and is a critical element of standard infection control precautions (SICPs). All staff and volunteers should decontaminate their hands with alcohol based hand rub (ABHR) when entering and leaving clinical areas.

Hand hygiene must be performed immediately before every episode of direct volunteer contact and after any activity or contact that potentially results in hands becoming contaminated, including the removal of PPE, equipment decontamination and waste handling.

Before performing hand hygiene:

- Expose forearms (bare below the elbows)
- Remove all hand and wrist jewellery (a single, plain metal finger ring is permitted but should be removed (or moved up) during hand hygiene); ensure finger nails are clean, short and that artificial nails or nail products are not worn;
- Cover all cuts or abrasions with a waterproof dressing.

Technique for hand washing and rubbing:

- Hand hygiene includes the use of ABHR for routine hand hygiene and hand washing with soap and water, including thorough drying, if hands are visibly soiled or dirty
- The technique for hand washing must be carried out thoroughly and for a time period sufficient to inactivate the virus i.e. 40 to 60 seconds. See *APPENDIX J*: Best practice on how to HAND WASH).
- ABHR must be available for all staff as near to point of care as possible, where this is not practical, personal dispensers should be used. The technique for use of ABHR to decontaminate hands must be carried out thoroughly and for a time-period sufficient to inactivate the virus i.e. 20 to 30 seconds (see *APPENDIX K*: Best practice on how to HAND RUB).

Disposable Apron/Gown

- Disposable plastic aprons must be worn to protect staff clothes from contamination when providing direct volunteer care and during environmental and equipment decontamination.
- Fluid-resistant gowns must be worn when a disposable plastic apron provides inadequate cover of staff clothes for the procedure/task being performed and when there is a risk of extensive splashing of blood and/or other body fluids e.g. during aerosol generating procedures (AGPs). However, no AGPS will be performed by any trial staff at any time. This means there is no need to wear a gown.
- Disposable aprons and gowns must be changed between patients and immediately after completion of a procedure/task.

Disposable Gloves

- Disposable gloves must be worn when having direct contact with volunteers and when exposure to blood and/or other body fluids is anticipated/likely, including during equipment and environmental decontamination.
- Gloves must be changed immediately following the care episode or the task undertaken, or if become heavily contaminated or torn.

Eye Protection/ Face Visor

- Eye/face protection should be worn when there is a risk of contamination to the eyes from splashing of secretions (including respiratory secretions from cough), blood, body fluids or excretions. An individual risk assessment should be carried out prior to/at the time of providing care.
- Eye/face protection can be achieved by the use of any one of the following:
    - surgical mask with integrated visor; full face shield/visor; polycarbonate safety spectacles or equivalent
- Disposable, single-use, OR reusable but dedicated use to one individual is preferred for any direct contact with volunteers.
- For any direct contact with asymptomatic volunteers (examination, taking observations, bloods): non-disposable safety spectacles (each pair allocated to one member of staff for their sole use and thoroughly cleaned with Clinell wipes between uses) can be used by trial staff.
- For review/ swabbing of symptomatic volunteers full face visors will be used. These are reusable but easily cleaned with Clinell wipes between uses and should again be allocated to one member of staff for their sole use.
- Regular corrective spectacles are not considered adequate eye protection.

Eye protection should be worn by ALL staff if having direct contact with volunteers. The latest PHE guidance also defines “direct” contact (or patient care) as being within 2 metres of an individual.

6.3.2 Transmission–based Precautions

In addition to standard infection control precautions (SICPs), droplet precautions should always be used when assessing symptomatic volunteers suspected/ known to be infected with COVID-19.

Fluid-repellent surgical mask

A fluid repellent surgical mask is worn to protect the wearer from the transmission of respiratory droplets. It should:

- be well fitted covering both nose and mouth;
- NOT be touched once it has been fitted
- NOT be worn around the neck or used masks carried in pockets

Surgical face masks must be worn:

- by ALL STAFF in both clinical and non-clinical areas
- by ALL TRIAL PARTICIPANTS on arriving for appointments and for the duration of that appointment (though this can be a homemade facial covering rather than a surgical mask)

These latest additions are in line with government advice announced on 5th June that from 15th June all NHS staff in England will be required to wear face masks (specifically disposable type 1/2 surgical masks rather than homemade facial coverings), in both clinical and non-clinical areas of the hospitals. Visitors and outpatients will also be required to wear a form of facial covering, so this will also apply to our trial participants. This is to maximise protection to staff and volunteers, acknowledging that the 2 metre distancing may be difficult to maintain at all times. However, the wearing of a mask is only an adjunct and should never replace the continued maintenance of 2-metre social distancing wherever possible.

The only exemption from this practice is if you are able to maintain social distancing AT ALL TIMES, with staff 2 metres apart, but in most cases "AT ALL TIMES" is not likely to be feasible

If you can't stay 2 metres apart at all times then you do need to wear a mask.

The following key points relate to wearing of masks in non-clinical areas:

- There is no set time or recommended number of times you should change your mask each day. But if your mask gets dirty, wet or damaged, or if you touch the inside of it, then you should change to a new one.
- When you take it off to eat or drink, you should dispose of the old mask, wash or sanitise your hands, and replace it with a new one once you have finished eating. Try and remain 2 metres distant from anyone else when you remove your mask to eat or drink.
- You do not need to take your mask off when using the toilet.
- You do not need to change masks between one non-clinical area and another, including between buildings, unless your mask has become contaminated.
- In a non-clinical area, masks can be disposed of into a pedal-operated domestic waste bin (lined with black bin liners). They should not be placed into recycling bins.

- Please note that if you suffer from breathing difficulties, or suffer from genuine discomfort or distress when wearing a mask, you must raise this with your line manager at the earliest opportunity. There are reusable washable masks that we may be able to obtain if someone is unable to tolerate a surgical mask, but these are not recommended by PHE.

In clinical areas staff can keep the same mask on (for up to a maximum of 3 hours) as long as 1) they don't touch them/ don't become contaminated and 2) they don't become moist.

- Once removed dispose of mask immediately into a clinical waste bin.
- NOTE: Used masks are potentially contaminated and pose a risk of transmission.
- Hand hygiene should be performed after disposal of masks.

Filtering face piece (class 3) (FFP3) respirators

Filtering face piece (class 3) (FFP3) respirators should be worn whenever there is a risk of airborne transmission of pandemic COVID-19 i.e. during aerosol generating procedures (AGPs). For the purposes of the trial there should be no need to wear an FFP3 respirator at any time as at no point will any trial staff be performing AGPs.

All tight fitting respiratory protective equipment (RPE) (i.e. FFP3 respirators) must be:

- single use (disposable) and fluid-resistant*;
- fit checked (according to the manufacturers' guidance) every time an FFP3 respirator is donned to ensure an adequate seal has been achieved;
- compatible with other facial protection used i.e. protective eyewear so that this does not interfere with the seal of the respiratory protection. Regular corrective spectacles are not considered adequate eye protection;
- disposed of and replaced if breathing becomes difficult, the respirator is damaged or distorted, the respirator becomes obviously contaminated by respiratory secretions or other body fluids, or if a proper face fit cannot be maintained; and
- be worn once and then discarded as clinical waste (hand hygiene must always be performed after disposal)
- removed in a safe area if there is possible ongoing risk of aerosol transmission in direct clinical area (for example, in the event of a cardiac arrest where AGPs are being performed FFP3 masks would be removed by the resuscitation team in an anteroom or nearby designated room). N.B. All other PPE should be removed in the direct clinical area (and hand hygiene performed) prior to exiting.

*If wearing a FFP3 that is not fluid resistant, a full-face shield/ visor must be worn. A FFP3 respirator, although 'single use', can be worn for as long as comfortable.

