Imperial College London

Predicting severity and disease progression in influenza-like illness (PREDICT-ILI)

RESEARCH PROTOCOL

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STUDY COORDINATION CENTRE: Section of Adult Infectious Disease, Department of Medicine, Imperial College London

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Study Management Group

Chief Investigator: Dr Christopher Chiu

Study Site

The study will take place at St Mary's, Charing Cross & Hammersmith Hospitals, London (part of the Imperial College Healthcare NHS Trust).

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

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Clinical Queries

Clinical queries should be directed to Dr Christopher Chiu who will answer or direct the query to the appropriate person.

Sponsor

Imperial College London is the research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity Ruth Nicholson at:

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Funder

The NIHR Imperial Biomedical Research Centre (BRC) has provided funding for this study. This protocol describes the above study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK policy framework for health and social care (V3.3 07/11/17). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate including Good Clinical Practice.

STUDY SUMMARY

TITLE Predicting severity and disease progression in influenza-like illness

DESIGN Observational study

AIM To identify and test predictors of disease progression and clinical deterioration in patients hospitalised with influenza-like illness

POPULATION Healthy persons aged ≥ 18 years

ELIGIBILITY Healthy persons aged ≥ 18 years that fit the inclusion and exclusion criteria

DURATION 1 Year

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ARI	Acute Respiratory Infection
BAL	Bronchoalveolar Lavage
BioAid	Bioresource for Adult Infectious Disease
BRC	Biomedical Research Centre
CRF	Case Report Form
CRP	C-Reactive Protein
DEG	Differentially Expressed Gene
DNA	Deoxyribonucleic Acid
ELF	Epithelial Lining Fluid
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICRF	Imperial Clinical Research Facility
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
MOSAIC	Mechanisms of Severe Acute Influenza Consortium
NIHR	National Institute for Health Research
NHS	National Health Service
NRES	National Research Ethics Service
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate-Buffered Saline
PCR	Polymerase Chain Reaction
PID	Personal Identifiable Data
PRB	Protocol Review Board
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAM	Synthetic Absorptive Matrix
WHO	World Health Organisation

KEYWORDS
Virus, viral lung disease, infection

INTRODUCTION

1.1. Background to research

Despite clinical advances and decades of research, our ability to reliably predict the course of respiratory viral diseases such as influenza and coronavirus infections remains poor. The aim of this project is to develop a platform for identifying and developing predictive tests by combining physiological data and correlates of severity in influenza-like infections so that progression to severe pulmonary involvement can be anticipated during respiratory viral infection. This would then permit safe discharge of patients with self-limiting disease or more rapid intensification of treatment as appropriate.

Respiratory infections are among the most important causes of severe disease worldwide, with the major respiratory viruses responsible for overwhelming pressure on health services each winter due to annual surges in incidence[1]. The two most common viral causes of severe lung disease, influenza and respiratory syncytial virus (RSV), are responsible for ~50% of hospital admissions in children and 22% in adults, with mortality greatest in older people. As the population ages, this burden of disease is steadily increasing. Furthermore, the continual risk of newly emergent pandemic influenza strains that arise unpredictably is universally considered one of the most critical threats to global health and socioeconomic stability. This has been demonstrated by the recent COVID-19 pandemic[2].

Options for prevention and management of respiratory virus infections remain inadequate. Respiratory virus vaccine development has seen conspicuous failures, with no vaccine yet available against most respiratory viruses and limited effectiveness of influenza vaccines due to continual viral mutation and incomplete understanding of human antiviral immunity[3]. While influenza antiviral drugs can reduce duration and severity of disease, they are usually administered late, thus limiting their efficacy. On the other hand, in most patients, respiratory viral infections resolve without specific intervention and might not even require hospital admission. Nevertheless, the dynamic nature of these acute infections means that rapid deterioration may occur if no treatment is given. Clinicians currently have few diagnostic tools to assist with this treatment dilemma in the period before onset of significant deterioration, relying on suboptimal clinical scoring systems and non-specific physiological and biological markers (e.g. white cell count, CRP)[4]. Over-treatment with unnecessary hospital admissions and antibiotics as well as under- or delayed treatment both regularly occur. With new antiviral drugs being licensed (such as the influenza polymerase inhibitor Baloxavir), options for treatment intensification with combination therapies are emerging but have implications for cost and patient tolerability[5]. New tests or combinations of tools to predict the dynamic course of respiratory viral disease are therefore urgently required to assist with individual patient management and for allocation of limited resources.

