UNIVERSAL

Understanding Infection, Viral Exacerbation and Respiratory Symptoms at Admission-Longitudinal (UNIVERSAL) Study

V8 07-Aug-2024

SPONSOR: University Hospital Southampton NHS Foundation Trust
COORDINATING CENTRE: Southampton Clinical Trials Unit

ISRCTN reference:	ISRCTN49183956
English Ethics reference number:	22/WM/0119
Scottish Ethics Reference number:	22-SS-0101
Sponsor reference number:	RHM MED1845
Funder reference number:	VAC18193RSV0005
ICD10	J00-J06, J09-J18, J20-J22

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FUNDER

This Study is primarily funded by Janssen Pharmaceuticals, AstraZeneca, Sanofi and Synairgen.

Protocol Information

This protocol describes the UNIVERSAL Study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- Study participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This Study will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARI	Acute Respiratory Illness
BD	Becton Dickinson
BP	Bordetella Pertussis
CI	Chief Investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
FACIT	Functional Assessment of Chronic Illness Therapy
GCP	Good Clinical Practice
HRA	Health Research Authority
HRG	Healthcare Resource Group
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
mPOCT	Molecular point-of-care testing
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroids
OSCI	Ordinal Scale for Clinical Improvement
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PRO	Patient Reported Outcomes
QALY	Quality-Adjusted Life Year
REC	Research Ethics Committee
RHDU	Respiratory High Dependency Unit
RiiQ	Respiratory Intensity and Impact Questionnaire
RVI	Respiratory Viral Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trials Unit
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TMF	Study Master File
TMG	Study Management Group
TSC	Study Steering Committee
UHS	University Hospital Southampton

KEYWORDS

Respiratory Viral Illness
Observational study
Covid
Biomarkers

STUDY SYNOPSIS

Short title/Acronym:	UNIVERSAL
Full title:	**Un**derstanding **I**nfection, **V**iral **E**xacerbation and **R**espiratory **S**ymptoms at **A**dmission- **L**ongitudinal (UNIVERSAL) Study

Study Phase:	Observational Cohort
Population:	All individuals admitted with respiratory syndromes to participating hospital sites who test positive for respiratory viral infection.
Primary Objective:	To develop phenotypic characterisation of the heterogeneous nature of acute respiratory viral infection and recovery seen in patients admitted to hospital with respiratory symptoms.
Secondary Objective:	• To enable accurate stratification of patients for optimal design of future studies of novel pharmacological and non-pharmacological treatment strategies. • To provide co-ordinated link to a central facility for sample storage. • To develop understanding of Healthcare Cost estimate for each patient through HRG coding.
Exploratory Objective:	To enable a precision medicine strategy through detection of immune and inflammatory biomarkers associated with virus type and disease trajectory.
Rationale:	The recent COVID-19 pandemic highlighted the need to link clinical care with research for more rapid translation of new treatment discoveries. The majority of winter pressures facing NHS acute trusts are as a result of acute respiratory viral infection. Whilst many patients recover without need for hospitalisation, a small proportion go on to develop severe disease. A better understanding of the natural history of acute respiratory viral infection and recovery will facilitate improved clinical management with the potential to identify options for intervention in those at risk of more severe disease
Study Design:	Prospective longitudinal observational database with sub-studies.
Sample size:	Consented: Approximately 2000 Positive for respiratory viral infection: 1000
Treatment/Intervention:	None

URL for Database:	https://prod.tenalea.net/ciru/DM/DELogin.aspx?refererPath=DEHome.aspx
Primary Study Endpoints:	• Determination of the incidence of different respiratory viruses in admitted patient population over a 12 month period, including a winter season, across UK sites. • Determination of the clinical and biological predictors of progression of disease, recovery and length of stay.
Secondary Study Endpoints:	Determination of time to recovery for different viruses and patient factors
Exploratory Endpoint:	Biomarker profiles associated with virus type and clinical outcome
Total Number of Sites:	Up to 10 UK secondary care sites

STUDY SCHEMA

Enrolment

Patient has a suspected respiratory viral infection: patient is approached, reads participant information sheet and has time to ask questions*.

Consent * form signed

Declines to participate

* If lacks capacity to consent, due to current illness, patient's consultee may be substituted here.

Day 1 (Stage 1)

Combined nose and throat swab taken and ran through Standard Molecular PCR test / BioFire® FilmArray® System.

Baseline data collection:

- Patient demographic data
- Presenting History and clinical findings from routine tests conducted as per local clinical practice
- Vaccine history

At sites where they are applicable, negative participants may be approached to take part in sub-studies.

NEGATIVE result on BioFire® FilmArray® System/alternate diagnostic PCR test for a respiratory viral infection - **participation in main study ends**

Testing **POSITIVE** on BioFire® FilmArray® System/alternate diagnostic PCR test for a respiratory viral infection (RVI) – participant carries onto **Stage 2**.

Day 1 (Stage 2)

Sample collection:

- Combined nose and throat swab
- Nasal swab in amies media
- Blood for plasma analysis (4ml EDTA)
- Blood for serum analysis (4ml BD Red Top)
- Whole blood sample for DNA analysis (8.5ml PAXgene)
- Whole blood sample for RNA analysis (2.5ml PAXgene)
- Nasosorption – wick
- Whole blood for PBMC isolation (4x10ml LiHep) **additional samples**

Data collection: FLU-PRO PLUS / EQ-5D-5L

Day 3

Sample collection (inpatient only):

- Combined nose and throat swab
- Blood for plasma analysis (4ml EDTA)
- Blood for serum analysis (4ml BD Red Top)
- Whole blood sample for DNA analysis (8.5ml PAXgene)
- Whole blood sample for RNA analysis (2.5ml PAXgene)
- Nasosorption – wick – **additional samples**
- Whole blood for PBMC isolation (4x10ml LiHep) – **additional samples**

Data collection (inpatient only): FLU-PRO PLUS / EQ-5D-5L

Day 7

Sample collection (inpatient only):

- Blood for serum analysis (4ml BD Red Top)

Data collection: FLU-PRO PLUS / EQ-5D-5L

Discharge

Data collection:

- OSCI daily until discharge
- Post-Viral Infection PRO Questionnaire
- EQ-5D-5L
- HRG Coding
- Discharge Summary including clinical findings and medications used as per local clinical practice

Follow-up

Data collected from enrolment until WEEK 12 (week 1 (Day 7 above), 2, 4, 8, 12)

- FLU-PRO PLUS / EQ-5D-5L

Data collected at Week 26

- EQ-5D-5L

Follow-up call from research nurse at WEEK 6, 12 and 26.

- Post-Viral Infection PRO Questionnaires

SCHEDULE OF OBSERVATIONS AND PROCEDURES – MAIN STUDY

Time (days):	Day 1	Day 3[14] (inpatient only)	Day 7[14, 15]	Discharge	Week 2[15]	Week 4[15]	Week 6[15]	Week 8[15]	Week12[15]	Week 26[15]
Informed Consent	X[A]									
Eligibility evaluation	X[A]									
Patient Demographics[1]	X[A]									
Vaccine history	X[A]									
Presenting History[1]	X[A]									
Differential Diagnosis	X[2, A]									
Co-morbidities	X[2, A]									
Previous[1] and current medication	X[2, A]			X[A]			X[A]		X[A]	X[A]
Observations[3]	X[A]									
Blood test results	X[4A]			X[2, A]						
Ordinal Scale for Clinical Improvement (OSCI)[5] score	X[A]			X[A]			X[A]		X[A]	X[A]
Charlson co-morbidity index score	X[A]									
BioFire FilmArray Respiratory panel test	X[A]									
FLU-PRO PLUS[6]	X	(X)	X		X	X		X	X	
EQ-5D-5L[6]	X[A]	(X)	X	X[16]	X	X		X	X[7, A]	X[A]
Blood Samples[8, 9]	X[A]	(X)[A]	X[10, A]							
Nose/Throat Swab[8]	X[11, A]	(X)[A, 17]								
Post-Viral Infection PROs [12, 13]				X			X		X	X
Length of Stay				X[2, A]						
Discharge Summary				X[A]						
Healthcare Utilisation							X		X[A]	X[A]

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

[1] Self-reported by the patient.

[2] Information taken from patient notes.

[3] Vital signs to be collected from patient notes. These include: Pulse (Beats per minute), Blood pressure (mmHg), Respiratory Rate (Breaths / minute), Oxygen Saturation (%), Inspired oxygen (air/liters/FiO2), Temperature (°C).

[4] Blood tests should be within 24 hours of presentation

[5] The OSCI to be used in this trial is the 12 June 2020 version as recommended by the WHO (1).

[6] FLU-PRO and EQ-5D-5L questionnaire to be completed (electronically, on paper or by phone) on enrolment, Day 3 if in hospital, Day 7 and then on week 2, 4, 8, 12.