6.3.3 "Levels" of PPE

PPE is often referred to as Level 1 or 2. In fact, Level 1 is a hybrid of standard precautions and transmission-based droplet precautions, as it incorporates a surgical mask. Level 2 PPE specifically relates to the risk from aerosol-generating procedures. To clarify any confusion around this:

Level 1 PPE comprises:

- Apron
- Gloves
- Fluid-repellent surgical mask
- (Eye protection, worn if risk of splash to the eyes, and now by all those with any direct patient contact)

Level 2 PPE comprises:

- 2 pairs of gloves
- Fluid-resistant gown
- FFP3 mask
- Eye protection/ face visor

Note no trial staff will need to wear level 2 PPE at any stage during the trial

6.4 Putting on and removing PPE

Before putting on any PPE, staff must ensure jewellery is removed, long hair is tied back (and before putting on a mask ensure you are well hydrated).

General procedures to follow:

- Keep hands away from face and PPE being worn
- Change gloves when torn or heavily contaminated
- Limit surfaces touched in the clinical care environment
- Regularly perform hand hygiene
- Always clean hands after removing gloves

Order for PUTTING ON PPE:

Apron/ Gown (Level 1/2) --> **Mask** --> **Eye protection** --> **Gloves**

Order for REMOVING PPE (Level 1):

Apron --> Gloves --> HAND SANITISE --> Eye protection --> Surgical Mask --> HAND SANITISE

The only exception to this removal order is when level 1 PPE (including face visors) are doffed after a swabbing session. Here, in order to minimise any contamination to the staff member while they are cleaning their visors, they should not immediately remove their apron. Instead, order for removal is as follows:

Remove Gloves > HAND SANITISE -> Apply new gloves -> Remove visor and clean (and hang to dry) -> Remove Apron -> Remove Gloves -> HAND SANITISE -> Remove mask last -> HAND SANITISE.

All clinical staff must remove all PPE (except surgical mask) before exiting the clinic room where a volunteer is being assessed and disposed of as clinical waste. PPE should NOT be worn into the waiting area or non-clinical areas. Where possible, runners should operate between clinic rooms (they only need to wear surgical masks as they are not having direct close contact with the volunteers) but if a member of clinical staff needs to leave the clinic room for any reason, PPE (other than masks) will be removed and then fresh PPE will need to be reapplied on return.

No masks that have been worn in the clinical areas should be taken into the non-clinical/ office areas, and vice versa. There should never be any transfer of PPE between clinic and office areas.

- All PPE should be immediately disposed of in a clinical waste bin in the same room in which the volunteer contact occurred (only exception is FFP3 respirator)
- Used PPE should never be transferred to another clinical area
- Face masks worn in non-clinical areas can be disposed of in a pedal-operated domestic waste bin and should not be recycled

Note on eye protection:

- Where eye protection is disposable (e.g. integrated visor worn during swabbing of symptomatic volunteers) then this should be disposed of as per other PPE
- Where eye protection is **not** disposable (safety spectacles) these should be carefully cleaned with Clinell wipes as soon as doffed, before being re-used. As for masks, these can be used for more than one successive clinical interaction as long as they have not been contaminated. These should never be given to another member of staff to wear – each member of staff should have (and keep) their own spectacles

6.5 PPE for different clinical scenarios/ procedures

- All study staff (including reception and office-only staff, i.e. whether based in clinical or non-clinical areas), should be wearing fluid-resistant surgical masks while at work.
- All staff having direct close contact with volunteers (defined as administering care within a 2-metre distance, e.g., examining/ taking blood/ swab) should also wear eye protection
- All trial volunteers are also required to wear some form of facial covering or mask

At the start of each volunteer review visit, volunteers will be escorted into a designated clinic room and asked to wash their hands/ use ABHR before the consultation begins.

Non-clinical staff (receptionist/ runners) should avoid accepting/touching items handled by the volunteers – e.g., when doing ID check or offering to help with bag/water bottle. If contact occurs, they should immediately hand sanitise before continuing their work.

Table 8 and detailed footnotes outline the recommended PPE for different scenarios/ procedures.

Table 8: Transmission based precautions (TBPs): Personal protective equipment (PPE) for care of volunteers in the COV001 trial

	Screening visit (PPE applies to all staff having direct close volunteer contact)	Vaccination with ChAdOx1-nCoV19	Routine follow-up of *asymptomatic* volunteers involving direct contact**	Clinical review and/or Swabbing of *symptomatic* volunteers	Cardiac arrest## (not considered aerosol generating for trial staff as intervention limited to AED application +/- chest compressions)
Disposable Gloves	Yes	Yes	Yes	Yes	Yes
Disposable Plastic Apron	Yes	Yes	Yes	Yes	Yes
Disposable Gown	No	No	No	No	Yes
Fluid-resistant (Type IIR) surgical mask (FRSM)	Yes	Yes	Yes	Yes	Yes
Filtering face piece (class 3) (FFP3) respirator	No	No	No	No	No[##]
Eye protection	Yes	Yes*	Yes	Yes[#] (full visors)	Yes[#]
scrubs	No	No	No	Yes[¥]	No

*** Eye protection** applies to staff member drawing up or administering the vaccine (GMO contamination risk) OR to any staff having direct contact with volunteer (from COVID risk perspective), as defined as being within 2 meters of volunteer.
Eye protection does not need to be disposable – can be reusable safety spectacles

**** "direct close contact"** includes examining volunteers, taking observations (blood pressure/temperature/oxygen saturations), performing phlebotomy. (all within a 2 metre distance).

[#]**additional risk of splash contamination when swabbing volunteers** (if cough induced at close range). Here eye protection should be a full-face visor. Note that the clinical review/swabbing of symptomatic volunteers will take place in separate clinic rooms with their own entrance. This means that these volunteers should always be physically separated from the main clinical area (including reception). Essentially, creating a clean main area and a dirty area (swabbing rooms).

[##]**Cardiac arrest**:
The latest PHE guidelines (as of 17th April 2020) state that **chest compressions and defibrillation** (as part of resuscitation) **are <u>not considered AGPs</u>**; first responders (in any setting) can commence chest compressions and defibrillation without the need for AGP PPE while awaiting the arrival of other clinicians to undertake airway manoeuvres.

This updated guidance can be applied to 2 different arrest scenarios:

1. Cardiac arrest in a healthy volunteer as a complication of vaccination (e.g., anaphylaxis):

   In this scenario, the risk to attending staff is very low and they should proceed with the application of AED pads and chest compressions as required, in level 1 PPE (adrenaline will already have been given and intravenous access secured). However, no airway manoeuvres should be attempted.

2. Cardiac arrest in a symptomatic volunteer, as a complication of COVID-19:

   If no AGPs are attempted the risk to attending staff should again be very low (already wearing level 1 PPE plus additional full face visor). However, as a further precaution in this situation to maximise trial staff safety, no chest compressions will be attempted. The only permitted interventions by trial staff will be the application of AED pads +/- intravenous access.

In both situations the resuscitation team and ambulance will be called immediately, and on arrival of the resuscitation team, pre-prepared complete packs of level 2 PPE (on the resuscitation trolley) will be provided immediately to all members of the team, so that they can proceed with airway manoeuvres/ AGPs as required. These staff will have previously been fit tested or fit "checked".

¥ **Scrubs** will be available to all members of the swabbing team so that staff can change out of their normal clothes and change into scrubs before donning PPE to assess/swab a symptomatic volunteer. Scrubs do not need to be removed after every PPE removal unless they have become contaminated, but should always be doffed and placed in the dedicated laundry point at the end of a swabbing session for washing. Scrubs should never be taken home for washing. Wearing of scrubs outside the clinical swabbing area is not permitted.

Wipeable shoes should also be worn and wiped with Clinell wipes before leaving the swabbing room.