Risk factors for severe influenza have been investigated extensively in clinical cohorts, with older age, co-morbidities, obesity and pregnancy all increasing the likelihood of severe disease[6,7]. However, accurate prognostic markers remain elusive and the dynamics of the response to respiratory viral infection has not been explored in naturally-infected patients. Furthermore, biomarker discovery has been limited by heterogeneity in virus strain and dose; delays in timing of presentation; and patient-level confounders. To address these issues, since 2010, we have conducted controlled human infections with influenza and RSV to investigate mechanisms of immunopathogenesis with a particular focus on disease in the human respiratory tract[8–10]. Experimental human infection models overcome some of the limitations of observational studies in naturally-infected patients by controlling inoculum and volunteer characteristics. Furthermore, they allow detailed longitudinal sampling and analysis of the dynamic changes occurring throughout the course of infection. Previous studies have successfully identified transcriptional signatures in blood that distinguish viral from bacterial infection, and diagnose influenza before the onset of symptoms[11,12]. These have been translated into diagnostic point-of-care tests currently undergoing clinical validation.

Recent preliminary data from a cohort of volunteers infected with the influenza A(H1N1)2009 strain showed that viral shedding and symptoms began concurrently at ~24 hours post-inoculation and peaked

at days 3-4 before resolving. These were paralleled by rapid changes in the transcriptome of whole blood. Within 2 days of virus exposure, a large number of differentially expressed genes (DEGs) dominated by innate antiviral immune response and cellular proliferation pathways were detectable. Furthermore, the coordinated regulation of these gene sets delineated the course of infection in the run-up to peak disease and during resolution, thus providing a biological timeline of influenza infection and clearly distinguishing disease onset from convalescence. During the 2009 influenza pandemic, similar studies were also performed with hospitalised patients[13]. There, transcriptomic analysis of blood showed similar antiviral signatures in less severely unwell individuals but divergent signatures associated with poor clinical outcomes. Thus, it is likely that biomarker signatures can diagnose progression to and resolution of influenza disease, using the hitherto unexplored contribution of complex dynamic changes to enhance accuracy of prediction.

The aim of this project is to identify and test predictors of disease progression and clinical deterioration in patients with influenza-like illness, in order to develop novel methods to more accurately determine the need for hospital admission and treatment intensification during respiratory viral infection. The project will build on a programme of experimental human influenza and respiratory syncytial virus (RSV) challenge studies since 2010 and natural infection studies (BioAid and MOSAIC) that have identified correlates and signatures of protection, pathogenesis and disease severity. To further develop and test these biomarkers in an independent cohort of naturally-infected patients, hospitalised adults with influenza-like illness will be recruited within 24 hours of admission to ICHNT and samples obtained from blood and nose at 3 subsequent time-points. This expands on the methods developed as part of the EU H2020 PREPARE consortium during multiple recent winter seasons.

Using data from infection challenge models, MOSAIC and BRC-funded BioAid projects, predictive transcriptomic signatures will be identified in collaboration with the BRC Genomics Theme. Longitudinal samples and clinical data will then be used to test, validate and refine them in affected local populations. These findings will then be translated into novel diagnostic tools to assist in rational treatment decisions that will benefit both individual patients and resource allocation. Additionally, this study will establish research preparedness for upcoming pandemics and provide an on-going resource for Imperial investigators to investigate the virology and immunopathogenesis of severe respiratory viral infections, while also providing a platform for novel diagnostics and clinical management testing.

1.2. Research Hypotheses

- Clinical improvement or deterioration in patients hospitalised with influenza-like illness may be predicted using dynamic biomarker signatures.