[7] EQ-5D-5L to be collected at end of study week 26.

[8] Samples obtained only if patient tests positive for respiratory viral infection on BioFire FilmArray Respiratory Panel or other diagnostic PCR test.

[9] Four different blood samples taken whilst an inpatient:

- Blood for serum analysis (4ml BD red top)
- Blood for plasma analysis (4ml EDTA)
- Whole blood sample for DNA analysis (8.5ml DNA PAXgene tube)
- Whole blood sample for RNA analysis (2.5ml RNA PAXgene tube)
- Additional blood samples for PBMC isolation taken if particpant consents.

[10] 4ml blood sample to be taken for serum analysis whist an inpatient

[11] Three different swabs will be taken whilst an inpatient:

- Combined nose and throat swab, or throat swab only is patient is not tolerating nose swab
- Nasal swab in amies media
- Nasosorption - wick

[12]Post-viral infection questionnaire to be completed electronically at discharge and at 6, 12 and 26 weeks post-enrolment.

[13] Post-viral infection questionnaire comprised of three patient reported outcome questionnaires:

- General Anxiety Disorder 7 Questionnaire (GAD-7)
- Patient Health Questionnaire (PHQ-9)
- FACIT Fatigue Scale (Version 4)

[14] +/- 1 day window for collection of samples and data whist in hospital

[15] +/- 3 days window data collection following discharge

[16] Required if not already completed when discharge is on Day 3 or 7

[17] Combined nose and throat swab only (or throat swab only if patient is not tolerating nose swab) if an inpatient on Day 3

[A] Main Study AND Virus-Negative Sub Study

1 INTRODUCTION

1.1 BACKGROUND

The global burden of hospital admissions due to respiratory viral illnesses is considerable across the lifespan(2-4). Treatment options are mainly supportive (5), with limited benefit to specific antiviral agents to date (6). Vaccination is the most effective public health measure currently available(7). Response to infection is variable, with some experiencing only mild symptoms that do not require admission, whilst others develop a severe response to infection and require higher level care. Rates of complications from respiratory viral infections appear comparable to influenza, suggesting greater attention needs to be focussed on non-influenza respiratory viral illness(8).

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT STUDY

The recent pandemic highlighted the need to link clinical care with research for more rapid translation of new treatment discoveries. The majority of winter pressures facing NHS acute trusts are as a result of acute respiratory viral infection. Whilst many patients recover without need for hospitalisation, a small proportion go on to develop severe disease. A better understanding of the natural history of acute respiratory viral infection and recovery will facilitate improved clinical management with the potential to identify options for intervention in those at risk of more severe disease, with resultant health economic benefits.

2 STUDY OBJECTIVES

	Objective	Endpoint
Primary:	• To develop phenotypic characterisation of the heterogeneous nature of acute respiratory viral infection and recovery seen in patients admitted to hospital with respiratory symptoms.	• Determination of the incidence of different respiratory viruses in admitted patient population during the winter season across UK sites. • Determination of the clinical and biological predictors of progression of disease, recovery and length of stay.
Secondary:	• To enable accurate stratification of patients for optimal design of future studies of novel pharmacological and non-pharmacological treatment strategies. • Health care Cost estimate for each patient • To provide co-ordinated link to the central facility for sample storage.	• Time to Recovery for different viruses and patient factors • HRG code on discharge
Exploratory:	To enable a precision medicine strategy through detection of immune and inflammatory biomarkers associated with virus type and disease trajectory	Biomarker profiles associated with virus type and clinical outcome

3 STUDY DESIGN

This is an observational cohort study to develop a prospective longitudinal clinical database. All adults admitted with respiratory syndromes to participating hospital sites will be asked to participate in the study. Those who test positive for respiratory viral infection will enter the second stage of the study and provide samples. Those who consent and test negative will have baseline data collection only, but there may also be the option to participate in the virus-negative and/or Bordetella pertussis sub-study as detailed in Section 6.0.

3.1 STUDY ENDPOINTS

3.1.1 Primary endpoints

- Determination of the incidence of different respiratory viruses in admitted, sampled patient population during the winter season across UK sites.
- Determination of the clinical and biological predictors of progression of disease, recovery and length of stay.

3.1.2 Secondary endpoint

- Time to recovery for different viruses and patient factors.
- Cost estimate per patient based on Healthcare Resource Group (HRG) coding.

3.1.3 Exploratory endpoint

- Biomarker profiles associated with virus type and clinical outcome.

3.2 DEFINITION OF END OF STUDY

The end of the of the study for each individual participant is when they have completed the EQ-5D-5L questionnaire at 26 weeks after registration into the study.

For patients testing negative for a viral infection the end of their involvement is expected to be the same day as enrolment. Participant withdrawal is discussed separately.

For REC, the end of study will be defined as the last patient providing 26 week data.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 IDENTIFICATION

The clinical teams in the various areas shall identify potentially eligible patients in the clinical areas by regularly reviewing the admitted patients and electronic admission systems against eligibility criteria and informing the research team. Many members of the research team are healthcare professionals who are looking after these patients directly. Patients will be informed about the study by site staff and will be invited to discuss the trial with the research team.

4.2 CONSENT

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

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

If the patient is able to, they will sign and date the informed consent document to indicate consent. If the patient is able to provide informed consent but has difficulty writing or otherwise

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

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

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

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

For potential participants with infection control concerns, local infection control processes should be followed to allow paper consent forms to be completed.

Only if informed consent has been provided for the SCTU to receive this information should a copy of the consent form be sent to the SCTU using the University of Southampton SafeSend Service (to monitorSCTU@soton.ac.uk) to allow for central monitoring.

4.3 INCLUSION CRITERIA

Patients must meet all the following Inclusion Criteria at screening to be eligible for the study.

Stage 1

1. Aged ≥18 years old
2. Has symptoms of an acute respiratory illness (ARI)*
3. Is a medical inpatient, admitted within the past 36 hours (defined as the time decision made to admit patient, not time of presentation to hospital)

Plus, for Stage 2

4. Has positive test result for respiratory **viral** infection on a BioFire® FilmArray® System or other diagnostic PCR test on the current admission.

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

4.4 EXCLUSION CRITERIA

A patient must not be enrolled into the study if they meet any of the following criteria at screening:

1. Combined nasal and throat swabbing cannot be performed (patient decision or contraindication to procedure)
2. Consent declined or consultee consent declined
3. Previously enrolled in Stage 2 of UNIVERSAL study.

Further inclusion / exclusion notes

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

Patients enrolled into interventional studies of antiviral or other trial therapies for viral respiratory infections will not be excluded but information on the study and treatment received will be collected.

The inclusion of pregnant women is permitted in the study. No additional risk is perceived to pregnant women or their offspring by any of the study procedures. No additional data collection or monitoring is therefore anticipated in this group. It may be especially important to include pregnant women in COVID-19 research, as infection with influenza is associated with worse outcomes in pregnancy (11).

4.5 SCREENING

Patients, or their consultee for those lacking capacity, with whom the UNIVERSAL study is discussed but who do not enter the study will be documented in the screening log maintained at each participating site, together with reasons for exclusion/decline. The screening log will be filed in the Investigator Site File.

4.6 REGISTRATION PROCEDURES

All consented patients will be logged and assigned a **registration number** until point-of-care testing via a standard molecular PCR diagnostic test or the study BioFire Film Array has been carried out. This will be in the format of a letter, starting with A, B, C a.s.o, followed by a 4 digit participant number. The 4 digit participant number will be assigned sequentially to each patient within each site starting with 0001 followed by 0002, and so on. A example registration numbers for University Hospital Southampton (UHS) are A0001, A0002 etc.

Those who test positive will be assigned a unique **participant identification number**. The unique participant identification number will consist of 4 digits made up of the site number (e.g. the site code for UHS is 1001) and a 4 digit participant number. The 4 digit participant number will be assigned sequentially as decribed in the Laboratory manual.

5 STUDY OBSERVATIONS AND PROCEDURES

5.1 STUDY PROCEDURES

5.1.1 Stage 1 (All consented patients)

Day 1

Prior to any testing of respiratory samples at point-of care or in a near patient setting, a local risk assessment must be performed and validation/verification of the BioFire test platform for the tested targets using the selected inactivation media must be carried out.

Sample collection:

Respiratory samples will be collected from patients by an appropriately trained member of research staff wearing full PPE as defined by local infection prevention and control policy. A combined nose and throat swab will be collected directly into a tube containing 1ml of

inactivation media and a molecular virus diagnostic test will be undertaken using the BioFire® FilmArray® System (or other diagnostic PCR test) at the point-of-care or in a near patient setting (see standard SOP or Lab Manual).