6.6 Infection Control Procedure if volunteer found to be symptomatic/ meets criteria for swabbing during a routine study visit (post enrolment)

This is an unlikely scenario given volunteers will be asked to report any symptoms and take their temperatures before coming to clinic on the morning of their visit. If, however, symptoms develop while being assessed in a clinic room OR they are found to have a temperature of ≥37.8C (single reading) in clinic:

- Volunteer will be asked to wash hands (they will already be wearing a mask).
- Attending clinical staff will remove their gloves and apron and wash their hands. Masks/ eye protection can remain in place.
- Volunteer will be escorted by same clinical staff to swabbing room ("dirty" area), as quickly as possible with guidance that they do not touch anything on the way. They will be escorted via the outside route, not through the main "clean" area.
- Clinic room will then receive an enhanced clean before any further consultations may proceed.
- Note: clinical staff should never wander outside the clinical area wearing PPE (other than masks) – all should be removed in the clinic room.

6.7 Room Preparation and Cleaning after Use

All non-essential equipment/ furniture should be removed from the clinic rooms and waiting area.

6.7.1 Surfaces

- **All frequently-touched surfaces** should be clutter-free and cleaned with **Clinell Universal Wipes** at a minimum of:
    - three times a day AND
    - between each volunteer appointment AND
    - when known to be contaminated with secretions, excretions or body fluids

  These include door/toilet handles, table/ trolley tops, call bells, bed rails/chair arms
- All surfaces should be wipeable

6.7.2 Equipment

- **Equipment –** should be single use where possible.
- **Reusable (communal) non-invasive equipment** (BP cuff, pulse oximeter, stethoscope, blue tray) MUST be decontaminated using **Green Clinell Universal Wipes**
    - after every patient use
    - after blood and body fluid contamination
    - at regular intervals as part of equipment cleaning

  Note: if clinical fellows use their own stethoscopes then these must be wiped down after each use.
- One dedicated set of equipment should be stored in the swabbing/symptomatic review room, not removed from the room or used for other purposes
- **Cardiac arrest equipment/ resuscitation trolley:** This will not be dedicated to the swabbing room so all parts of this equipment will need careful cleaning prior to the arrest trolley leaving the swabbing room.

6.7.3 Enhanced clean of symptomatic volunteer/swabbing rooms

- In addition to the normal cleaning schedule, a daily **enhanced clean** of the symptomatic volunteer/swabbing clinic rooms must be performed using either:
    - A combined detergent/disinfectant solution at a dilution of 1,000 parts per million available chlorine (ppm chlorine (av.cl.)); or
    - **A general purpose neutral detergent in a solution of warm water followed by a disinfectant solution of 1,000ppm av.cl.**
    - *(In practice Clinell Universal Wipes are adequate and compatible with most equipment/surfaces, including stethoscopes)*

6.7.4 Management of Spills

Haztab granules must be used for large spillages of blood and blood-stained body fluids

N.B. Haztab granules must not be used on urine (can use clinell wipes)

6.7.5 Environment: General Decontamination Principles

- **An increased frequency of decontamination** should be incorporated into the environmental decontamination schedules for other areas where there may be higher environmental contamination rates: e.g. toilets
- **Domestic cleaning staff** performing environmental decontamination should:
    - be allocated to specific area(s) and not be moved between COVID-19 and non-COVID-19 care areas; i.e. different cleaners should be allocated to symptomatic volunteer review/swabbing rooms from the rest of the clinical area
    - be trained in which PPE to use and the correct methods of wearing, removing and disposing of PPE.
        - Cleaners need to wear gloves, apron AND mask at all times unless they are in an empty office after hours in which case a mask is not required)
- Ventilation**: Adequate natural ventilation must be maintained in all clinical areas/rooms** (there is no assisted supply/extract air circulation system in the clinical areas)

ASSOCIATED DOCUMENTS

APPENDIX A: Example Website Text COV001

COV001 Website text V2.016th April 2020

COVID-19 Vaccine Study
COV001

What is the purpose of this trial?

The purpose of this study is to test a new vaccine against COVID-19 in healthy volunteers.

A new virus causing respiratory disease emerged in Wuhan, China in December 2019 and has since rapidly spread to many other countries around the world, despite unprecedented containment efforts. The virus is part of the Coronavirus family which may cause respiratory infections ranging from the common cold to more severe diseases. This recently discovered coronavirus causes coronavirus disease COVID-19.

Common symptoms of COVID-19 include fever, tiredness, and dry cough. Whilst about 80% of infected people have only mild symptoms and will recover from the disease without needing special treatment, 1 in every 6 people who gets COVID-19 becomes seriously ill. Older people and those with underlying medical problems are more likely to develop serious illness. Thousands of deaths have been reported so far.

The WHO declared the COVID-19 epidemic a Public Health Emergency of International Concern on 30th January 2020. There are no currently licensed vaccines or specific treatments for COVID-19. Vaccines are the most cost effective way of controlling outbreaks and the international community have stepped-up their efforts towards developing one against COVID-19.

This study will enable us to assess if healthy people can be protected from COVID-19 with this new vaccine called ChAdOx1 nCoV-19. It will also give us valuable information on safety aspects of the vaccine and its ability to generate good immune responses against the virus. We will do this by randomly allocating participants to receive the COVID-19 vaccine or a control injection in addition to doing blood tests and collecting information about any symptoms that occur after vaccination.

COV001 Website text V2.016th April 2020

Condition Studied
COVID-19

Trial Length
6 months (with optional 1 visit at 1 year post vaccination)

Number of visits
4-12 (depending on the group)

Am I eligible to participate?

You must:	You must **NOT**:
• Be aged 18-55 years old • Be in good health • Be based in Thames Valley Area	• Have tested positive for COVID-19 • Be pregnant, intending to become pregnant or be breastfeeding during the study • Have previously taken part in a trial with an adenoviral vaccine or received any other coronavirus vaccines

Thames Valley Area: Please note you will only be eligible if you are currently living in the Thames Valley Area.

What does the trial involve?

During this study, we will recruit a total of 1112 volunteers, of which up to 561 will be vaccinated with the candidate vaccine ChAdOx1 nCoV-19, and up to 551 will be vaccinated with a control vaccine. Volunteers will be blinded to what group they are in (except group three).

If you are in group 1, you will have 8 visits over a period of 6 months with an optional extra visit a year from the vaccination.

Group 2 volunteers will have 4 visits over a period of 6 months with an optional extra visit a year from the vaccination.

Group 3 volunteers will attend 11 visits over a period of 6 months, also with an optional extra visit a year from the first vaccination.

Group 4 volunteers will attend 4 visits over a period of 6 months, also with an optional extra visit a year from the first vaccination.

Vaccine appointments usually last around 90 minutes, and follow-up appointments around 20 minutes. Please note visits may take longer due to the high number of planned volunteers in the trial.

Is there any reimbursement for the trial?

You will receive compensation for your time, travel and contribution. If you participate in the study until the end, you will receive a total payment of £190-625.

What are the advantages of taking part?

Knowledge gained from this study will help us develop a vaccine against the newly emerging coronavirus disease COVID-19. There are no direct benefits of taking part, however you will receive a full medical examination at your screening appointment as part of the study.

Are there any risks from taking part in the study?

Although this is the first time this vaccine has been administered to humans, similar investigational vaccines have been widely administered for many pathologies without significant safety concerns.

The risks and side effects of the proposed study procedures are:

- Blood samples: drawing blood may cause slight pain and occasionally bruising
- Vaccinations: Common side effects are some mild redness and swelling at the injection site. You may feel like you have flu-like symptoms within 24 hours of the vaccinations. These usually resolve within 48 hours.

Please refer to the information sheet for full details of procedures and potential risks.

What will happen if I don't want to carry on with the study?

Participation is voluntary and you are free to change your mind and withdraw at any time. You do not need to provide a reason. This will not affect your subsequent medical care in any way. If you withdraw we might need to offer you a follow up visit, for example to check the vaccination site or a blood result.

For more details about the study, please read the full information sheet.

You can make a difference.