STUDY OBJECTIVES

1.3. Primary Objective:

- Describe the aetiology, clinical management and outcomes of adults hospitalised with influenza-like illness

1.4. Secondary Objectives:

- Identify changes in inflammatory mediator levels in blood and respiratory mucosa that are associated with worsening clinical outcome in adults with influenza-like illness

1.5. Exploratory Objectives:

- Test the association between transcriptomics signatures of disease progression and clinical outcomes in adults with influenza-like illness

PARTICIPANT ENTRY

1.6. Recruitment

Subjects will be recruited by research nurses and doctors. We aim to enrol up to 100 participants. Potential participants will be identified and asked by a member of their immediate care team to give a verbal consent to be approached by research staff who are not members of their care team. If they agree to this then the verbal consent will be recorded in the participant's medical record. The Participant Information Sheet will then be presented by GCP-trained study staff.

1.7. Screening and enrolment

1.7.1. Screening

If the participant meets the inclusion/exclusion criteria, they will be asked if they would like to be part of the study. Potential patients for the study will be assessed for eligibility against the criteria listed below. A screening log will be kept all the patients who undergo screening regardless of whether they decide to participate in the study.

1.7.2. Enrolment

Potential subjects will be given a participant information sheet (PIS) detailing the study and procedures. This will also be discussed with them by the study doctor or nurse. When the subject has had enough time to consider their participation in this study, ask any questions they may have, and only when they have agreed to take part will they be asked to read, sign and date a consent form in the presence of the study doctor or nurse who will also sign the consent form. Consent will be obtained prior to any samples being taken. A copy will be kept in the research file, a copy given to the patient and a copy put into their medical notes.

1.8. Inclusion criteria

- Healthy persons aged ≥ 18, and able to give informed consent
- Patient is admitted to hospital
- Primary reason for hospital admission is clinical suspicion of a new episode of ARI
- Onset of the following symptoms within the last 12 days: i. Sudden onset of self-reported fever OR temperature of ≥ 38°C at presentation

  AND ii. At least one respiratory symptom (cough, sore throat, runny or congested nose, dyspnoea)

  AND iii. At least one systemic symptom (headache, muscle ache, sweats or chills or tiredness).

1.9. Exclusion criteria

- Patient lacks capacity to provide informed consent
- Patient has been transferred from another hospital
- Patient has been previously enrolled in the study

1.10. Withdrawal criteria

Any subjects can withdraw from the study at any time if they wish to. Subjects can also be removed from the study if an investigator feels this is necessary or appropriate.

If a participant loses capacity during the study, identifiable data or tissue already collected with consent would be retained and used in the study. In addition, data regarding clinical progress and outcomes would continue to be obtained from their medical record. No further blood or tissue would be collected,

or any other research procedures carried out on or in relation to the participant until they are once again able to consent. In the event of loss of capacity, advice from a consultee would be sought in order to continue data collection from the medical records. If possible, this will be done face-to-face in the hospital environment. Where this is not possible, a member of the research team can contact the participant's next-of-kin by telephone, and then send a Consultee Declaration Form to sign via post, including a stamped envelope to return the document.

STUDY DESIGN

1.11. Study schedule

The study has up to three in-patient sampling time points and one convalescent sampling appointment as out-patient. Subjects will have samples taken at Day 0, at Day 2 (if they remain in hospital), with a final in-patient sample at discharge. At Day 28 the patient will attend the ICRF or clinic, or if not possible, be visited at home. If still an in-patient, samples will still be collected (See Table 1).

