Screening Protocol for a dose finding human experimental infection study in healthy subjects using a GMP-produced SARS-COV-2 wild type strain

Short Title:	SARS-CoV-2 Screening Protocol
Version and Date of Protocol:	Version 8 Date 19-Jul-2021
hVIVO Protocol Number:	HVO-vCS-003 Screening Protocol
Sponsor:	Imperial College London Room 221 Level 2, Medical School Building Norfolk Place, London W2 1PG
Compound Number (if applicable):	Not applicable
EudraCT Number:	Not applicable

Confidentiality and Protections Statement:

This document contains confidential information. This document must not be disclosed to anyone other than the study staff and members of the Independent Ethics Committee/Institutional Review Board or Competent Authorities. The information in this document cannot be used for any purpose other than the conduct or evaluation of the clinical investigation without the prior written consent of hVIVO.

Personal data included in the protocol is subject to General Data Protection Regulation (GDPR: EU 2016/679) considerations and protections.

Sponsor Statement

This protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study intervention, and with the moral, ethical and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP).

Sponsor Signatory:

23 Jul 2021

Ruth Nicholson

Head of Research Governance and Integrity

Date

Investigator Agreement:

I have read the protocol, and agree to conduct the study in accordance with the approved protocol and any future amendments, the Declaration of Helsinki, the principles of ICH GCP, the current regulatory requirements as detailed in the Medicines for Human Use (Clinical Trial) Regulations (Statutory Instrument 2004/1031) and all subsequent amendments, the UK Data Protection Act 2018, any other applicable laws and guidance.

I agree to conduct the procedures described in this protocol according to these guidelines and to appropriately direct and assist the staff under my control.

Principal Investigator Signatory:

Name (typed or printed):	Christopher Chiu
Institution and Address:	Department of Infectious Disease, Imperial College London
	Hammersmith Campus, DuCane Road
	London W12 0NN, United Kingdom

Signature: _____ Date: 23 Jul 2021

(DD MMM YYYY)

Study Contact Information

CONTACT	DETAILS
Sponsor	Imperial College London Room 221 Level 2, Medical School Building Norfolk Place, London W2 1PG
Sponsor's Representative	hVIVO Services Limited Queen Mary BioEnterprises Innovation Centre 42 New Road, London, E1 2AX, United Kingdom

Refer to the Trial Master File for a complete list of the study personnel contact details.

Protocol Amendment Summary of Changes Table

PROTOCOL HISTORY		
Document	**Date**	**Amendment Type**
SA 3	*19-Jul-2021*	*Substantial*
SA 2	*22-Feb-2021*	*Substantial*
NSA 1	*09-Dec-2020*	*Non-substantial*
Original Protocol	*02-Dec-2020*	*N/A*

Amendment NSA 1 09-Dec-2021

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Inclusion Criteria	Update to inclusion criteria	Administrative error
Overall document	Minor administrative corrections	Administrative error

Amendment SA 2 16-Feb-2021

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
2.2 Exclusion	Exclusion criterion 27	Brought in line with main protocol
3 Screening Process	7-day isolation and 72 hours PCR test	Stay at home for 7 days required prior to quarantine to follow pre-admission infection control procedure agreed with the RFH. PCR test required 72 hours prior to admission.
4.1.2 Ethics	Corrected typographical error	HRA approval is not required for either screening or main protocol as there are no NHS trusts involved in the study.
4.1.2 Ethics	Corrected typographical error	CCC is not required for either screening or main protocol as there are no NHS trusts involved in the study.
4.1.3 Consent	Remote consent	Participants screened prior to implementation of this amendment will require re-consenting. The process for this has been described.
4.1.8 Audits	Corrected typographical error	Removed reference to imperial college healthcare NHS trust as sponsor. ICL is the sponsor only.