If you think you are interested in this study, please complete our pre-screening questionnaire (linked)

APPENDIX B: Example Pre-Screening Questionnaire Text COV001

COV001 PRE-SCREENING QUESTIONNAIRE

1. Are you aged 18-55?

2. Do you live in the Thames Valley Area? (see map below) * Thames Valley area map*

3. Are you registered with a GP Practice in the UK?

4. Are you able to travel to appointments without relying on public transport or taxis (e.g. either by driving yourself or driven by someone in your household)?

5. Are you currently living with anyone over 70 years old or anyone who has been identified as at high risk for severe COVID-19 disease?

6. Are you or have you been at high risk of exposure to COVID-19 before enrolment (including but not limited to: close contacts of confirmed COVID-19 cases, anyone who has had to self-isolate as a result of a symptomatic household member, frontline healthcare professionals working in A&E, ICU and other high risk areas)?

7. Are you currently taking any medication?
   a. Please give details of any medication you are currently taking.

8. Are you currently under the care of, or waiting for an appointment with, a hospital specialist?

a. Please give details of any specialist care or appointments.

9. Have you been diagnosed with COVID-19?

10. Have you had a fever, cough, shortness of breath or loss of taste/smell since February 2020?

11. Do you have any chronic (long-term) heart problems (including hypertension)?

12. Do you have epilepsy?

13. Do you have any chronic (long-term) respiratory disease e.g. asthma (this does not include resolved childhood asthma)?

14. Do you have chronic (long-term) liver disease (excluding Gilberts Syndrome)?

15. Do you have chronic (long-term) kidney disease?

16. Do you have any long-term neurological conditions (excluding migraine)?

17. Do you have diabetes?

18. Are you seriously overweight (BMI≥40 Kg/m^2) or underweight (BMI≤18 Kg/m^2)?

19. Do you have any problems with your immune system (including problems with your spleen)?
    a. Please specify:

20. Are you taking any immunosuppressant medication?
    a. Please specify what medication you are taking:

21. Are you under the care of a psychiatrist?

22. Any other health conditions:

23. Have you previously taken part in a clinical trial involving a vaccine?
    a. Please give details of any trials you have previously participated in that have involved a vaccine (if possible: the disease studied, vaccine given, who the study was with).

24. Have you received any vaccinations in the past 30 days or do you have any planned vaccinations coming up?

25. Are you currently pregnant, breastfeeding or planning on becoming pregnant over the next 6 months?

26. Do you have any plans to travel in the next 6 months?
    a. Please give details of where you are planning to travel to and dates.

27. How did you hear about us?
    - Facebook
    - Instagram
    - Twitter
    - Word of mouth
    - Poster
    - Email Circular
    - Online Search
    - Daily Info
    - Other ***if other, please specify:**

Thank you for your interest in our study. Based on your responses, you are eligible to proceed to screening. Please complete the below questions and we will be in touch with more information about the study and to arrange a screening appointment.

Thank you for your interest in our study. Based on your responses, you might be eligible to proceed to screening. Please complete the below questions and we will be in touch if you are eligible or if we have any more questions.

Thank you for your interest in our study. Based on your responses, you are not eligible to take part. If you are interested in hearing more about our other studies, you can sign up to our monthly newsletter here: http://newsletter.ovg.ox.ac.uk/OVG/lists/?p=subscribe&id=1

Demographics

1. What is you first name?

2. What is your last name?

3. What is your date of birth?

4. What is your email address?

5. What is your phone number?

6. What is the first part of your postcode (e.g. OX4)?

7. What are your GP Practice details?

APPENDIX C: Vital signs grading

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially Life threatening
Fever (oral)	38.0°C - 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C	> 40°C
Tachycardia (bpm)*	101 - 115	116 – 130	>130	A&E visit or hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia
Systolic hypertension (mmHg)	141 - 150	151 – 155	≥155	A&E visit or hospitalization for malignant hypertension
Diastolic hypertension (mmHg)	91 - 95	96 – 100	>100	A&E visit or hospitalization for malignant hypertension
Systolic hypotension (mmHg)***	85 - 89	80 – 84	<80	A&E visit or hospitalization for hypotensive shock
Respiratory Rate –breaths per minute	17 - 20	21-25	>25	Intubation

Table 11. ***Severity grading criteria for physical observations.*** **Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)*

APPENDIX D: Severity Grading Hypoxia

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Hypoxia (oxygen saturations)	95-96%	93-94%	92% or lower	imminent respiratory arrest

APPENDIX E: Laboratory grading of AEs

Adapted from FDA guidelines (using local NHS Trust laboratory reference ranges)

Haematology			Lab Range	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin Absolute	Male	g/l	130 - 170	115-125	100-114	85-99	<85
Haemoglobin Absolute	Female		120 - 150	105-113	90-104	80-89	<80
Haemoglobin Decrease from Baseline			n/a	10-15	16-20	21-50	>50
White Blood Cells	Elevated	x109/l	11	11.5-15.00	15.01-20	20.01-25	>25
White Blood Cells	Low		4.0	2.5-3.5	1.5-2.49	1.0-1.49	<1.0
Platelets	Low		150-400	125-140	100-124	25-99	<25
Neutrophils	Low		2.0-7.0	1.5-1.99	1.0-1.49	0.5-0.99	<0.50
Lymphocytes	Low		1.0-4.0	0.75-0.99	0.5-0.74	0.25-0.49	<0.25
Eosinophils	Elevated	x109/l	0.02 - 0.5	0.65-1.5	1.51-5.00	>5.00	Hypereosinophilia
Biochemistry							
Sodium	Elevated	mmol/l	145	146-147	148-149	150-155	>155
Sodium	Low		135	132-134	130-131	125-129	<125
Potassium	Elevated	mmol/l	5	5.1-5.2	5.3-5.4	5.5-6.5	>6.5
Potassium	Low		3.5	3.2-3.3	3.1	2.5-3.0	<2.5
Urea	Elevated	mmol/l	*2.5 - 7.4	8.2-9.3	9.4-11.0	>11.0	Requires dialysis
Creatinine	Elevated	µmol/l	*49 - 104	1.1-1.5xULN 114-156	>1.5-3.0xULN 157-312	>3.0xULN >312	Requires dialysis
Bilirubin	Normal LFTs	µmol/l	0-21	1.1-1.5xULN 23-32	>1.5-2xULN 33-42	>2-3xULN 43-63	>3xULN ≥64
Bilirubin	Abnormal LFTs	µmol/l	0 - 21	1.1-1.25xULN 23-26	>1.25-1.5xULN 27-32	>1.5-1.75xULN 33-37	>1.75xULN >37
ALT		IU/l	*10 - 45	1.1-2.5xULN 49-112	>2.-5xULN 113-225	>5-10xULN 226-450	>10xUPN >450
Alk Phosphatase	Elevated	IU/l	*30 -130	1.1-2xULN 143-260	>2.-3xULN 261-390	>3-10xULN 391-1300	>10xULN >1300
Albumin		g/l	32-50	28-31	25-27	<25	-
CRP	Elevated	mg/l	<10	>10-30	31-100	101-200	>200

** A value < the lower range listed in this table will be classified as Grade 0.*

APPENDIX F: Procedure for urinalysis and pregnancy tests at the screening visit

1. Visit staff label urine sample pot with participant sticker and write room number, plus male or female (m/f) in permanent marker.
2. Visit staff instruct participant to give mid-stream sample and to drop off sample in specimen box outside sluice (N.B. for screenings conducted in the bay area, the participant will be asked to leave the sample in the bathroom).
3. Urinalysis tester performs urinalysis and pregnancy test.
4. Urinalysis tester collects result readouts, attaches to investigator comments sheet and reviews results for ≥+ or 30mg/dL protein – if present, urinalysis tester puts sample in biochemistry sample request bag. Samples will not be disposed of until end of all morning or afternoon visits, as applicable, in case results have been missed and additional analysis is required.
5. Screening clinician reviews results and follows steps below, as appropriate.

- **If <u>results normal</u>**
    a. Screening clinician signs results on investigator comments sheet.
    b. Enter results on eCRF.