Table 1

Procedures	Day 0	Day 2	Discharge	Day 28
Screen	X			
Consent	X			
Data collection	X	X	X	X
Nasal SAM	X	X	X	X
Nasal wash	X	X	X	X
Nasal scrape	X	X	X	X
Blood – serum	10			10
Blood – PBMCs	20	20	20	20
Blood – RNA (mls)	5	5	5	5
Blood – plasma (mls)	6	6	6	6
Bronchoaveolar lavage fluid	*If available*			

Day 0 - within 24h of hospital admission
Day 2 - two days after hospital admission. Delay of Day 2 sample collection up to Day 4 will be permissible
Discharge - if discharged before or on Day 2, the discharge samples will replace the Day 2 samples
Day 28 - this visit can be -3/+21 days

1.11.1. Day 0

At Day 0 the participant will be screened and consented to the study as previously described. Nasal and blood samples will be taken (see Table 1), and data collected. Data to be collected will consist of; past medical history, current health, clinical signs and symptoms relating to this admission, vitals observations, demographics, drug history, current prescribed medication, laboratory results including microbiological testing and interventions such as oxygen therapy and ventilation.

1.11.2. Day 2

At Day 2 the participant will have data, nasal and blood samples collected (see Table 1).

1.11.3. Discharge

At Discharge the participant will have data, nasal and blood samples collected (see Table 1)

1.11.4. Day 28

At Day 28 the participant will have nasal and blood samples collected (see Table 1). Data collection will consist of clinical diagnosis at discharge, any febrile illness in the 7 days preceding the visit, mortality and complications between Day 0 and 28.

STUDY PROCEDURES

A variety of procedures are carried out during the study period. The frequency and timing of these procedures are shown in Table 1 above. For Day 0, Day 2 and Discharge, procedures will take place in the in-patient area the participant is admitted to at that time. For Day 28, procedures will take place at ICRF, ICRRU, ICHNT out-patient clinics or in the patient's home. Samples taken for the purpose of medical management will, at all times, have priority over samples requested for research reasons. Research samples will, wherever possible, be collected at a time coinciding with samples taken for routine care.

1.12. Nasal sampling procedures

1.12.1. Nasosorption

One strip of SAM will be placed against the inferior nasal turbinate for 2 minutes to obtain a sample of neat nasal lining fluid (NLF). This is a painless minimally invasive procedure that will not require any local anaesthetic. Following sampling, SAM will be placed in a 1mL microfuge spin filter tube containing 100µL of elution buffer (PBS/1% bovine serum albumin/0.05% azide/0.05% Triton®). Further details are given in the SOP Human Sampling Procedures.

The SAM will be transported on ice to the laboratory and NLF will be collected by centrifugation before storage at -80°C. NLF will be used for analysis of cytokines, chemokines and other proteins.

1.12.2. Nasal lavage

Nasal lavage is performed using the following technique:

- 5-10mL of 0.9% saline is introduced into one nostril using a syringe attached to a nasal olive, with the subject sitting with the head tilted forward
- The saline is then washed in and out of the nose approximately 10 times by alternately withdrawing and advancing the plunger of the syringe while the subject maintains a tight seal between the nasal olive and the nostril; the aim is to recover ~80% of the saline from the nose
- The same procedure is repeated in the other nostril
- The fluid is then aliquoted into sterile microfuge tubes and centrifuged for analysis of cells

Lavage fluid will later be analysed to quantify the degree of viral shedding. Supernatants will be frozen and stored at -80°C before further analysis of antibody levels and other proteins. Further details are given in the SOP Human Sampling Procedures.

1.12.3. Nasal scrape using Rhinopro®

Rhinopro® curettes will be used to obtain a sample of nasal epithelial cells from each nostril. This is a painless procedure and will not require local anaesthetic. The following technique is used:

- The subject should be sat comfortably, ideally with their head fixed, looking forward, while their chin rests on a support (if available)
- Tear bag and remove the flexible plastic Rhinopro® without contaminating the scoop end
- Place a speculum in the nose to keep the cavity open and employ good lighting
- Under direct visual inspection, insert the cupped probe onto the surface of the mid-inferior portion of the inferior turbinate. Note: Avoid the anterior bulb
- The Rhinopro® should be 3cm up the nose; the floor of the nostril can be used to rest on

- Have the cup of the Rhinopro® at the correct angle
- Gently press the cupped tip on mucosal surface and move out and in of nostril 3mm up to 3 times
- Note that this area has limited sensitivity and the subject should not find this procedure painful, although a nasolacrimal reaction usually occurs

The cell harvest is epithelial cells, goblet cells and mast cells. It does not contain deeper layers of the mucosa. The sample obtained should be placed immediately into a tube containing RNA Cell Protect® (Qiagen) or Trizol and frozen at -80°C for storage prior to analysis by transcriptomics and qPCR.