Data collection:

- Patient demographic data (Gender, Age at enrolment, height, weight, ethnicity, post code, number of people in household, smoking history)
- Presenting History and clinical findings from routine tests conducted as per local clinical practice (such as chest x-ray and blood test results)
- OSCI score (WHO recommended 10 point score - See Appendix 1)
- Co-morbidities
- Previous and current medication
- At-risk status
- Vaccine history
- Use of Antibiotics or neuraminidase inhibitor or other antivirals for this illness
- Use of corticosteroids
- Use of COVID-19 therapies
- Vital signs
    - Pulse (Beats per minute)
    - Blood pressure (mmHg)
    - Respiratory Rate (Breaths per minute)
    - Oxygen Saturation (%)
    - Inspired oxygen (air/litres/FiO2)
    - Temperature (°C)

For those participants enrolled into an interventional study of an antiviral therapy for viral respiratory infection

- Study name
- Treatments received

Those patients who test positive for a viral infection will continue into Stage 2 of the study. Participation in the study for those patients who test negative for a viral infection will end the main study at this point. Patients who test negative for a viral infection at participating sites may be approached to participate in a sub-study detailed in Section 6.0.

5.1.2 Stage 2 (Patients who are RVI positive only)

Day 1/Baseline

Two types of biological sample will be collected from consenting patients for translational research within the UNIVERSAL study:

- peripheral bloods
- nose and throat swabs

All samples will be sent, processed and stored at a locally agreed laboratory prior to release for translational research within the UNIVERSAL study (or future ethically approved research). All samples will be sent pseudo-anonymised, fully labelled with the study name, sample type, patient ID number barcode and the date of sample collection to the processing laboratory.

All sites will keep a record of all samples processed, stored, and shipped.
A detailed Laboratory Manual will be provided to sites which will include details regarding sample preparation, handling, and shipping.

Sample collection

- Combined nose and throat swab collected into tube containing 1ml viral transport media (eg Copan or medical wire) for storage for laboratory PCR. A throat swab only can be collected in cases where the patients is not tolerating a nose swab.
- Nasal swab in amies media
- Nasosorption - wick

Blood sampling to be carried out in this order

- Blood for serum analysis (4ml BD red top)
- Blood for plasma analysis (4ml EDTA)
- Whole blood sample for DNA analysis (8.5ml DNA PAXgene tube)
- Whole blood sample for RNA analysis (2.5ml RNA PAXgene tube)

Data collection:

- FLU-PRO+
- EQ-5D-5L

Day 3 (if patient is in hospital):

Weekend sample and data collection will not be expected of sites and hence sampling days which fall on a weekend are subject to a window of +/- 1 day.

Sample collection:

- Combined nose and throat swab collected into tube containing 1ml viral transport media (eg Copan or medical wire) for storage for laboratory PCR. A throat swab only can be collected in cases where the patients is not tolerating a nose swab.

Blood sampling to be carried out in this order

- Blood for serum analysis (4ml BD red top)
- Blood for plasma analysis (4ml EDTA)
- Whole blood sample for DNA analysis (8.5ml DNA PAXgene tube)
- Whole blood sample for RNA analysis (2.5ml RNA PAXgene tube)

Data collection:

- FLU-PRO+
- EQ-5D-5L

Day 7:

Sample and data collection whist in hospital are subject to a window of +/- 1 day. Data collection post discharge is subject to a window of +/- 3 days.

Sample collection (if patient is in hospital):

- Blood for serum analysis (4ml BD red top)

Data collection via research team if in hospital or online if discharged:

- FLU-PRO+
- EQ-5D-5L

5.1.3 Discharge

On discharge, patients will be asked to complete the EQ-5D-5L questionnaire as well as post-viral infection patient report outcome measures:

- General Anxiety Disorder 7 Questionnaire (GAD-7)
- Patient Health Questionnaire (PHQ-9)
- FACIT Fatigue Scale (Version 4)

In instances where the patient is discharged on Day 3 or Day 7 and has already completed the PRO questionnaires for that time point in hospital, the EQ-5D-5L is not required on discharge.

In instances where the patient is discharged before the above data can be collected, e.g. when discharged on a weekend, it may be collected retrospectively through an unscheduled phone call by a member of the research team as specified on the delegation log.

Once patients have been discharged, clinical data will be collected retrospectively from electronic and physical case notes, discharge summary and information relevant to HRG coding* including:

- Use of index medications: Antibiotics, OCS, antivirals, monoclonal treatment
- Use of oxygen and respiratory support
- time to clinical stability
- duration of supplementary oxygen use
- OSCI score on discharge**
- duration of hospitalisation
- complications including ICU and RHDU admission,
- representation and readmission to hospital within 30 days
- final diagnosis
- mortality

* Information from the discharge summary and CRF will be used to independently generate HRG codes via a central coding team. The research nurses will check and confirm that the participant comorbidities are adequately captured. In addition, research nurses will also input locally generated HRG codes in a subset of centres to allow comparison. This quality control process on discharge information will improve data quality as a study (9) has suggested considerable inaccuracies in HRG coding.

** On point of discharge, information on the patient's journey through their inpatient stay is required. The highest OSCI score documented or indicated from medical notes should be recorded for each day of inpatient stay.

For those participants enrolled into an interventional study of an antiviral therapy for viral respiratory infection during their time in hospital, the following information is also collected;

- Study name
- Treatments received.

The local site study team will collect contact details (including 1-2 phone numbers and an email address) from all participants to enable contact during the study and allow follow up phone calls. Contact details will be stored securely at site in a restricted locked environment, in accordance

with the General Data Protection Regulation (GDPR). Contact details will be shared securely with the UNIVERSAL study team at Southampton Clinical Trials Unit (SCTU) and stored securely. The study team at SCTU will access the contact details to make follow up phone calls, send text reminders and disseminate study results (at the end of the study). Contact details should be sent to the UNIVERSAL trial email account (universal@soton.ac.uk) using SafeSend (https://safesend.soton.ac.uk/). This is a safe and secure (data protection compliant) mechanism for the sites to send the relevant contact information to the UNIVERSAL email account as it is hosted by the University of Southampton and supports both in-transit and at-rest encryption.

5.2 FOLLOW UP

Follow up starts as soon as patient is discharged, which may be any time after Day 1. During follow up, patients will be asked to complete two PRO questionnaires (FLU-PRO PLUS and EQ-5D-5L) at weeks 1, 2, 4, 8 and 12 (+/- 3 days) from admission to hospital followed by only the EQ-5D-5L at 26 weeks post enrolment (at +/- 3 days).

PRO questionnaires will primarily be completed electronically, although paper format or collection over the phone could also be offered if required. In cases where participants request paper, paper packs, along with a free post envelope will be sent to participants at 3 timepoints. Where possible, patients will be sent reminders by text or email to complete the questionnaires. Non-responders will be contacted by telephone to collect PRO data.

At 6, 12 and 26 weeks post enrolment, patients will receive an additional follow-up phone call from the research nurse when the following data will be collected:

- OSCI score
- Healthcare utilisation since last visit
- Any new investigations relating to the index illness since last visit
- Any new medications relating to the index illness since last visit
- Absence from work or college for the index illness

Patients will also be asked to complete post-viral infection patient report outcome questionnaires at 6, 12 and 26 weeks. These will be completed at the time of the follow-up call from the research nurse, unless already completed.

5.3 DEVIATIONS AND SERIOUS BREACHES

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms by the SCTU who will onward report to the Chief Investigator and Sponsor immediately.

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the sponsor. Frequent non-compliances could potentially be classified as a serious breach.

Any Study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the Sponsor immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

Any serious breaches of the protocol or of the principles Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the research participants, or the scientific value of the research will be reported to the REC and the Sponsor.

5.4 STUDY DISCONTINUATION/WITHDRAWAL

The participant, or their consultee where a participant lacks capacity, is free to withdraw consent from the study at any time without providing a reason, and with no detriment to their medical care or legal rights. Patients will be able to withdraw from the study at any time and this will be recorded on the study database. It should be ascertained and documented whether the participant wishes to withdraw from the study completely or only from specific parts. Should the participant wish, any samples will be disposed of and no further data will be collected.

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

Any patient or their consultee (where a patient lacks capacity) who is withdrawing from the study can either withdraw while allowing data and/or samples collected thus far to be retained by the study team or withdraw and have their data and/or samples destroyed. For the latter option, signed consultee declaration forms, minimal personal identifiable information to record the withdrawal, and any completed point-of-care test result will be retained).

If a patient loses capacity after enrolment but before the study procedures are completed, consultee consent must be sought to continue with any study procedures, or the participant must be withdrawn.
Details of study discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

5.5 PROHIBITED AND RESTRICTED THERAPIES DURING THE STUDY

This section is not applicable to this study.

5.6 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

This section is not applicable to this study.