- If **<u>urine ACR needed</u>** (≥+ or 30mg/dL protein on urine dip),
    a) At the end of the visit, visit staff collect urine sample in biochemistry sample bag, add participant sticker to request form and place in pathology sample bag to be sent to lab (as per blood samples).
    b) Screening clinician
        I. Signs results and documents "ineligible – abnormal finding, urine ACR needed" on investigator comment sheet.
        II. Enters results into "screening urine" eCRF and marks further action required – recording here that urine ACR needed and that sample has been sent (results will be reviewed at the time of eligibility sign-off).

- **If ≥ + blood and repeat test needed:**
    a) Visit staff give participant new sample pot labelled with participant number and specimen bag.
    b) Participants should be asked to drop off the sample between 9 and 11am at reception – male participants will be instructed to return in 3 days and females will be asked to return a minimum of 2 days after period finished.
    c) Screening clinician
        a. Signs results and documents "ineligible - abnormal finding" on investigator comment sheet.
        b. Enters results into "screening urine" eCRF and marks further action required – recording here that repeat sample required and participant instructed to drop off repeat sample.
    d) Repeat urine samples dropped off by participants are tested by nurse or medical student stationed in sluice room.
    e) Results are reviewed by a screening clinician and entered into the screening urine results eCRF.
    f) Where results are abnormal, it is the responsibility of the reviewing clinician to act on the abnormal result, this may involve a handover to another clinician, e.g. clinician reviewing eligibility (steps should be followed as per clinically significant abnormal findings at screening).

- **<u>If glucose present:</u>**
    a. Screening clinician documents "ineligible – abnormal finding" on investigator comments sheet and signs result.
    b. Enter results on Redcap
    c. Screening clinician follows steps as per clinically significant abnormal finding

- I**<u>f urinary pregnancy test borderline or positive</u>**
    a) <u>Follow steps as per SOP OVG058.</u>
    b) <u>M</u>ark as "ineligible" on investigator comments sheet.
    c) Enter urine results on Redcap

6. Admin team will update Access database (Screening clinical tab) based on investigator comments sheet in CRF pack with
    a. If results normal and signed off – select Yes to urine eligible field
    b. If ineligible – select no to urine eligible field
    c. If "ineligible- abnormal finding"
        i. Select NO to urine eligible field
        ii. select Yes in "abnormal finding action required" field

Oxford Sponsored COVID trials SAE form completion guidance

Report Number

- Leave this blank, the SAE number will be added on receipt.

Study details

- Enter site name and PI Name.

Participant details

- Enter subject ID
- Select gender
- Enter age at time of event in years.

Report details

- Select box to indicate whether this is an initial SAE report or an update report. If completing an update report, indicate number of report (e.g. 1st update report would be number 01).
- Indicate what date the site became aware of this SAE. Note, if this is an AE that has progressed to an SAE, the date entered here must be the date the site became aware the AE had progressed to serious.

SAE Classification

- Select SAE classification that most appropriately describes the event. If the SAE applies to multiple categories, the most severe of the options should be ticked (e.g. life threatening supersedes hospitalisation). For other medical events ensure the description of events (see below) includes why the event is deemed serious e.g. laboratory event (see protocol for further information).

Diagnostic Term

- Enter diagnosis
- Only enter one main event per form
- Do not enter symptoms here.

SAE start and end dates and Outcomes

- Enter start date of SAE. This may be different to the date site became aware of the SAE. If an AE is classified as a SAE due to a hospital admission, even if the participant's symptoms started before admission, it is the admission date that would be the start date.
- For SAEs that are ongoing or with an unknown End date tick the relevant box.
- Outcomes and End Dates: As a general principle, SAEs must be followed up and reported to resolution. For SAEs with an outcome of "resolved/ recovered" or "resolved with sequelae" enter End date of the SAE; N.B. if the outcome is marked "resolved with sequelae" this closes the SAE report. Therefore, if these sequelae need to be followed or it is likely that further clinically-relevant information is going to become available, it is best to leave the outcome as "ongoing" to allow recording of further updates within the SAE form, before the SAE is finally closed. This is to avoid multiple separate SAE reports being made in relation to the same

participant (e.g., in the context of a chronic condition such as malignancy, where multiple hospital admissions are likely to occur). By contrast, for a hospital admission where no further follow-up of the condition is required once the participant is discharged from hospital (i.e., the outcome is resolved/recovered) then the End data can be the date of hospital discharge.

Study vaccine administration details

- Enter date of study vaccine administration and injection site details for prime and if applicable boost. If participant is in a one dose group or in two dose group but has not yet received their booster vaccine, please score out the second study vaccine administration and injection site details line with a single line, date and initial.

Causality assessment

- An appropriately delegated clinician at site must make an initial assessment of the relationship of the event to the administration(s) of the vaccine. An interpretation of the causal relationship of the intervention(s) to the SAE in question must be made, based on the type of event; the relationship of the event to the time of vaccine administration(s); and the known biology of the vaccine therapy (Table A). Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination should be considered and investigated.
- If a participant has received 2 doses of vaccine the clinician must consider both doses in reaching a causality decision.
- Select appropriate box to indicate assessment of causality.

0	**No Relationship**	No temporal relationship to study product ***and*** Alternate aetiology (clinical state, environmental or other interventions); ***and*** Does not follow known pattern of response to study product
1	**Unlikely**	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	**Possible**	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines
3	**Probable**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions ***or*** Known pattern of response seen with other vaccines
4	**Definite**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***and*** Known pattern of response seen with other vaccines

Table A. Guidelines for assessing the relationship of vaccine administration to an AE

Description of events

- Provide a description of events including symptoms, investigations/diagnostic tests, diagnosis, follow-up plan, as well as pre-existing conditions and concomitant medications of relevance to the event. This can be similar in format to that of a discharge summary. If admitted to hospital include admission and discharge dates.
- Ensure details (name, role and signature) of the clinician completing the SAE form and date the form was completed are entered at the bottom of page 1.

SAE updates

- An update form should be provided if further clinical information becomes available and when the SAE has resolved or if there is any change to the SAE classification, the diagnostic term, the SAE end date, SAE outcome or SAE causality assessment. A new form is to be submitted for each update. A narrative describing and summarizing the events since the initial SAE report is needed in the description of events section. If you have been given the coordinating centre's reference number please include it in the subject line of follow up emails. If you have not yet received it please include the volunteer's ID number.

Submission of forms

- If a delegated clinician is not available another member of the study team may submit a draft initial report without causality in order to meet the requirement for reporting to the sponsor within 24 hours. They should not sign as the bottom of the form as this must be a delegated clinician. They should clearly print their name, role, signature and date in the narrative section. A clinician must carefully review the information and submit an updated form with causality assessment as soon as possible.
- **Send forms to the SAE Oxford email within 24 hours of the site becoming aware of the event. Original report should be retained at site and filed in ISF along with all communication related to the SAE.**
- Please call *Insert Oxford number* for all enquiries relating to serious adverse events.