Amendment SA 3 19 Jul 2021

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
2.1.3 Inclusion Criteria	Change to wording – removal of Sero-negative to Sero-suitable subjects	Wording changed to reflect the purpose of the Extension Phase of the current protocol – to include previously vaccinated subjects.
2.1.4 Inclusion Criteria	Change to contraception wording for women.	Extension of time for contraception post-viral challenge – wording changed from 30 days to 6 months after receipt of study virus.
2.1.5 Inclusion Criteria	Change to contraception wording for men.	Extension of time for contraception post-viral challenge – wording changed from 30 days to 6 months after receipt of study virus.
2.1.8 Inclusion Criteria	Removal of QCOVID tool wording – adding requirement of evidence of completed COVID-19 vaccination course	Evidence required that subjects have received both doses of COVID-19 vaccine.
2.2.3 Exclusion Criteria	Addition of wording	No previous SARS-Cov-2 infection.
2.2.12 Exclusion Criteria	Removal of wording Hb1A1C	Hb1A1C – will be 'optional' as random glucose also recorded.
2.2.17 Exclusion Criteria	Removal of wording stating, 'no travel restrictions post D28 follow-up.'	Precaution to advise subjects to restrict travel should they be re-infected by D28
2.3 Personalised risk assessment using the QCOVID tool	Removal of Section.	QCOVID – no longer part of exclusion criteria.
3 Screening Process	Include new wording for volunteer identification	Use of ethically-approved volunteer database if available.
3 Screening Process	Include new wording for assessing inclusion/exclusion criteria	Inclusion/exclusion criteria at screening will be assessed based on available evidence
3 Screening Process	7-day isolation amended to 'up to' 7-day isolation	Brought in line with main protocol and main PIS-ICF, able to follow current restrictions in place at the Quarantine Unit
4.1.8 Audits	Corrected typographical error.	Corrected wording.
4.2 Appendix 2	Corrected typographical error	Typographical error in email address corrected

4.4 Appendix 4	Table of toxicity grading scale replaced	Brought in line with main protocol

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1. Introduction

The aim of this screening protocol is to assess volunteers for their potential eligibility to participate in a dose finding human experimental infection study in healthy subjects using a GMP-produced SARS-CoV-2 wild type strain.

2. Study Population

Recruitment will be done through a number of channels:

- Approved advertising, including social medial
- hVIVO volunteer database
- Referral
- Organic search, i.e. where the volunteer has learned of this study by doing a Google search or through friends or family rather than due to any advertising

Following Research Ethics Committee approval of the full study, screened subjects who confirm their willingness to participate in the SARS-CoV-2 human infection challenge characterization study will be invited to consider the study-specific PIS-ICF and enter the final study consenting process.

The number of subjects who are to be recruited will depend on specific sample-size requirements for the SARS-CoV-2 human infection characterization study.

2.1. Inclusion Criteria

The main inclusion criteria for the SARS-CoV-2 challenge study are listed below.

NO	INCLUSION CRITERIA
1	An informed consent document signed and dated by the participant and the Investigator.
2	Male or female, age between 18 and 30 years inclusive (at the time of the study consent)
3	Sero-suitable i.e. with evidence of SARS-CoV-2 vaccine-induced antibody responses but no evidence of previous SARS-CoV-2 infection by an authorised serology test. Those with indeterminate levels and no history of laboratory-confirmed SARS-CoV-2 infection may be included or excluded at the PI's discretion on a case-by-case basis.
4	Women of childbearing potential with a documented menstrual period within 28 days before the first dose (unless using a contraceptive method that suppressed menstruation as indicated in the study protocol) and willing and able to use contraception as described in the study protocol from 2 weeks before the scheduled date of viral challenge until 6 months after receipt of the final dose of study virus or intervention treatment (whichever occurs last). Negative urine pregnancy test will be required at screening plus, on admission to the quarantine unit, a Negative serum beta human chorionic gonadotropin (β-hCG) is a required. A negative urinary pregnancy test prior to virus challenge is also required.
5	Men who are willing to use one of the contraception methods described in the study protocol, from the time of the date of viral challenge, until 6 months after receipt of the final dose of study medication.