6 RESEARCH PILOT STUDIES

6.1 VIRUS NEGATIVE SUB-STUDY

6.1.1 Background

The UNIVERSAL study aims to identify clinical and biological predictors of disease severity, length of stay and time to recovery in hospitalised patients with acute respiratory illness (ARI) who test positive for respiratory viral infection (RVI). Collection of clinical outcome data for patients with ARI but who test negative for RVI will provide a control data set for comparison and experimental analyses. The UNIVERSAL study offers an excellent opportunity to study this virus negative ARI cohort in more detail and potentially provide understanding into the pathophysiology at play.

Additionally, data collection and sampling within the virus negative cohort of UNIVERSAL participants will support the exploratory endpoint of UNIVERSAL, namely, the identification of biomarker profiles associated with RVI. Immune and inflammatory profiling within the virus

negative group will aid in the determination of physiological pathways and potential therapeutic targets that are specific to viral infections.

A subset of participants enrolled in stage 1 of the UNIVERSAL study, that test negative for respiratory viral infection after Biofire FilmArray or alternative viral PCR diagnostic will be approached to participate in a virus negative sub-study. Consenting participants will undergo nasal swabbing, combined nose and throat swabbing, blood sampling and limited follow up with research nurse led phone-calls.

6.1.2 Objectives

1) Collect clinical, severity and recovery data for the respiratory virus negative cohort of participants with ARI to provide a control data set and aid the primary and exploratory endpoints of UNIVERSAL.
2) To aid the exploratory endpoint of UNIVERSAL by providing immune and inflammatory biomarker profiles in the virus negative cohort of hospitalised adults with ARI.

6.1.3 Study design

- This is an observational cohort sub-study of UNIVERSAL.
- Aim to recruit 100 participants admited to hospital with ARI who have been enrolled in Stage 1 of UNIVERSAL and tested negative for viral infection on viral PCR testing.

6.1.4 Consent/Recruitment

The generic consent and recruitment strategy described in section 4.2 applies.

Patients who are enrolled in Stage 1 of the UNIVERSAL study and who test negative for a respiratory viral infection on BioFire® FilmArray® System/alternate diagnostic PCR test for a respiratory viral infection will be approached to take part in the virus negative sub-study.

Please be aware that patients recruited into this sub study must consent to the virus negative sub study specific parts of the informed consent form provided by sites participating in this sub study.

6.1.5 Inclusion criteria

Patients must meet all the following Inclusion Criteria at screening to be eligible for the study.

Stage 1

1. As stated in UNIVERSAL protocol section 4.3.

Plus, for Stage 2

2. Has **negative** test result for respiratory **viral** infection on a BioFire® FilmArray® System or other diagnostic PCR test on the current admission.

6.1.6 Exclusion criteria

1. As stated in UNIVERSAL protocol section 4.4.
2. Participant has not consented to/is not willing to take part in the virus-negative sub-study.

6.1.7 Study procedures

Stage1:

Stage 1 procedures are carried out as per UNIVERSAL protocol section 5.1.1

If patient tests negative for respiratory viral infection and consents to take part in the virus-negative sub-study, they progress to Stage 2.

Stage 2:

Day 1/Baseline

Sample collection

- Combined nose and throat swab collected into tube containing 1ml viral transport media (eg Copan or medical wire) for storage for laboratory PCR. A throat swab only can be collected in cases where the patients is not tolerating a nose swab.
- Nasal swab in amies media
- Nasosorption - wick

Blood sampling to be carried out in this order

- Blood for serum analysis (4ml BD red top)
- Blood for plasma analysis (4ml EDTA)
- Whole blood sample for DNA analysis (8.5ml DNA PAXgene tube)
- Whole blood sample for RNA analysis (2.5ml RNA PAXgene tube)

Data collection:

- EQ-5D-5L

Day 3 (if patient is in hospital):

Weekend sample and data collection will not be expected of sites and hence sampling days which fall on a weekend are subject to a window of +/- 1 day.

Sample collection:

- Combined nose and throat swab collected into tube containing 1ml viral transport media (eg Copan or medical wire) for storage for laboratory PCR. A throat swab only can be collected in cases where the patients is not tolerating a nose swab.

Blood sampling to be carried out in this order

- Blood for serum analysis (4ml BD red top)
- Blood for plasma analysis (4ml EDTA)
- Whole blood sample for DNA analysis (8.5ml DNA PAXgene tube)
- Whole blood sample for RNA analysis (2.5ml RNA PAXgene tube)

Day 7 (if patient is in hospital):

Sample and data collection whist in hospital are subject to a window of +/- 1 day. Data collection post discharge is subject to a window of +/- 3 days.

Sample collection (if patient is in hospital):

- Blood for serum analysis (4ml BD red top)

6.1.9 Discharge and Follow-up

This information will be collected in line with procedures in the UNIVERSAL protocol section 5.1.3 and 5.2, but only the limited information detailed below will be collected:

Once patients have been discharged, clinical data will be collected retrospectively from electronic and physical case notes, discharge summary and information relevant to HRG coding including:

- Use of index medications: Antibiotics, OCS, antivirals, monoclonal treatment
- Use of oxygen and respiratory support
- time to clinical stability
- duration of supplementary oxygen use
- OSCI score on discharge
- duration of hospitalisation
- complications including ICU and RHDU admission,
- representation and readmission to hospital within 30 days
- final diagnosis
- mortality

At 12 and 26 weeks post enrolment, patients will receive an additional follow-up phone call from the research nurse when the following data will be collected:

- OSCI score
- Healthcare utilisation since last visit
- Any new investigations relating to the index illness since last visit
- Any new medications relating to the index illness since last visit
- Absence from work or college for the index illness

Patients will also be asked to complete an EQ-5D-5L questionnaire at 12 and 26 weeks. These will be completed at the time of the follow-up call from the research nurse.

6.2 BORDETELLA PERTUSSIS (BP) - PILOT STUDY

Detection of a *Bordetella pertussis* (BP) signal within an adult UK population hospitalised with acute respiratory illness (ARI).

6.2.1 Background

Pertussis (whooping cough) is an acute respiratory illness caused by the bacteria *Bordetella pertussis* (BP) and is vaccine preventable. Unvaccinated infants and the elderly are the most vulnerable groups in which the infection can be fatal. Pertussis can affect all ages with adults and adolescents often presenting with non-febrile cough. (15) Adults and adolescents may present with non-specific signs of pertussis leading to misdiagnosis or delays in diagnosis, and may represent significant vectors for transmission to more vulnerable groups. (16)

The UK vaccination schedule has led to a reduction in UK pertussis cases. Despite vaccinations, cyclical peaks of infection occur every 3-4 years, most notably during the 2012 UK pertussis outbreak. (17) Since 2012, smaller cyclical peaks in UK pertussis cases have been observed in both 2016 and 2019. The majority of laboratory confirmed pertussis cases are reported in individuals greater than 15 years of age. (18)

The introduction of infection control measures during the SARS-CoV-2 pandemic was associated with a reduction in UK pertussis cases since 2020. The relaxation of social distancing measures from July 2021 onwards, has prompted the re-emergence of other infectious diseases.(18) This phenomenon was demonstrated by the return of winter respiratory virus outbreaks, including RSV and Influenza A, during the UK winter season 2022-2023. Given the cyclical nature of pertussis outbreaks and the

removal of social distancing measures, an increase in cases is anticipated in the near future, but is difficult to predict.

Pre-pandemic, there were 969 laboratory confirmed cases of pertussis in the UK from April to June 2019. This contrasts with 133, 9 and 15 cases detected in the UK during the same period in 2020, 2021 and 2022, respectively. (18) European data suggests increased cases of pertussis infections in 2023, with Denmark reporting a pertussis epidemic in September 2023. (19)

Reported incidence of pertussis infection varies greatly across European countries, likely in part due to under-reporting/detection. Retrospective serological studies have reported up to 6% of adults (aged 20-39 years) had antibody levels indicative of recent pertussis exposure. (20) A large retrospective UK study in 2023 reported the incidence rate of pertussis in those >50 years at 5.8 per 100,000 person-years, and pertussis diagnosis was associated with increased healthcare and economic burden. (21)

Multi-centre, prospective UK population studies aimed at determining the incidence and burden of pertussis infection in adults are needed, but these require very large sample sizes, high level d2, resource and infrastructure. We propose an initial pilot study to detect the presence of pertussis infection in hospitalised adults with acute respiratory illness (ARI) in 2024.