1.13. Blood sampling

Serum will be taken and stored at -80°C before measurement of antibody levels and other proteins. Serum will also be used in future serological tests for comparison purposes. Blood for gene expression profiling will collected in Tempus or PaxGene tubes and processed according manufacturers' instructions. These will be stored at -80°C for later processing and analysis by transcriptomics and qPCR. Plasma will be taken and stored at -80°C before measurement of cytokines, chemokines and other proteins and metabolites. Fresh whole blood may be used for analysis of immune cell phenotypes by flow cytometry. Otherwise, peripheral blood mononuclear cells (PBMCs) will be isolated by density gradient centrifugation and stored in liquid nitrogen for later analysis of B cells and T cells responding to infection (see Table 1).

ADVERSE EVENTS

1.14. Definitions

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

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

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

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

1.15. Risks and expected adverse events

1.15.1. Risk Determination

All study procedures involve no more than minimal risk to participants. Similar procedures have been used for many years without severe adverse effects. These include blood and nasal sampling; participants will be counselled as follows:

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

SAM strip (a soft strip placed up the nose for two minutes), nasal lavage (washing), and nasal curettage (scrape): may tickle, make their eyes water or be slightly uncomfortable. They should not be painful.

1.16. Reporting procedures

All adverse events should be recorded in the case report forms. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. In the event of an SAE, an SAE form should be completed and emailed to the Chief Investigator and the Sponsor within 24 hours of the event having been discovered by or notified to the study team.

1.16.1. Non serious AEs

All such events, whether expected or not, should be recorded.

1.16.2. Serious AEs

An SAE form should be completed and faxed to the Chief Investigator and the Sponsor within 24 hours. The safety monitoring committee will also be informed, and a meeting convened as soon as possible.

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

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

Reports of related and unexpected SAEs should be submitted to ethics, the sponsor and the R&D office within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies.

Contact details for reporting SAEs

Please send SAE forms to:
Joint Research Compliance Office, Imperial College London
jrco@imperial.ac.uk
Principal Investigator: Dr Christopher Chiu
c.chiu@imperial.ac.uk
Section of Adult Infectious Disease, Imperial College London,
Hammersmith Campus, Du Cane Road, London W12 0NN
Tel: 020 8383 2301 (Mon to Fri 09.00-17.00)

ASSESSMENT AND FOLLOW-UP

Study participants will have their treatment managed by their individual medical care team, as such we will not be assessing these patients outside of any study procedures. However, any significant medical findings detected during follow-up will be reported to the patient's GP and medical team with the patient's consent as appropriate. For any queries or issues regarding the study, they will be given contact details for the study team.

Subjects will have completed the study when they have had final convalescence investigations, expected to be 28 days after the Day 0 visit. This visit can be -3/+21 days from Day 28. The overall study will be completed when sufficient numbers of subjects have been recruited. The end of the study is defined as the last visit of the last participant.

When participants have completed the study, they will not be routinely followed-up by the research team. If a participant loses capacity during the study, identifiable data or tissue already collected with consent would be retained and used in the study. In addition, data regarding clinical progress and outcomes would continue to be obtained from their medical record. No further blood or tissue would be collected, or any other research procedures carried out on or in relation to the participant until they are once again able to consent. In the event of loss of capacity, advice from a consultee would be sought in order to continue data collection from the medical records.

The study is a low-risk non-CTIMP, carried out by an experienced PI and study team. The study has appropriate risk assessments in place and will be checked through the PRB system at ICRF. Local monitoring will be carried out by study staff to ensure that CRFs are being completed correctly, with no key data missing. Any deviations or incomplete records identified on monitoring will be reported to the PI and the study team will be asked to make corrections and/or write deviation file notes as required.