6	In good health with no history of clinically significant medical conditions (as described in Exclusion criteria) that would interfere with subject safety, as defined by medical history, physical examination and routine laboratory tests, ECG, and Chest X-Ray* and determined by the Investigator at a screening evaluation and/or at admission to the Quarantine Unit.
7	Subjects will have a documented medical history either prior to entering the study and/or following medical history review with the study physician at screening
8	Evidence of having had a complete COVID-19 vaccination course (as one or two intramuscular injections depending on the authorisation schedule) with the last injection at least 14 days before enrolment
9	Willing and able to commit to participation in the study

* No radiological assessments will be conducted as part of this screening process. Chest X-Ray may only be performed after volunteer signs main PIS-ICF.

2.2. Exclusion criteria

The main exclusion criteria for the SARS-CoV-2 challenge study are listed below.

NO	STANDARD EXCLUSION CRITERIA
Any potential subject who meet any of the criteria below will be excluded from participating in this study.	
Clinical history	
1.	History or evidence of any clinically significant or currently active cardiovascular, (including thromboembolic events), respiratory, dermatological, gastrointestinal, endocrine, haematological, hepatic, immunological, rheumatological, metabolic, urological, renal, neurological, psychiatric illness. Specifically: a) Subjects with any history of physician diagnosed and/or objective test confirmed asthma, chronic obstructive pulmonary disease, pulmonary hypertension, reactive airway disease, or chronic lung condition of any aetiology or who have experienced: ○ Significant/severe wheeze in the past ○ Respiratory symptoms including wheeze which has ever resulted in hospitalisation ○ Known bronchial hyperreactivity to viruses

NO	STANDARD EXCLUSION CRITERIA
	b) History of thromboembolic, cardiovascular or cerebrovascular disease c) History or evidence of diabetes mellitus d) Any concurrent serious illness including history of malignancy that could interfere with the aims of the study or a subject completing the study. Basal cell carcinoma within 5 years of treatment or with evidence of recurrence is also an exclusion e) Migraine with associated neurological symptoms such as hemiplegia or vision loss. Cluster headache/migraine or prophylactic treatment for migraine f) History or evidence of autoimmune disease or known immunodeficiency of any cause. g) Other major disease that, in the opinion of the Investigator, could interfere with a subject completing the study and necessary investigations. h) Immunosuppression of any type.
2.	Any significant abnormality altering the anatomy of the nose in a substantial way or nasopharynx, a clinically significant history of epistaxis (large nosebleeds) within the last 3 months, nasal or sinus surgery within 6 months of inoculation.
3.	Clinically active rhinitis (including hay fever) or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine.
4.	History of anaphylaxis and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.
5.	History or presence of alcohol addiction, or excessive use of alcohol (average weekly intake in excess of 28 units alcohol; one unit being a half glass of beer, a small glass of wine or a measure of spirits).
6.	Psychiatric illness including subjects with a history of depression and/or anxiety with associated severe psychiatric comorbidities, for example psychosis. Specifically, a) Subjects with history of anxiety-related symptoms of any severity within the last 2 years if the Generalized Anxiety Disorder-7 score is ≥4 b) Subjects with a history of depression of any severity within the last 2 years if the Patient Health Questionnaire-9 score is ≥4
7.	Current smokers or subjects who have smoked ≥5 pack years at any time [5 pack years is equivalent to one pack of 20 cigarettes a day for 5 years]. • Subjects who have smoked <5 pack years - at any time in the 3 months prior to admission to the quarantine unit they have used tobacco in any form (e.g.,