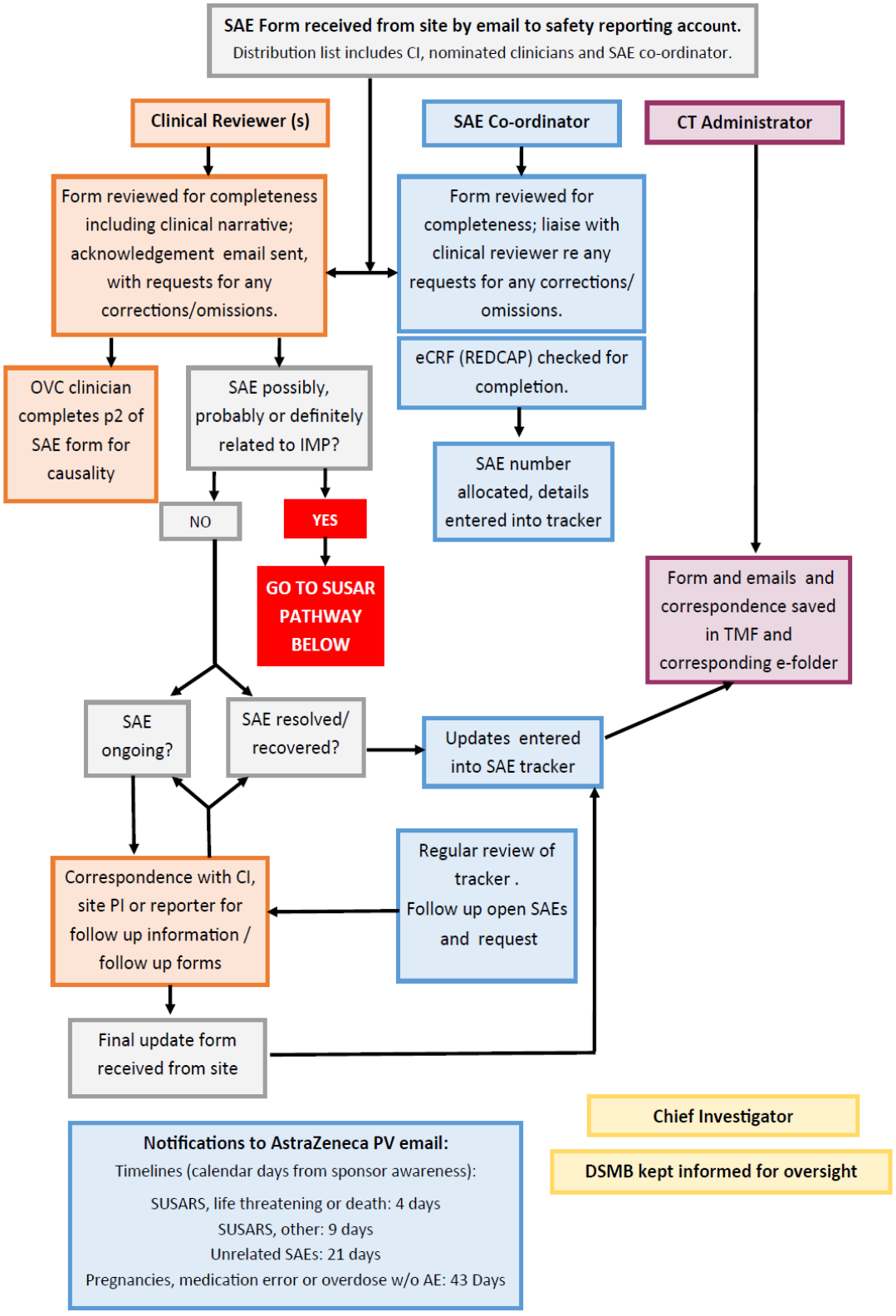
REDCap

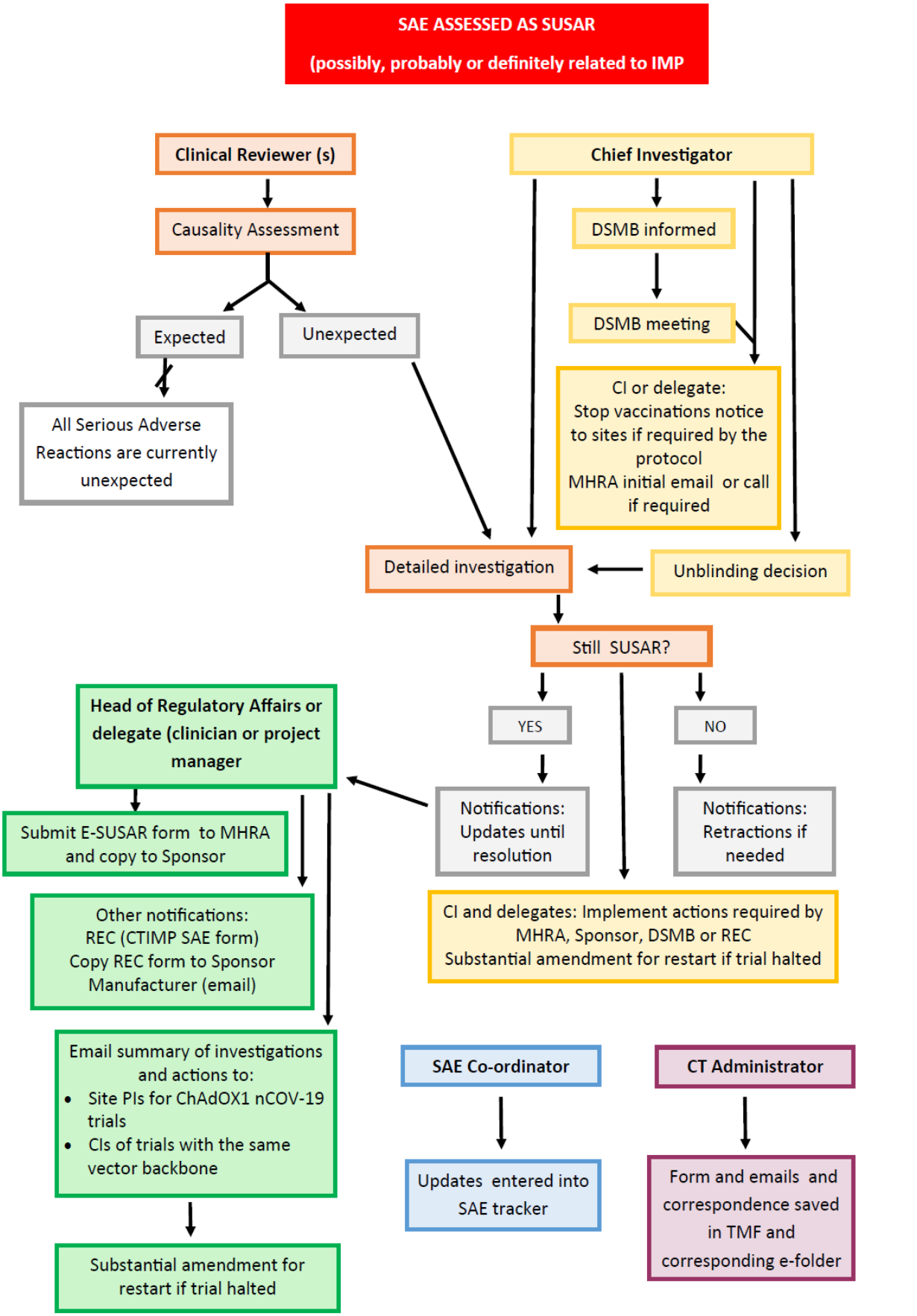
- Ensure the SAE is entered on the AE eCRF even if entered elsewhere.

AESI and Grade 4 Lab AEs

- Adverse Events of Special Interest are listed in the study protocol. These should be reported as SAEs with the exception of 'Thrombocytopenia' which should only be reported as an SAE if it's at grade 3 or above (<100 $x10^9$/L). Pseudo thrombocytopenia (e.g. EDTA induced clumping) should not be recorded as SAEs
- Grade 4 lab AEs will be recorded as SAEs. Medical conditions leading to the Grade 4 abnormality should be recorded as the event term, rather than the lab abnormality itself. The description of the event on the SAE form should state that reason for reporting the event as an SAE is the grade 4 lab abnormality where the event itself wouldn't have necessarily met the SAE reporting criteria (e.g. grade 4 raised ALT due to acute EBV infection). Thrombocytopenia should be reported as SAE when grade 3 or above (as described above) and eosinophilia will be reported as SAE when grade 2 or above (as per protocol).
- Solicited AEs will only be reported as SAEs when serious (i.e. if they meet the SAE criteria listed in the study protocol).
- All AESI (including serious solicited AEs) and Grade 4 Lab AEs will be assessed for causality as described above.