STATISTICS AND DATA ANALYSIS

The ultimate aim of this study is to detect differentially expressed genes triggered by the major respiratory viral pathogens (i.e. influenza virus, RSV, coronavirus) as assessed by RNA transcriptome at the time of admission that correlate with clinical outcomes. We assume that the expression of each gene is normally distributed on the log scale and that the variance is the same in the different groups and thus the only difference between the groups is the mean. At an alpha of 0.05 and at an expected standard deviation of the gene intensity measurements on the base-two logarithmic scale of 0.7 (realistic for genes that are expressed at moderate to high levels), we expect to be able to detect 90% of >2 fold differentially expressed genes (i.e. an absolute effect size of 1 on a base-two logarithmic scale) between groups of 11 patients. The calculation was based on the Affymetrix HG U133plus2 microarray platform, which contains 54,515 probe-sets. The proportions of patients recruited with each of the major pathogens (influenza virus, RSV, coronavirus) is difficult to predict following the major COVID-19 pandemic, but we anticipate that by recruiting ~100 patients, at least 11 severe and 11 non-severe patients with influenza and COVID-19 will be enrolled.

Table 2 Power calculations

	Effect size in fold change		
Power	**2**	**1.75**	**1.5**
60%	5	8	15
70%	7	10	18
80%	8	12	23
90%	11	16	31
95%	13	20	38

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period according to Imperial College London policy.

REGULATORY ISSUES

1.17. Ethics approval

The Study Coordination Centre has obtained approval from the Essex Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

1.18. Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, time allowed for consideration, and any questions participants may have answered. Signed participant consent will be obtained prior to any screening tests being carried out. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

1.19. Confidentiality

The Chief Investigator and all of the research team will preserve the confidentiality of participants taking part in the study and abide by the Data Protection Act. All personal/identifying information will be stored in password protected files, accessed via on password protected computer accounts. Only the study research nurses and doctors will have access to this information. PID (Personal Identifiable Data) will be stored for 10 years as per College retention policy. Paper medical records will be stored as per Trust policy, within a key-coded and fireproof door medical records storage facility within the ICRF. The site file and paper CRFs will be kept in a locked filing cabinet, in a locked office within the Commonwealth building at Hammersmith campus. The investigators will adhere to the GDPR and Imperial College London policies (UK Policy Frame Work for Health and Social Care Research) for handling any data.

Indemnity
Imperial College London as sponsor of this study holds negligent and non-negligent harm insurance policies which apply to this study.

Sponsor
Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trust taking part in this study.

Funding
This study is funded by the NIHR Imperial Biomedical Research Centre (BRC). They are acting as sole funders and this agreement is in place. The investigators will not receive any additional payment above their normal salaries. Participants in the study will have be compensated £50 on the Day 28 visit due to the time and inconvenience taken. If they do not complete the out-patient visit, this donation is not applicable.

1.20. Audits and inspections

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

1.29. Sample storage and usage

Samples of tissue, cells and fluids will be stored at the Commonwealth building and Medical School building sites at Imperial College London. Samples will be pseudonymised. These may be used for further assays or in other ethically approved studies. Samples and data may be shared with UK and international collaborators in studies that have been approved by local ethics committee and subject to a valid Materials Transfer Agreement. Data and samples sent outside the UK will be pseudonymised with no patient identifiable data transferred.

STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Christopher Chiu, Clinical Senior Lecturer and Honorary Consultant in Infectious Diseases. In addition, a safety monitoring committee will convene monthly during the study to discuss all adverse events, protocol deviations, and other safety issues.

PUBLICATION POLICY

Our expectation is that after analysis the data from this study will be widely distributed in the medical and scientific community. Facilitated with presentations at local, national and international meetings, we hope to publish widely in the medical literature. In addition we have an excellent media department at Imperial College and will publicise research that has public interest when it is published. No identifying participant information will be published. The study will be registered on clinicaltrials.gov.

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