NO	STANDARD EXCLUSION CRITERIA
	smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch) or electronic cigarettes.
8.	Family history of 1st degree relative aged 50 years or less with sudden cardiac or unexplained death
9.	Family History of Severe COVID or response to any other viral disease e.g. Guillain–Barré
Measurements and investigations	
10.	A total body weight of ≤ 50g and a Body Mass Index (BMI) ≤18 kg/m2 and ≥28 kg/m2. The upper limit of BMI may be increased to ≤ 30kg/m2 at the PI's discretion, in the case of physically fit muscular individual
11.	Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
12.	Any clinically significant abnormal finding on screening biochemistry, haematology and microbiology blood tests or urinalysis i.e. grade 1 lab abnormalities (or above, see Appendix 4 Toxicity Grading Scale for Laboratory AEs) apart from minor deviations which are clinically acceptable and approved by the Principal Investigator a) Elevated random glucose. b) Positive HIV, active/chronic hepatitis A, B or C test. c) Confirmed positive test for drugs of abuse on admission and urinary cotinine at quarantine.
13.	A forced expiratory volume in 1 second (FEV1) and a forced vital capacity (FVC) <80% of predicted value calculated using ATS/ERS guidance
14.	Twelve-lead ECG recording with clinically relevant abnormalities as judged by the study physician/PI.
Recent respiratory infection	
15.	History of, or currently active symptoms suggestive of upper or lower respiratory tract infection (including reduced sense of taste and smell, raised body temperature and/or persistent cough) within 6 weeks prior to viral challenge.
16.	Presence of cold-like symptoms and/or fever (defined as subject presenting with a temperature reading of >37.9ºC)
17.	History of previous SARS-CoV-2 infection at any time
Receipt of medications and interventions	

NO	STANDARD EXCLUSION CRITERIA
18.	Evidence of a live vaccine within 60 days prior to the planned date of viral challenge, a non-live vaccine within 30 days prior to the planned date of viral challenge (except for COVID-19 vaccines), or intention to receive any vaccination(s) before the day 28 follow-up visit.
19.	Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 3 months prior to the planned date of viral challenge or planned during the 3 months after the final visit.
20.	Medications a) Use of any medication or product (prescription or over-the-counter), for symptoms of hayfever, nasal congestion or respiratory tract infections or dermatitis/eczema including the use of regular nasal or medium-high potency dermal corticosteroids, antibiotics and First Defence™ (or generic equivalents) within 7 days prior to the planned date of viral challenge apart from those described and allowed in Permitted Medication or agreed by the Principle Investigator b) Receipt of any investigational drug within 3 months prior to the planned date of viral challenge. c) Receipt of three or more investigational drugs within the previous 12 months prior to the planned date of viral challenge. d) Prior inoculation with a virus from the same virus-family as the challenge virus. e) Receipt of systemic (intravenous and/or oral) glucocorticoids or systemic antiviral drugs within 6 months prior to the planned date of viral challenge. f) Over the counter medications (e.g. paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date of viral challenge had exceeded the maximum permissible 24-hour dose (e.g., >4g per day of paracetamol over the preceding week). g) Use or anticipated use within 7 days prior to the planned date of viral challenge and during the conduct of the study of concomitant medications (prescription and/or non-prescription), including vitamins or herbal and dietary supplements within the specified windows. h) Chronically used medications, vitamins or dietary supplements, including any medication known to be a moderate/potent inducer or inhibitor of cytochrome P450 enzymes, within 21 days prior to the planned date of viral challenge. i) Subjects who have received any systemic chemotherapy agent, immunoglobulins, or other cytotoxic or immunosuppressive drugs at any time.
21.	Prior participation in another human viral challenge study in the preceding 12 months taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study.
22.	Any nasal sampling procedure in the 6 months before date of expected viral challenge in this study. Nasal swabs are allowed.

NO	STANDARD EXCLUSION CRITERIA
General	
23.	Subject was mentally or legally incapacitated in the opinion of the Investigator.
24.	Females who: a) Are breastfeeding within 6 months of study commencement, or b) Had been pregnant within 6 months prior to the study, or c) Had a positive pregnancy test at any point during screening or prior to inoculation with challenge virus
25.	Those in close domestic contact (i.e. sharing a household with, caring for, or daily face to face contact) with children under 3 years, the elderly (>65 years), immunosuppressed persons, or those with chronic respiratory disease
Other	
26.	Was employed or was a first-degree relative of anyone employed by the Sponsor, a participating clinical trial site, or any Contract Research Organisation involved in the study.
27.	Any other reason that the Investigator considered made the subject unsuitable to participate.
28.	Participants with no knowledge of their family history

2.3. Screen failures

Volunteers that do not enroll on HVO-vCS-003 will be recorded as screen failures and may be eligible to participate in other studies.