SAE review flowcharts




SAE ASSESSED AS SUSAR
(possibly, probably or definitely related to IMP
Clinical Reviewer (s)
Causality Assessment
Expected
Unexpected
All Serious Adverse Reactions are currently unexpected
Chief Investigator
DSMB informed
DSMB meeting
CI or delegate: Stop vaccinations notice to sites if required by the protocol MHRA initial email or call if required
Detailed investigation
Unblinding decision
Still SUSAR?
YES
NO
Notifications: Updates until resolution
Notifications: Retractions if needed
CI and delegates: Implement actions required by MHRA, Sponsor, DSMB or REC Substantial amendment for restart if trial halted
Head of Regulatory Affairs or delegate (clinician or project manager
Submit E-SUSAR form to MHRA and copy to Sponsor
Other notifications: REC (CTIMP SAE form) Copy REC form to Sponsor Manufacturer (email)
Email summary of investigations and actions to:
Site PIs for ChAdOX1 nCOV-19 trials
CIs of trials with the same vector backbone
Substantial amendment for restart if trial halted
SAE Co-ordinator
Updates entered into SAE tracker
CT Administrator
Form and emails and correspondence saved in TMF and corresponding e-folder

APPENDIX H: Tabulated self-isolation guidance

NHS Occupational Health Advice always takes precedence over study advice.

Follow https://www.gov.uk/coronavirus for latest advice

Situation	Participant Advice	Household Contact Advice
Post-vaccination fever		
Fever ≥37.8^{O}C in first 48 hours post vaccination	Must self-isolate, isolation ends once afebrile for 24 hours If fever persists for >48 hours meets case definition for COVID-19 swab (see below)	End self-isolation at same time as participant
Symptomatic participants meeting case definition for clinic COVID-19 swab		
No swab result	If no swab result for any reason, self-isolate as per latest government advice from date of symptoms meeting criteria for swabbing	Self-isolation as per latest government advice for contacts of suspected cases
S0 COVID swab positive	Self-isolate as per latest government advice	Self-isolation as per latest government advice
S0 COVID swab negative	Self-isolate from onset of symptoms until swab result, can end self-isolation with negative swab result, if afebrile for 48 hrs	End self-isolation at same time as participant
S3-5 COVID swab positive	Advised to self-isolate as per latest government advice for positive cases even if symptoms have resolved and had previously stopped isolation	Self-isolation as per latest government advice for contacts of positive cases
External PCR		
External PCR positive for the first time	Self-isolation as per latest government advice	Self-isolation as per latest government advice

APPENDIX I: Additional Symptomatic Pathway FAQs

Q: What do we do if a participant doesn't inform us of symptoms until a few days after they have occurred?

These need to be judged on a case by case basis. Discuss with senior clinician on call if uncertain.

As a general guide:

When the participant does inform the study team, whether or not they have any residual symptoms or their symptoms have completely resolved, they should still be brought in for an S0 swab/clinic review/safety bloods if within the S0 window (symptom onset within the last 7 days if symptoms fully resolved or within the last 14 days if ongoing symptoms). This is to avoid missing a genuine COVID short symptomatic phase illness.

An exception to this would be if they had received a swab outside the trial at least 24 hours after their symptom onset. If this was confirmed negative and they had no residual symptoms then there would be no need to bring them back for swabbing or clinical review as the likelihood of an initial false negative is currently low with the lower prevalence in the community. However, if community prevalence rises this may be reconsidered. If they do have a swab taken elsewhere it is important to document in the Investigator Comments CRF where the PCR was done and which assay was used (validated or otherwise), where known.

Q: What do we do if participants decline to come in for their S0 visit?

Participation in the study is of course voluntary but we must try and mitigate against this situation arising at screening by making sure they understand how important it is to comply with all study procedures, particularly if they become symptomatic. This is crucial for their safety (to allow a clinical assessment of their condition and to look for any evidence of vaccine-enhanced disease, supported by blood tests), as well as for the ability of the study to capture its primary efficacy endpoint. If the investigator feels there is any doubt as to whether a participant would comply with these requirements then they should not be enrolled in the study.

If participants say they are too sick to travel for their appointment then they should be assessed over the phone as to whether they need to be urgently re-directed to 999 emergency services.

Q: Is there any flexibility in the timing of the S0 visit to minimise pressure on staffing?

The S0 visit should be conducted a minimum of 24 hours after the onset of symptoms and ideally within 1-2 days of symptom onset. The P7 visit has a 48-hour window (refer to protocol schedule of attendances), meaning it can be conducted from 5-9 days after the positive S0 or S3-5 swab was taken visit.

Q: What do we advise if a symptomatic participant cannot attend for their S0 visit without using public transport?

It should be made clear to participants at screening that they are required to have the means to travel to clinic by a method other than public transport or taxi (if they were to become symptomatic) and that if they cannot guarantee this they will be excluded from participating. If, in spite of this, the situation arises, then all efforts must be made by the study team to facilitate the participant's safe travel, without putting the public at risk e.g. utilising systems for hospital patients who are unable to take public transport.

Q: How do we record adhoc swab results taken outside of the study remit?

These should be recorded in a separate swab results eCRF in REDCap, detailing the name of the testing centre/lab (and whether this is UCAS-accredited) and the type of assay used (and whether this is CE-marked or MHRA derogated) if this information is known

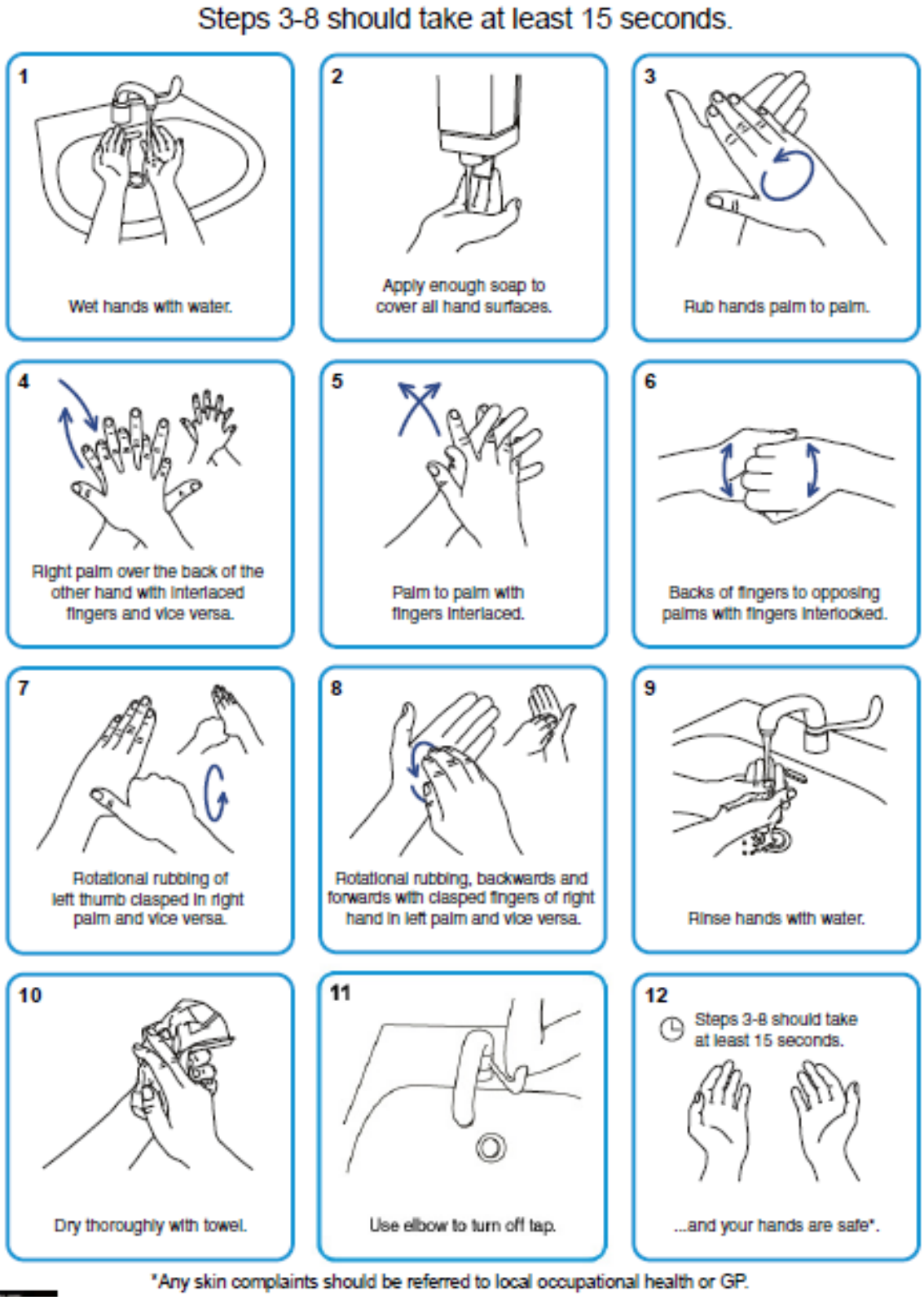
Q: What does it mean when a participant gets a result of 'unclear'?