Rationale for study design and sample size:

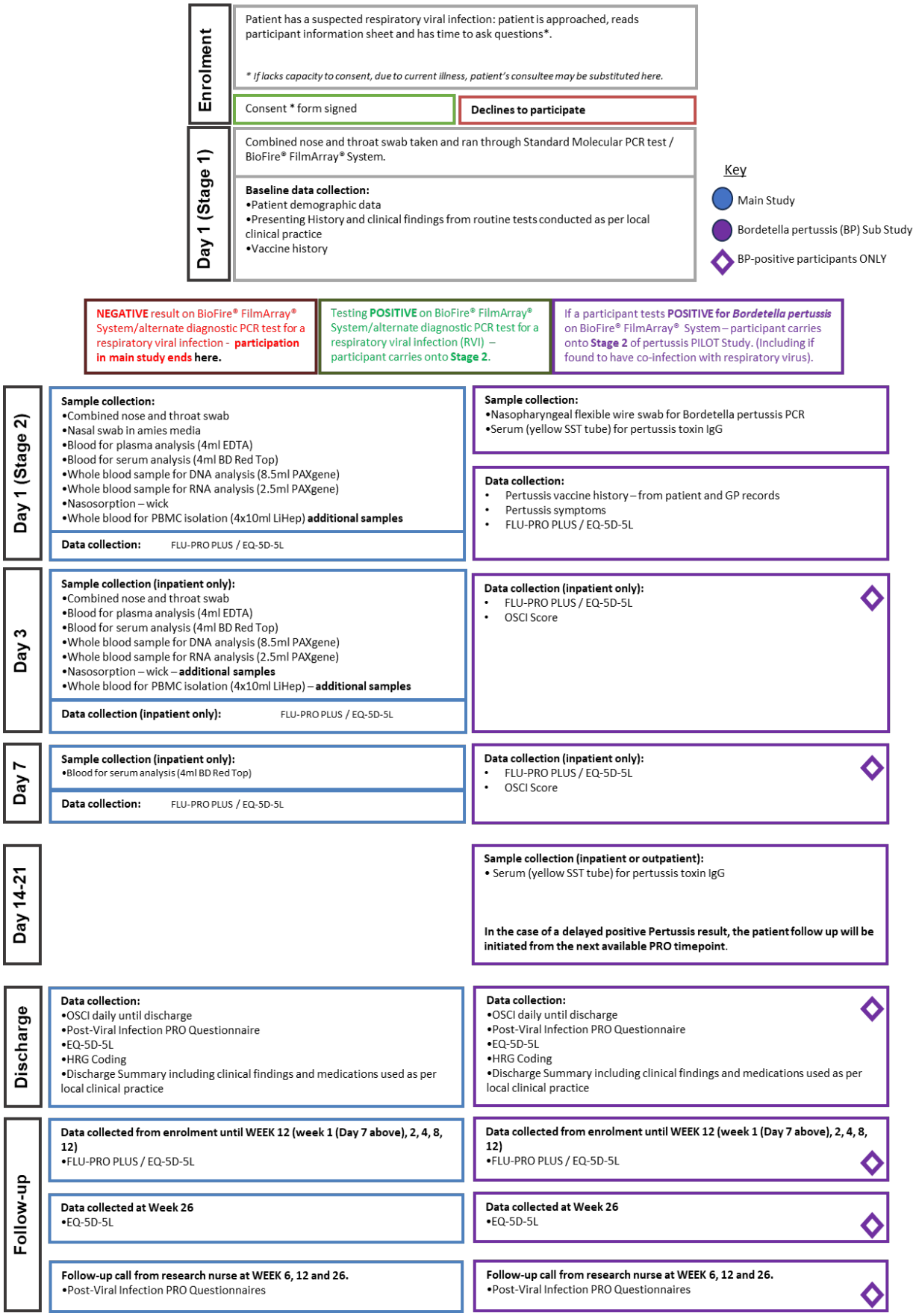
The UNIVERSAL study provides a unique opportunity to detect BP within an adult hospitalised population with ARI. Participants consented to the UNIVERSAL study with respiratory symptoms are tested for respiratory viral infection using the BioFire® FilmArray® System. On testing negative or if found to have a co-infection with respiratory virus, these participants can be enrolled in the BP-pilot and provide biological samples for pertussis testing. Additionally, established study infrastructure will allow collection of demographic, clinical severity and recovery data for detected cases of BP infection.

This initial pilot study includes an achievable sample size, given current resource and funding, of 100 participants with the aim of detecting pertussis infection in a hospitalised, adult cohort. Detection of a small number of cases is expected, but if achieved, will inform future study design and allow collection of preliminary severity and outcome data for adults with pertussis infection.

Study Limitations:

- Small sample size – the study team acknowledge that very low numbers of pertussis infection may be detected. The purpose of this initial pilot study is to detect the presence of pertussis in this adult cohort and to inform the design of future larger scale studies.
- Single centre – the population may not be representative of the UK as a whole but is limited to a single centre given current budget and resources.
- The majority of pertussis cases may be in the community and may not be admitted to hospital – there are a lack of studies investigating the presence of pertussis in adults hospitalised with ARI. This pilot is designed in an attempt to identify even low numbers of pertussis cases and provide valuable preliminary data to stimulate interest in larger population based pertussis studies.
- Vaccination history may not be complete in particular in the older cohort. These details will be collected from participants and medical records as available.

STUDY SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

Time (days):	Day 1	Day 3[11, A] (inpatient only)	Day 7 [9, 10, A]	Day 14-21[13]	Discharge [A]	Week 2[10, A]	Week 4[10, A]	Week 6[10, A]	Week 8[10, A]	Week12[10, A]	Week 26[10, A]
Previous[1] and current medication	X[2]				X			X		X	X
Observations[3]	X										
Blood test results	X[4]				X[2]						
Ordinal Scale for Clinical Improvement (OSCI)[5] score	X				X[A]			X		X	X
FLU-PRO PLUS	X	(X)	X			X	X		X	X	
EQ-5D-5L[6]	X	(X)	X		X[11]	X	X		X	X[7]	X
Post-Viral Infection PROs [7, 8]					X			X		X	X
Pertussis Vaccine History	X										
Samples for pertussis PCR Testing[12]	X			X							
Length of Stay					X[2]						
Discharge Summary					X						
Healthcare Utilisation								X		X	X

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

[1] Self-reported by the patient.

[2] Information taken from patient notes.

[3] Vital signs to be collected from patient notes. These include: Pulse (Beats per minute), Blood pressure (mmHg), Respiratory Rate (Breaths / minute), Oxygen Saturation (%), Inspired oxygen (air/liters/FiO2), Temperature (°C).

[4] Blood tests should be within 24 hours of presentation

[5] The OSCI to be used in this trial is the 12 June 2020 version as recommended by the WHO (1).

[6] EQ-5D-5L to be collected at end of study week 26.

[7] Post-viral infection questionnaire to be completed electronically at discharge and at 6, 12 and 26 weeks post-enrolment.

[8] Post-viral infection questionnaire comprised of three patient reported outcome questionnaires:

- General Anxiety Disorder 7 Questionnaire (GAD-7)
- Patient Health Questionnaire (PHQ-9)
- FACIT Fatigue Scale (Version 4)

[9] +/- 2 day window for collection of samples and data whist in hospital

[10] +/- 3 days window data collection following discharge

[11] Required if not already completed when discharge is on Day 3 or 7

[12] Two different sample types are to be collected:

- Nasopharyngeal flexible wire swab for Bordetella pertussis PCR
- Serum blood sample (yellow SST tube) for pertussis toxin IgG

[13] One further visit with a 7-day period to give a further yellow SST tube blood sample

[A] Bordetella pertussis (BP) POSITIVE Participants ONLY

6.2.2 Objectives

Primary objectives:

1) To detect a positive signal of pertussis infection in a hospitalised UK adult cohort with non-viral acute respiratory illness (ARI).
2) To inform the design of future pertussis population studies in adults.

Exploratory objectives:

1) To characterise clinical symptoms associated with adult *pertussis* infection.
2) To allow an extrapolation of pertussis incidence in UK adult population.
3) To enable estimation of health economic impact for hospitalised patients with *pertussis* infection.

6.2.3 Study design

This is a pilot single site observational cohort study with the primary endpoint of detecting cases of BP infection in 100 patients admitted to Southampton General Hospital (SGH) with acute respiratory illness (ARI) over a 6-8 month period. This sample size is determined on convenience as this is a pilot.

Participants admitted to SGH with ARI will provide written consent to partake in the BP-pilot study. They will be tested for presence of respiratory viral infection using BioFire® FilmArray® System. Those testing negative for respiratory virus by PCR will be enrolled into the BP-pilot study. Participants that test positive for BP infection on BioFire® FilmArray® System will also be included in the pilot study, including those with respiratory virus - pertussis co-infection.

In addition to baseline data collected as part of the UNIVERSAL study, the following additional information will be collected:

- Whooping cough symptomatology – paroxysmal cough, inspiratory whoop, post-tussive emesis.
- Childhood vaccination status – collected as available, from direct questioning and GP records. For some participants this may be incomplete.
- Recent pertussis vaccination status – any pertussis vaccination in the last year.