3. Screening process

The screening process will consist of several stages:

Volunteers interested in participating will be asked to register their details on a SARS-CoV-2 specific web page UKcovidchallenge.com unless they have previously registered via the hVIVO volunteer database or other ethically-approved volunteer database. All advertising and media will direct volunteers to this web page to register their interest. Volunteers already registered with any other hVIVO database or ethically-approved volunteer database may be contacted to determine their interest in participating in SARS-CoV-2 research.

On the registration form, they will Agree with the Privacy Policy. When beginning the application, they will enter the following details:

- Full Name
- Gender
- Date of Birth
- Email
- Phone number

If they fit the age criteria, they will be contacted and guided to a short webform questionnaire to be performed prior to a follow-up telephone questionnaire or will be asked to complete a telephone questionnaire where the following details will be collected. All volunteer communications and appointment scheduling are managed by the Flucamp recruitment team. Flucamp are the volunteer recruitment function within hVIVO.

Webform Questionnaire (to be followed with a telephone questionnaire):

- Do you have a valid photo ID, UK Driving license or Passport?
- Are you registered with a GP in the UK?
- Do you currently have asthma?
- Do you have COPD as diagnosed by a doctor?
- Are you or your partner pregnant or trying to get pregnant?
- Have you ever been diagnosed with anxiety or depression?
- Do you have any viral blood conditions such as HIV, Hepatitis A, B or C?
- Are you currently suffering from any illness or health related condition (e.g. coughs & colds, stomach problems, chest complaints, dizziness, headaches, eczema etc.)?
- Are you taking any medicines, either prescribed by a doctor, or bought from a chemist/pharmacy (This includes contraception, vitamins and supplements)?
- Height & Weight

Telephone Questionnaire (prior Webform Questionnaire completion is not compulsory):

- Home Address
- Ethnicity
- BMI
- Have you suffered from cold or flu symptoms in the last two weeks?
- Are you available to take part in a clinical trial in the next 12 months?

- Can you read and write in English?
- Do you have photo ID?
- Are you registered with a GP?
- Have you used recreational drugs in the last 3 months?
- Are you a smoker or ex-smoker? If so, how many cigarettes per day and how long for?
- Are you currently suffering from any illness or health-related condition? (coughs, colds, stomach problems, chest complaints, dizziness, eczema, headaches etc.)
- Have you ever been diagnosed with anxiety or depression?
- Are you taking medicines prescribed by a doctor or bought from chemist/pharmacy (includes contraception, vitamins, supplements)?
- Are you or your partner trying to get pregnant?
- Do you have any viral blood conditions (e.g. HIV, Hepatitis A, B or C)?
- Are you employed or related to anybody at hVIVO?
- Do you have asthma?
- Have you had Asthma in childhood?
- Do you have COPD as diagnosed by a doctor?
- Complete a COVID-19 symptom assessment

If inclusion/exclusion criteria are provisionally met based on answers to these questions, an appointment for a first screening visit will be scheduled and a confirmation email and a screening Participant Information Sheet (PIS)/Informed Consent Form (ICF) will be sent to volunteers.

Screening appointments will be conducted at hVIVO. First, the screening process will be discussed with the participant by the study doctor or nurse. When the subject has had enough time to consider their participation in screening, ask any questions they may have, and only when they have agreed to take part will they be asked to read, sign and date a consent form in the presence of the study doctor or nurse who will also sign the consent form. Written consent for screening will be obtained prior to any history-taking, examination or tests are carried out. A copy will be kept in the research file, a copy given to the patient and a copy put into their medical notes.

Following informed consent, the following assessments will be completed.