A: "Unclear" result means the PCR assay has not worked for some technical reason e.g. the PCR run has failed or the kit has taken too long to arrive in the lab. Clinical discretion will be required to determine if a repeat S3-5 swab should be taken, either via repeat self-swab or in clinic.

Q: Why do participants need to come for an S0 visit when they can just take a self-swab using the DHSC kits?

This is primarily for the participant's safety so that a doctor can properly assess their symptoms and examine them/take relevant blood tests. In addition, the home swabbing pathway does not turn samples around in a quick enough time frame to be able to be used for clinical decision making and a swab collected in clinic by a HCW will be of higher sensitivity.

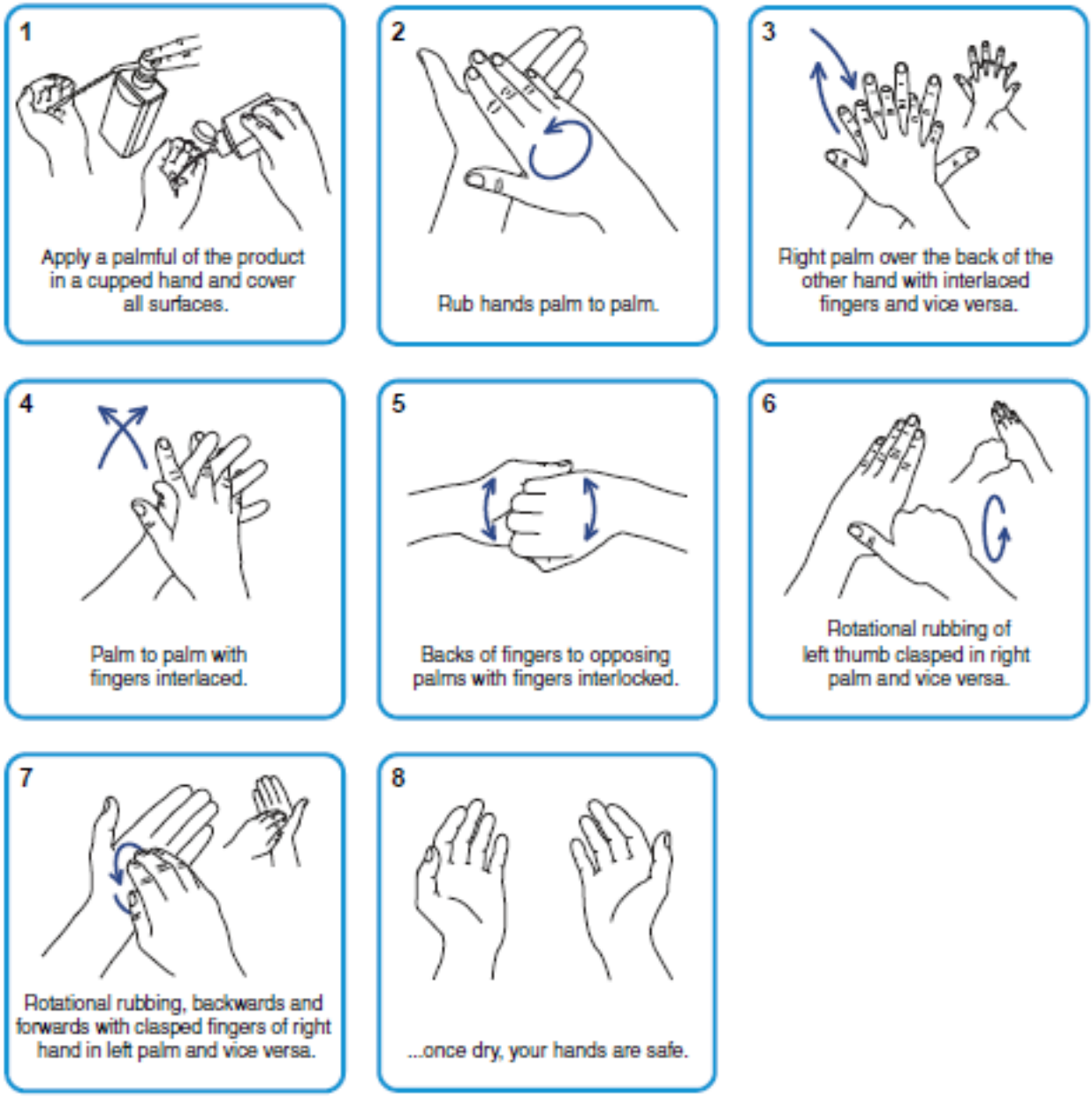
APPENDIX J: Best practice on how to HAND WASH



Taken from PHE Guidance

APPENDIX K: Best practice on how to HAND RUB

Duration of the process: 20-30 seconds.



Taken from PHE Guidance

APPENDIX L: PPE AT A GLANCE: WHAT TO WEAR AND WHEN

Quick removal guide at end of sessional review of healthy asymptomatic vaccinees

(in between volunteers, eye protection/face mask can stay on).

- **All PPE must be disposed directly in to the clinical (yellow) waste bins, except for reusable spectacles/ face visors.**
- **Remove apron first**
- **Remove gloves (pinch n pull technique)**
- **Sanitize hands**
- **Remove eye protection and clean**
- **Sanitize hands**
- **Remove Facemask.**
- **Wash your hands**

ALL STAFF (clinical or non-clinical) must wear a surgical mask at work from 15/06/2020

Reception (no direct contact with volunteers – aim to maintain 2 metre distance)

- Mask (not changed between volunteers, continuous use to max 3 hrs or sooner if wet)

Runners (no direct contact with volunteers – aim to maintain 2 metre distance)

- Masks (not changed between volunteers, continuous use to max 3 hrs or sooner if wet)
- Gloves/Apron when cleaning room (Changed with each cohort)

Urinalysis (no direct contact with volunteers but in clinical area)

- Mask (continuous use to max 3 hrs or sooner if wet)
- Gloves/Apron (worn in sluice only)

Nurses/doctors/medical students
(conducting clinical activity involving direct contact with volunteer – i.e., within 2 metres)

- Mask (not changed between volunteers, continuous use to max 3 hrs or sooner if wet)
- Eye protection (cleaned if become contaminated/ need to be removed and at the end of exposure-prone clinical activity)
    - Safety spectacles for routine review of asymptomatic volunteers
    - Full face visors for review of symptomatic volunteers (swabbing team)
- Gloves (changed as required by activity)
- Apron (changed between volunteers)

Nurses/doctors/medical students
(in room but Not conducting clinical activity involving direct contact with volunteer)

- Mask (not changed between volunteers, continuous use to max 3 hrs or sooner if wet)
- Gloves (changed as required by activity)
- Apron (changed between volunteers)