Study endpoints

Primary study endpoint

- Detection of Bordetella pertussis infection within a UK hopsitalised adult group of 100 patients with ARI.

Exploratory study endpoints:

- Collection of preliminary data on symptoms and severity of BP infection in hospitalised adults.
- Inform future large scale population studies on BP infection in adults in the UK.
- Estimation of health economic impact for individuals with BP infection that are hospitalised in the UK.

End of study:

- 100 participants enrolled, tested for BP infection and completed 26 week follow-up in positive cases.

6.2.4 Consent/Recruitment

Identification and consent of participants will be carried out in accordance with section 4 of the UNIVERSAL study protocol.

Participants recruited into this pilot study must consent to the Bordetella Pertussis pilot study specific parts of the informed consent form.

6.2.4.1 Inclusion criteria

Stage 1

1. As stated in UNIVERSAL protocol section 4.3.

Plus, for Stage 2

2. Has a **negative test result** for respiratory **viral** infection OR a **positive test result** for ***Bordetella Pertussis* (BP)** infection on a BioFire® FilmArray® System or other diagnostic PCR test on the current admission.*
3. a history of acute cough or worsening of existing chronic cough on this admission.
    a. OR any of the whooping cough symptomatology:
        i. Paroxysmal cough**
        ii. Inspiratory whooping**
        iii. Post-tussive emesis
        iv. Cough that wakes the patient at night

The above eligibility criteria for stage 2 will be used for the first 50 recruits. At this point a review will take place by the Trial Management Group. If no positive pertussis cases have been identified, a more stringent set of inclusion criteria may be used to recruit the remaining participants.

*Note: If participant tests positive for BP infection on BioFire® FilmArray® System they will be enrolled into Stage 2 of the BP-pilot study. This includes those participants that have also tested positive for both viral infection and BP infection on BioFire® FilmArray® System i.e virus-BP co-infection.

**Paroxysmal cough – defined as rapid, violent and uncontrolled coughing fits.
**Inspiratory Whoop - Long inspiratory effort accompanied by a high-pitched “whoop” at the end of the paroxysms of cough.

6.2.4.2 Exclusion criteria

1. As stated in UNIVERSAL protocol section 4.4.
2. Participant has not consented to/is not willing to take part in the Bordetella pertussis sub-study.

Further guidelines on recruitment, consenting and registration procedures are outlined in **Section 4** of UNIVERSAL study protocol.

6.2.5 Study procedures

6.2.5.1 Stage 1:

Stage 1 study procedures will be carried out as per section 5.1.1 of the Universal protocol.

Point of care testing for BP infection:
BioFire® FilmArray® System testing will be carried out at SGH by trained staff as per UNIVERSAL protocol. Appropriate quality control and validation will be carried out by trained staff to ensure validity of results. The BioFire® FilmArray® System results are received within 1 hour to allow prompt decision on enrolment into Stage 2 of the BP-pilot study.

Biofire RP2.1plus for detection of pertussis is based on the Pertussis Toxin Promoter (ptxP) while other tests include additional targets such as IS481. This means there is potential to detect alternative Bordetella species resulting in false positives. The limit of detection for BiofireRP2.1plus for B. pertussis is $1x10^3$ CFU/mL. Previous studies have indicated that the Biofire RP2.1plus panel detected B. pertussis only at higher conentrations.(22) In order to reduce the risk of false positives and negatives, participants testing positive for B. pertussis on Biofire RP2.1plus panel will also be tested using a validated laboratory test for B. pertussis.

6.2.5.2 Stage 2: RVI negative OR BP positive on BioFire® FilmArray® System.

Participants who test negative for respiratory viral infection OR test positive for Bordetella pertussis (BP) infection on BioFire® FilmArray® System will be approached to participate in the BP-pilot study. If participant provides consent, two types of clinical samples will be collected on day 1 for BP testing and additional data detailed below will be collected.

Day 1 sample collection (both swab and blood to be collected):

- Nasopharyngeal flexible wire swab for *Bordetella pertussis* PCR.*
- Blood sample for serum analysis (yellow Top bottle) for pertussis toxin IgG.

*If the patient does not tolerate a nasopharyngeal swab, an oropharyngeal swab may be performed instead. This involves collecting an oropharyngeal swab placed into viral transport media (VTM).

Day 1 data collection:

- Whooping cough symptom screening and duration– paroxysmal cough, inspiratory whoop, post-tussive emesis, cough that wakes the patient at night.
- Pertussis vaccination history – both historical and recent vaccination history will be collected by direct questionning and review of GP records as available. This information may be incomplete for some participants.
- FLU-PRO PLUS / EQ-5D-5L

Laboratory testing for BP infection:

Nasopharyngeal swabs and serum samples taken for laboratory PCR and serology BP testing will be delivered directly to the UHS pathology lab. This is an NHS laboratory with a highly sensitive and validated method for testing BP infection. Testing will be carried out in line with local NHS laboratory manual and guidelines.
Turnaround time for laboratory PCR and serology test results is 2-3 days. Results will be released via the UHS clinical results system..

- Laboratory PCR testing for BP – PCR is carried out for two BP target genes (IS481 and ptxP) and can distinguish Bordetella pertussis from other Bordetella species. Ct values are available if a positive result is detected.
- Laboratory serology testing for BP – anti-pertussis toxin IgG is detected. Antibody level cut offs: Positive >100 IU/mL, equivocal = 40-100 IU/mL, negative <40 IU/mL.

Note on clinical care of participants:

Any positive cases will be reported in a timely fashion to the clincal team and to PHE as per the notifiable diseases guidelines in the UK.
Study procedures should not interfere with standard clinical care and this must take precedence over study procedures. In general, participants will be admitted for at least 24 hours if taking part in the study to allow time for study procedures to be carried out.

Convalescent sampling: Day 14-21 days post-enrolment:

- Blood sample for serum analysis (yellow Top bottle) collected for pertussis toxin IgG

Participants in the BP-pilot study will be requested to provide a convalescent serm sample for pertussis toxin IgG at day 14-21 after enrolment in the study. This can be performed as an inpatient or outpatient as a return visit, if the participant has been discharged.
The day 14 convalscent serology sample is not mandatory. The participant will be asked if they wish to consent to day 1 and day 14 sampling separately on the Bordetella pertussis sub-study consent form. If the participant declines to return for the day 14 sample, they can still take part in Stage 2 of the BP-pilot study and provide day 1 samples for the study.

The day 14 sample is subject to a window of 8 days, meaning the sample can be collected between days 14 and 21. Participants who have been discharged from hospital by Day 14 will be required to return to the hospital for the blood test. Participant parking costs can be provided for participants taking part in this substudy.

The convalescent serology test result is interpreted using the following antibody level cut offs:
Positive >100 IU/mL, equivocal = 40-100 IU/mL, negative <40 IU/mL.
A positive result will result in the patient entering Stage 3 of the study. In the case of a delayed positive Pertussis result i.e. after day 14-21 serology, the patient follow up will be initiated from the next available PRO timepoint.

6.2.5.3 Stage 3: Participants testing positive for BP infection only.

Stage 3 will include participants testing positive for BP infection on BioFire® FilmArray® System, laboratory PCR or laboratory serology testing.
As noted above, in the case of a participant testing positive for BP infection, the clinical team and PHE will be notified in a timely manner.
Participants testing positive for BP infection will be notified and will complete 26 week follow up including PROs and nurse lead telephone follow up as detailed below.
Data is collected in line with the main UNIVERSAL protocol.

Day 3 data collection (If BP infection positive and remains inpatient):

- FLU-PRO PLUS / EQ-5D-5L

In the case of pending BP test results or data collection falling on a weekend, these are subject to a window of +/- 2 day.

Day 7 data collection (If BP infection positive and remains inpatient):

- FLU-PRO PLUS / EQ-5D-5L

In the case of pending BP test results or data collection falling on a weekend, these are subject to a window of +/- 2 day.

Discharge data collection:

- Discharge information collection as per section 5.1.3

Follow-up:

- Follow up phonecalls at week 6, 12, 26 and PRO collection as per section 5.2
- This will include PRO collection at week 1, 2, 4, 8, 12 and EQ-5D-5L only at week 26.

There is no PRO or telephone follow-up for participants testing negative for BP infection.
For study deviations and withdrawls see UNIVERSAL protocol sections 5.3 and 5.4.

6.2.6 Data transfer

The pseudonymised clinical data set, from the BP-pilot study will be made available to Sanofi. This data will include (but not limited to) patient demographics, co-morbidities, vaccine status, pertussis symptom screening on admission, acute medication, presenting history, questionnaire data and outcome data at discharge.
Bordetella pertussis PCR results including, where possible, Ct values and *Bordetella pertussis* serology results will be provided to Sanofi for the 100 recruited participants.