- Confirmation of name, age, gender, and contact details
- Full medical history including questions about past and present health including clinically significant family history
- Optional - Quality of life questionnaires including the GAD-7 Anxiety Test questionnaire and PHQ-9 Depression Test questionnaire.
- Questions about current weekly alcohol and/or smoking consumption and an alcohol breath test will be performed.
- Check of any previous participation in clinical trials via The Over-Volunteering Prevention System (TOPS).
- Examination for signs of illness or disease (a medical examination).
- Height and weight
- Pulse rate, blood pressure, temperature and breathing rate checked (Vital Signs).
- Electrocardiogram (ECG)
- Urine samples for:

  - Evidence of infection or kidney/urinary tract conditions
  - Test for pregnancy
  - For drugs of abuse & cotinine
- Provide an airway sample (i.e. nasal swab as a tolerance test for the respiratory screen for pathogens and/or immune status). It will be optional to conduct a BioFire test at the discretion of the PI.
- Safety blood tests, including full blood count, renal and liver function tests.
- Testing for SARS-CoV-2 virus (COVID-19) antibodies
- Samples for Hepatitis A, B and C and/or HIV (the virus that causes AIDS)
- Lung function tests.

Inclusion and exclusion criteria will be assessed based on evidence available at the time of screening, any non-applicable aspects of the criteria will be checked upon admission.

The volunteer's medical history will be requested from their GP and reviewed to assess suitability. Subjects may be invited for repeat assessment where / if required at the PI's discretion. For participants contacted via the hVIVO volunteer database, GP medical histories that have been previously received by hVIVO may be used for screening purposes if they were obtained within the screening window of the study (i.e. within 90 days to -3 days prior to date of virus inoculation).

As soon as the SARS-CoV-2 human challenge characterization study is approved, potential participants who have passed screening up to that point will be given or sent the study specific participant information sheet (PIS) detailing the full study and experimental procedures. This will be done in advance of the first study specific visit to give participants enough time to read the PIS, discuss the study with family and friends, as well as being able to call the hVIVO medical team to ask any questions they may have. A follow-up appointment (to be conducted remotely due to the COVID-19 pandemic) will be arranged to go through the details of the study with a study team member and to answer any questions, if this was not already done at the screening visit. Additional calls may be arranged as needed. Participants will be advised that they will be required to self-isolate (stay at home) for up to 7 days immediately prior to admission to the Quarantine Unit. They will also be asked to take a nasal pharyngeal swab (NPS) 72 hours prior to admission to be returned to hVIVO for PCR testing. The samples from this test will be collected by a courier and delivered to the hVIVO laboratory to be analysed.

When the subject has had enough time to consider their participation in this study, ask questions and if they are still willing to take part in the study, they will be invited to be admitted to the quarantine unit (Day -2). Before any study specific procedures are attempted, the study physician will again discuss the study and study procedures with the potential participant and answer any questions. After that, participants will be asked to read, sign and date the full study ICF in the presence of the study doctor or nurse, who will also sign the consent form. A copy of the consent will be given to the participant and another copy will be filed in their medical notes.

4. Supporting Documentation and Operational Considerations

4.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

4.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

4.1.2. Ethics approval

The Study Coordination Centre has obtained approval from the Specialist Adhoc Research Ethics Committee (REC). The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

4.1.3. Consent

The Investigator will obtain a signed screening ICF from each participant before any screening or study specific procedures are performed as described in section 3.

Potential participants will be sent a copy of the Screening ICF when their Screening Visit is arranged and at least one day prior to the visit, and will be encouraged to read it prior to their appointment. Upon arrival at the Screening Visit the Screening ICF is discussed, and they will be given the opportunity to ask any questions, and may take the information sheet away to consider their participation. Participants will be informed that a further discussion with the full study PIS/ICF will be scheduled at a later point (if necessary) and that they will be free to withdraw at any point before or after that.

All participants will be required to have a good understanding of English and the Investigator will be responsible for ensuring that the subject understands the information contained in the ICFs. Once they have confirmed that the subject has understood the study, including the benefits and risks of participation, the subject and the Investigator can sign and date the ICF.

The ICF must be signed and dated by the subject and countersigned by the Investigator (whoever conducted the consent discussion). A copy of the ICF will be given to the subject, and the original will be held in the full study TMF. The consent process will be documented in line with hVIVO SOPs, which require that documented and signed evidence must be available to confirm staff obtaining consent are trained and passed as competent, prior to independently obtaining consent. The Investigator will document the consent process in the subject notes and progress notes as

applicable. This documentation will include details of capacity assessment, discussion with subject, and when/how consent has been obtained.

Participants who were consented prior to implementation of Substantial Amendment 2 will require re-consent to incorporate the up to 7 day stay at home isolation period and PCR test. This process will be done remotely to avoid unnecessary travel by the participants. The process will be as follows:

1) The participant will be emailed (if they have a printer) or posted (if they do not have a printer or indicate this as a preference) a copy of the PIS/ICF.
2) A zoom call will be arranged between the participant and the research physician.
3) The new procedures will be explained to the participant and the option to ask any questions will be presented.
4) The participant and the research physician will each sign a copy of the PIS/ICF. The research team will then arrange for a courier to collect the partially signed PIS/ICF from the participant's home and it will be collated with the partially signed PIS/ICF on site. Once the documents are combined the consent will be considered valid.
5) The participant will be posted a copy of the consent via tracked delivery

Participants will be assured that they can withdraw from the study at any time and for any reason without prejudice to their future medical care, and that they will be informed in a timely manner if new information becomes available that may affect their willingness to continue their participation in the study. This information will be included within the ICF.

The ICF will contain a separate section that addresses the use of samples for future research. The investigator or authorised designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason.

4.1.4. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

4.1.5. Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. hVIVO holds negligent harm insurance policies which apply to this study.

4.1.6. Sponsor

Imperial College London will act as the Sponsor for this study. Delegated responsibilities will be assigned to hVIVO Services Ltd.

4.1.7. Funding

This study is funded by the UK Vaccines Taskforce and Department of Business, Energy and Industrial Strategy. They are acting as sole funders and this agreement is in place. The investigators will not receive any additional payment above their normal salaries. Participants will be given a donation of up to £70 to compensate for the time and inconvenience of attending the screening visit. Additional visits will be compensated with £20 per visit.

4.1.8. Audits

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

4.1.9. Sample and data storage and usage

Samples of tissue, cells and fluids will be stored according to Imperial College London and hVIVO SOPs as appropriate. Samples will be pseudoanonymised with participant identification numbers only and the anonymisation key kept in a separate locked location accessible only to the hVIVO clinical study team. Samples may be used for further assays or in other ethically approved studies. Samples and data may be shared with UK and international collaborators in studies that have been approved by local ethics committees and subject to a valid Materials Transfer Agreement. Data and samples sent outside the UK will be labelled with the identification number only and no patient identifiable data transferred. Screening data is recorded on paper case books. Data is QC'd and only data for enrolled subjects is transcribed to the study data base, as per the hVIVO Data Monument Plan. Data and all appropriate documentation will be stored for a maximum of 25 years after the completion of the study, including the follow-up period according to Imperial College London policy.

At the end of the study any remaining samples will be either destroyed, transferred to the sponsor or subject to consent, transfer to and maintained under hVIVOs HTA licenses.

4.1.10. Data Protection

Participants will be assigned a unique identifier by hVIVO. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law and EU GDPR. The level of disclosure including the participant's rights under the applicable data protection laws must also be explained to the participant in the ICF.

The participant must be informed that his/her medical records may be examined by third parties such as Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate REC members, and by inspectors from regulatory authorities.

4.2. Appendix 2: Adverse events

4.2.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- **Requires hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

4.2.2. Risks and expected adverse events

4.2.2.1. Risk Determination

All screening procedures involve no more than minimal risk to participants. Similar procedures have been used for many years without severe adverse effects. These include blood sampling and ECG. Participants will be counselled about the following:

Blood draws: risks include discomfort as the needle goes through the skin and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

ECG: risks include skin irritation due to ECG electrodes.

4.2.3. Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs
All such events, whether expected or not, should be recorded - it should be specified if only some non-serious AEs will be recorded. Any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs
An SAE form should be completed and emailed to the Chief Investigator within 24 hours.