7 SAFETY

No specific therapeutic intervention is proposed: this study consists only of deriving biomarker information from blood and nasal samples alongside clinical information about participants to develop a prospective longitudinal clinical database for patients admitted to hospital with acute viral respiratory tract infections. The risks of adverse events occurring following respiratory tract sampling and additional blood tests being taken are minimal and where occurring, these are likely to be mild. No additional adverse events related to molecular point of care testing (mPOCT) for respiratory viruses including COVID-19 are anticipated.
Taking combined nose and throat swabs and bloods are common practice and the likelihood of a serious event occuring is low. Any procedure related Serious Adverse Event will be reported to the SCTU. The site will manage the event as per standard practice.

7.1 TRIAL SPECIFIC REQUIREMENTS

Only serious adverse events deemed to have resulted from administration of any of the research procedures (sample collections) are to be reported to the SCTU.

A Serious Adverse Event (SAE) is defined as an untoward occurrence that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect
or (f) is otherwise considered medically significant by the investigator

7.1.1 Seriousness

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation log; this is usually the investigator.

7.2 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the REC will be informed of both parties' points of view.

Relationship	Denoted
Related - There is evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	*No SAEs are expected for this trial* therefore all reportable SAEs will be denoted as Related and Unexpected SAE
Unrelated - There is no evidence of any causal relationship	SAE **note that these events do not need reporting for this trial.*

7.3 EXPECTEDNESS

There are no expected serious adverse events for this trial.

7.4 PREGNANCY

The inclusion of pregnant women is permitted in the study. No additional risk is perceived to pregnant women or their offspring by any of the study procedures. No additional data collection or monitoring is therefore anticipated in this group.

7.5 REPORTING DETAILS

See Appendix 2 for details on how to report an SAE and their associated timeframes.

7.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING

SCTU will notify the necessary REC, Janssen and Sponsor of all trial procedure related SAEs within 15 days.

8 STATISTICS AND DATA ANALYSES

A variety of statistical methods will be employed to support a range of assessment needs. A full statistical analysis plan will be developed and reviewed by the study management group prior to final analysis.

An initial characterisation of both the initial cohort and the cohort who test positive for viral infection will be undertaken using descriptive statistics. Descriptive analyses will be used to explore the characteristics of illnesses caused by different viral pathogens. If appropriate, clustering techniques will be used to explore similar patterns with respect to symptoms, severity and duration.

In those who test positive, univariate analyses will be used to explore the relationship between key characteristics and the outcome measures. Associations between potential risk factors and outcomes will also be tested via multiple logistic regression analysis with backward selection. All analyses will be exploratory and no formal adjustments for multiple testing performed. Results will be reported as odds ratios with associated 95% confidence intervals. Results will be reported in line with STROBE guidelines Assuming a suitable sample size has been recruited, we will use this logistic regression model as the basis for a clinical prediction model for progression of illness. Overall model performance will be assessed using the Brier score (10). Model calibration (agreement between outcomes and predictions) will be assessed visually, comparing observed and predicted probabilities (11). Model discrimination (predictions for those with and without the outcome) will be assessed using area, or partial area, under

the ROC curve. The data will also be available for secondary analysis using novel artificial intelligence and machine learning methods.

8.1 SAMPLE SIZE

The primary analyses in this study are exploratory, seeking to establish associations between key variables and outcome measures and to explore the clustering of signs/symptoms on presentation and disease outcomes. As such a formal sample size is not required. In terms of descriptive statistics on the incidence of viral illness, 2000 participants would conservatively allow the estimation of incidence with a 95% confidence interval +/- 2.2%

There is little consensus in the literature on how best to calculate a formal sample size cluster analysis such as latent class modelling. However, simulation studies have suggested that sample sizes in the order of 500 to 1000 participants are usually sufficient even in the presence of weak class-indicator associations for 80% power or greater (12,13).

To develop a clinical prediction model of progression of illness, a minimum sample size of 932 would be required. This assumes that for a model to be useful it would need to have an area under the ROC curve of at leas 0.85 and is based on an outcome prevalence of 10% and up to 18 parameters in the final model.

8.2 INTERIM ANALYSIS

No formal interim analyses are planned.

8.3 ECONOMICS DATA PLAN

Data will be collected on cost and Quality Adjusted Life Years (QALYs). An estimated cost of each Finished Consultant Episode will be done using the the relevant HRG attached by the hospital. HRGs are based factors such as diagnosis, age, sex and presence/absence of co-morbidities, as well as urgent/planned admission. A national HRG tariff is used to pay NHS hospitals for patients treated. Respiratory illness has 160 different HRGs. Each patient in the study will be allocated to the relevant HRG by the hospital linked to the relevant Finished Consultant Episode.

EQ-5D-5L is the main tool, recommended by NICE, used to collect data on each patient's health status at a particular point in time. These values form the basis of QALYs. EQ-5D-5Lwill be administered at each data collection point in the study.

These costs and EQ-5D-5L data are intended for future use in trials of interventions rather than to estimate cost per QALY within the proposed dataset. In any such trials, further data might be required such as the cost of the intervention being trialled and any knock-on effects on post hospital services.

8.4 SAMPLE ANALYSIS

8.4.1 AZ BIOMARKER ANALYSIS

There is emerging evidence that a dysregulated host response can lead to worse outcomes in adults hospitalised with RVI and specific intervention to modulate the host response may improve outcomes (14). To further characterise markers of harmful inflammation and their relationship with virus type, clinical features and clinical outcomes a subset of samples will be analysed as below as part of the exploratory objective of the study.

- Markers of inflammation in the nasal lining fluid and serum samples on 300 subjects at baseline, day 3 and day 7
- O-link analysis in serum and nasal fluid on 300 subjects at baseline
- Blood transcriptomics and Genomic sequencing on 300 subjects at baseline

The full de-identified or pseudonymised clinical data set for the UNIVERSAL study will be transferred to AZ. This will include (but not limited to) patient demographics, co-morbidities, vaccine status, previous and current medication, presenting history, questionnaire data, outcome data, disease severity data. In addition, laboratory and biomarker data generated form the study (including but not limited to virus status, blood cell differential) will be transferred. Additional analyses may be performed subject to agreement between AZ and Investigators. All data generated at AZ will be made available to Investigators.

8.4.2 SANGER METAGENOMIC SEQUENCING

The lung microbiome (including viruses and bacteria) can modulate severity of respiratory viral infection. This relationship is complex and further investigation is required to characterise the microbiome during viral infection, to identify novel biomarkers of severity and discover the impact on patient outcomes. In line with the exploratory objectives of the UNIVERSAL study, a microbiome analysis using metagenomic sequencing techniques of the respiratory samples collected during the UNIVERSAL study will be carried out in collaboration with The Sanger Institute.

The nose and throat swab samples collected from UNIVERSAL (including the green top VTM swabs and the purple Amies swabs) and associated clinical data will be sent to the Sanger institute in Cambridge for metagenomic sequencing analysis for investigation of the respiratory tract microbiome (including virome and bacteriome). This may include viral/bacterial typing and quantification. The Sanger will then make the resulting data available to the Trust/supplier for academic research, educational and training purposes, including publications, presentations, and future research collaborations with potential funding bodies. The data produced from their analysis will also be available on a public repository as per the Sanger Institute data sharing policy.

8.4.3 BIOMERIEUX/SYNAIRGEN AUTOANTIBODIES

The aim of this sample analysis will be to evaluate the association between viral load, type I interferon autoantibodies, baseline factors and clinical outcome in patients admitted to hospital with a respiratory viral infection.

Serum aliquots collected from 400 UNIVERSAL participants at baseline will be sent to Biomérieux in France for analysis to verify and/or assess the performance of their VIDAS auto-antibody anti-IFN alpha prototype. Clinical Data from will be sent to Synairgen for monitoring and analysis, followed by statistical analysis exploring the relationship between viral load, type I IFN autoantibodies, baseline factors and clinical outcomes using the results produced from Biomérieux. All resulting data will be made available to the Trust and Southampton Clinical Trials Unit for academic research, educational and training purposes, including publications, presentations, and future research collaborations with potential funding bodies.

9 REGULATORY

9.1 CLINICAL STUDY AUTHORISATION

This study is not considered to be a clinical study of a medicinal product, so clinical study authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

10 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation of the study procedures. The right of the participant to refuse to participate in the study without giving reasons must be respected. The participant remains free to withdraw at any time from study follow-up without giving reasons and without prejudicing their further treatment.

10.1 SPECIFIC ETHICAL CONSIDERATIONS

Adults who lack capacity may be included in the study. The study will be conducted in accordance with the provisions of the Mental Capacity Act (2005) (Nhs.uk,2018) and recruitment and consent procedures will adhere to requirements of the Act and in accordance with GCP guidance. For detailed information see section 5.