All SAEs should be reported to the Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs

RGIT@imperial.ac.uk

CI email (and contact details below)

Email: c.chiu@imperial.ac.uk for the attention Dr Christopher Chiu

Please send SAE forms to: Department of Infectious Disease, Imperial College London, Commonwealth Building, Hammersmith Campus, Du Cane Road, London W12 0NN

Tel: 020 8383 2301 (Mon to Fri 09.00 – 17.00)

4.3. Appendix 3: Abbreviations

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALRI	Acute Lower Respiratory Infection
ALT	Alanine Aminotransferase
AP	Analytical Plan
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BD	Twice Daily
BMI	Body Mass Index
cGMP	Current Good Manufacturing Practices
CK	Creatine Kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-reactive Protein
CYP450	Cytochrome 450
DNA	Deoxyribonucleic acid
DMID	Division of Microbiology and Infectious Disease
ECG	Electrocardiogram
ECSC	European Coal and Steel Community
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
ERS	European Respiratory Society

EU	European Union
FEV	Forced Expiratory Volume
FOT	Forced oscillation technique
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HAV	Hepatitis A
HbA1c	Haemoglobin A1c
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HVC	Human Viral Challenge
ICF	Inform Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
IMP	Investigational Medicinal Product
IUD	Intrauterine Device
IV	Intravenous
LMIC	Low to Medium Income Country
LRT	Lower Respiratory Tract
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCID	Minimal Clinically Important Difference
MCV	Mean Corpuscular Volume
MHRA	Medicines and Healthcare products Regulatory Agency
MOI	Monoamine Oxidase Inhibitors
NIMP	Non-Investigational Medicinal Product
NPS	Nasopharyngeal Swab
PBMC	Peripheral Blood Mononuclear Cell
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PFM	Peak flow meter
PFU	Plaque Forming Unit
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin Time
qRT-PCR	Quantitative Reverse Transcriptase-Polymerase Chain Reaction
RBC	Red Blood Cell
REC	Research Ethics Committee

RNA	Ribonucleic acid
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SME	Sponsor's Medical Expert
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Adverse Reaction
T	Troponin
TDS	Three Times Daily
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
TSH	Thyroid Stimulating Hormone
TSS	Total Symptoms Score
UK	United Kingdom
URT	Upper Respiratory Tract
WBC	White Blood Cell
β-HCG	β-human chorionic gonadotrophin

4.4. Appendix 4: Toxicity Grading Scale for Laboratory AEs

Toxicity Grading Scale for Lab AEs			**Lab Range**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Sodium	**Elevated**	**mmol/L**	145	146-147	148-149	150-155	>155
Sodium	**Low**	**mmol/L**	135	132-134	130-131	125-129	<125
Potassium	**Elevated**	**mmol/L**	5.1	5.2-5.3	5.4-5.5	5.6-6.5	>6.5
Potassium	**Low**	**mmol/L**	3.5	3.2-3.3	3.0-3.1	2.5-2.9	<2.5
Urea	**Elevated**	**mmol/L**	1.7-8.3	8.4-9.3	9.4-11.0	>11.0	Requires Dialysis
Creatinine (Female)	**Elevated**	**µmol/L**	49-92	101-138	139-276	>277	Requires Dialysis
Creatinine (Male)	**Elevated**	**µmol/L**	66-112	123-168	169-336	>336	Requires Dialysis

Bilirubin	**Normal LFTs**	**µmol/L**	0-20	22-30	31-40	41-60	>60
Bilirubin	**Abnormal LFTs**	**µmol/L**	0-20	22-25	26-30	31-35	>35
ALP (Female)	**Elevated**	**IU/L**	104	114-208	209-312	313-1040	>1040
ALP (Male)	**Elevated**	**IU/L**	129	142-258	259-387	388-1290	>1290
ALT (Female)	**Elevated**	**IU/L**	35	39-88	89-175	176-350	>350
ALT (Male)	**Elevated**	**IU/L**	50	55-125	126-250	251-500	>500
AST (Female)	**Elevated**	**IU/L**	31	34-78	79-155	156-310	>310
AST (Male)	**Elevated**	**IU/L**	37	41-93	94-185	186-370	>370
Albumin	**Low**	**g/L**	34-50	28-31	25-27	<25	-