Permissions will also be sought to enable surplus samples to be stored for future research. This will form part of the patient information sheet and consent form.

10.2 ETHICAL APPROVAL

The study protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

10.3 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

Any data collected as part of the trial will be securely stored in line with the Data Protection Act and GDPR.

11 SPONSOR

University Hospital Southampton NHS Foundation Trust is the legal sponsor for the study.

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the study task allocation matrix.

The duties assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body, Health

Research Authority (HRA), main research ethics committee (REC) and that local permission has been obtained prior to any subject recruitment.

All substantial amendments and non-substantial amendments (as determined by the sponsor) will not be implemented until HRA/REC have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial amendments and non-substantial amendments. Relevant approvals must be obtained before any substantial amendment and non-substantial amendments may be implemented at sites.

All correspondence with the HRA and the REC will be retained in the Trial Master File and the Investigator Site File (maintained by the site).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within 90 days after the end of the trial (as defined in section 3.2), the CI/Sponsor will ensure that the HRA and the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

All results will be published on a publicly accessible database.

11.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.2 FUNDING

Janssen, AstraZeneca, Sanofi and Synairgen are funding this as an Investigator Lead, Non-commercial study.

11.3 SITE PAYMENTS

The payments assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

This study may be adopted onto for the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required

11.4 PARTICIPANT PAYMENTS

Participants will not be paid for participation in this study.

11.5 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

12 STUDY OVERSIGHT GROUPS

The day-to-day management of the study will be co-ordinated through the SCTU and oversight will be maintained by the Study Management Group, the Study Steering Committee and the Data Monitoring and Ethics Committee.

12.1 STUDY MANAGEMENT GROUP (SMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The UNIVERSAL TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other study committees.

12.2 STUDY STEERING COMMITTEE (SSC)

As there are no safety concerns with this study, an SSC will not be convened. The study will be overseen as part of the non-cancer director oversight meetings held by the SCTU and any data release requests will be reviewed and approved via the SCTU data sharing committee (see Section 13).

12.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

No IDMC or DMEC will be convened for UNIVERSAL.

13 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the study will be available and a Study Schedule with planned and actual milestones, CRF tracking and central monitoring for active study management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the study team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the study after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

14 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by studies, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site,] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

15 MONITORING

15.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the study database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the study data, which are detailed in the study monitoring plan.

15.2 CLINICAL SITE MONITORING

If any issues arise from central monitoring, an ad hoc site monitoring visit may be conducted.

15.3 SOURCE DATA VERIFICATION

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to study staff and departments.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site without informed consent

16 RECORD RETENTION AND ARCHIVING

Archiving of the TMF and other relevant documentation is the responsibility of the Chief Investigator.

Archiving will be authorised by the Sponsor following submission of the end of study report.
Location and duration of record retention for:

- Essential documents: Patient case notes will be stored and maintained according to standard rules and procedures. Pathology results are stored and maintained according to standard procedures.
- Study data will be held for minimum of 5 years

Destruction of essential documents will require authorisation from the Sponsor.

Study documents will be retained in a secure location during and after the study has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure the PI will maintain all source documents and study related documents. All source documents will be retained for a period of 10 years following the end of the study.

Sites are responsible for archiving the ISF and participants' medical records.

17 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the study until the Study Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Study Manager, and Statistician(s) involved in the study. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

17.1 DISSEMINATION

If the participant agrees to receiving the information, patients or carers will be notified of the results of the study, in an appropriate format and language suitable for lay members. The data will be published in a peer reviewed journal and available in the public domain. The study will be registered on a publicly available database that will be regularly updated throughout the life of the study and will include the final report when available.

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APPENDIX 1
ORDINAL SCALE FOR CLINICAL IMPROVEMENT

The OSCI to be used in this study is the 12 June 2020 version as recommended by the WHO (1).

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

NVI – non-invasive ventilation; ECMO - extracorporeal membrane oxygenation

Whilst hospitalised as an inpatient, the OSCI assessment should be carried out once a day at approximately the same time each day from enrolment until discharge. It is recommended that this assessment should be carried out by a clinically qualified member of the study team, i.e. a medical doctor or a qualified nurse. Before discharge, the assessment may be carried out face to face and post-discharge over the phone/video link or retrospectively obtained by analysing patient observations.

Patients' status on the day of hospital discharge should be assessed as ambulatory/uninfected (WHO OSCI score of 0, 1 or 2). Following discharge, OSCI assessment will occur

On the day of hospital discharge and during the follow-up call from the research nurse on Week 6, 12 and 26, participants should be asked the below questions about their clinical status and return to the pre-infection level of activity. If the patient is discharged before an OSCI assessment has been completed, these questions can be asked via a phone call.

- "In the past 24 hours, did you experience any signs or symptoms of your respiratory viral infection?" "Yes" or "No" answer will be required.

- "In the past 24 hours, did you feel that your usual activities (e.g. work, study, housework, family or leisure activities) have returned to the level from before your respiratory viral infection and did not require additional assistance/support*?" "Yes" or "No" answer will be required.

* assistance/support is defined as additional help of other people and/or requirement for supplemental oxygen (or a higher level of supplemental oxygen), compared to the pre-viral respiratory infection state.

In order to minimise any potential influence on the participants, the interviewers will be required to read the questions to participants verbatim and not to change or interpret them in any way.

The result of the OSCI assessment, from the day of hospital discharge, must be based upon the patient's responses to the two questions specified above and must not be adjusted based on the results from other outcome assessments (e.g. BCSS, BPI, long COVID-19 symptom assessment, and EQ-5D-5L), even if these data provide conflicting clinical information.

APPENDIX 2
REPORTING OF SERIOUS ADVERSE EVENTS

For all reportable SAEs (those deemed to have resulted from administration of any of the research procedures), an SAE report form should be completed (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event. The SCTU can be contacted by phone for advice.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event
ctu@soton.ac.uk
FAO: Quality and Regulatory Team
For further assistance: Tel: 023 8120 5154 (Mon to Fri 09:00 – 17:00)

1. GRADES:

The event term should be the most appropriate medical term or concept and grades given in accordance with the following. (Taken from Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Publish Date: November 27, 2017)

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

2. REPORTING TIMELINES

Any events meeting the above reportable criteria (SAE resulted from administration of any of the research procedures) should be reported from the date of informed consent to 14 days post enrolment.

All unresolved reported SAEs should be followed by the investigator until 30 days post enrolment or one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At discharge from hospital, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial that occurs up to 14 days post enrolment.

20 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V2.0 12-Aug-2022	Addition of inclusion criteria, participants must be inpatients. Change of the OSCI score to up-to-date 10 point score. Change of the PID from 6 to 8 digits. Addition of +/- 1 day sampling window while participants are still in hospital.
V3.0 02-Nov-2022	• Updated the list of abbreviations and database URL • Clarifications of timings of data collection throughout study and reduction in frequency of data collection between week 4 and 12 • Clarification around collection window for samples and data whilst in hospital (+/- 1 day) and post-discharge (+/- 3 days) • Clarification that other diagnostic PCR test to BioFire Film Array system are permitted • Clarification of timing of recruitment post admission (within 36 hours) • Clarified the registration procedures • Addition of collection of throat swab only if patient is not tolerating combined nose and throat swab • Clarification that bloods and nose/throat swabs on Day 3 and 7 should only be collected if participants are in hospital. • Removal of the Nottingham Extended Activities of Daily Living (ADL) scale questionnaire • Addition of unscheduled phone call to collect discharge data on occasions when patient is discharged before the research team can collect these, such as over the weekend • Clarifications about generation of HRG codes • Addition of Research Pilot Study • Clarification around the OSCI assessment
V4.0 06-Dec-2022	• Clarification that the Research Pilot Study is part of the exploratory objective of the trial and no additional samples are acquired.
V5.0 10 – Feb-2023	• Addition of the Scottish IRAS and REC IDs as requested by the Scottish REC. • Clarification around the paper questionnaires and patient diaries
V6.0 20-Sep-2023	• Reduction in the frequency of questionnaires at follow up, and the removal of the RiiQ questionnaire from the follow up schedule. • Removal of Dry Swab, replaced by Nasal Swab in Amies Media. • Addition of Virus Negative Sub-Study.
V7.0 09-Apr-2024	• Addition of Bordetella-pertussis Sub-Study • Addition of 'Sample Analysis' section including AstraZeneca, Sanger and Synairgen/Biomerieux sample analyses
V8.0 07-Aug-2024	• Correction of date on front page of protocol • Change of wording for Bordetella-pertussis Sub-Study samples to 'flexible wire swab' from 'swab in amies media'. • Clarification to schedule of observations for BP Sub-Study.