Assessment of viral shedding week following administration of live attenuated influenza vaccine in children: FluSHED-2 study

VERSION 1.0, 3 July 2018

SPONSOR: Imperial College London (JRCO ref 18SM4658)

FUNDING: NIHR HPRU in Respiratory Infections at Imperial College London
Further mechanistic assessments funded by Medical Research Council

STATEMENT OF COMPLIANCE

This protocol describes the FluSHED-2 study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other 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 centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Protocol authorised by:

Name & Role	Date	Signature

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	*Details of Changes made*

PROTOCOL SYNOPSIS

Title	Assessment of daily viral shedding in the week following administration of live attenuated influenza vaccine in children: Flu-shed-2 study
Abbreviated title	Flu-shed 2
Eudra CT registration no.	2018-002470-42
HRA NRES Number	18/LO/1317
Sponsor R&D Number	18SM4658
Clinicaltrials.gov no.	NCT03735147
HRA IRAS reference	250312
Primary objective	To measure kinetics of type-specific vaccine virus shedding in 2018/19 following LAIV administration.
Intervention and key procedures	Single dose of intranasal LAIV. A blood sample, oral fluid sample and nasal swab will be collected pre- and 4 weeks after vaccination. Daily nasal swab (collected by parent) for the week following vaccination. (To fulfil a duty of care, influenza vaccine-naïve individuals under 9 years of age AND at high risk for influenza infection will be eligible for a second dose 4 weeks later, as per Department of Health /PHE guidelines).
Safety	Participants will be immunised in hospital by qualified staff, and observed for at least 20 minutes following a dose.
Patient group	Children (age 6-15 years) who are eligible (according to current UK guidance) to receive LAIV and who are attending a paediatric facility at St Mary's Hospital, London. Target recruitment of 30 subjects.
Primary outcome	To measure type-specific vaccine virus shedding in 2018/19 and how this varies in the 8 days following vaccination.
Secondary outcomes	Quantitative analysis of immunogenicity using a range of indicators (including HI and/or MN, and nasal IgA responses), and to measure the association between type-specific vaccine immunogenicity and virus shedding.
Sponsor	Imperial College London
Funding	NIHR HPRU in Respiratory Infections at Imperial College London MRC grant to Prof A Lalvani, Imperial College London

Study Management

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Co-investigators:	Prof Ajit Lalvani, Chair of Infectious Diseases & Director of NIHR Health Protection Research Unit (HPRU) in Respiratory Infections, Imperial College London
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Study Coordination

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

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Clinical Queries

Clinical queries should be directed to Dr Paul Turner who will 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 Regulatory Compliance at:

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Imperial College London and Imperial College Healthcare NHS Trust
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Funding

NIHR HPRU in Respiratory Infections at Imperial College London, with further mechanistic assessments funded through a Medical Research Council grant (reference MR/K010468/1) to Prof Ajit Lalvani, Imperial College London.

This protocol describes the FluSHED-2 study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary.

Problems relating to this trial should be referred, in the first instance, to the study centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CMI	Cell mediated immunity
CRF	Case Report Form
CTA	Clinical Trial Authorisation
ELISA	Enzyme-linked Immunosorbent Assay
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRAS	Integrated Research Application System
µg	Micrograms
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
PHE	Public Health England
PIL	Parent Information Leaflet
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. INTRODUCTION

1.1 BACKGROUND

LAIV was introduced into the UK immunisation schedule for children in 2013/14, and Public Health England has since been closely monitoring programme performance. In 2015/16, the UK found evidence of significant effectiveness of LAIV against laboratory confirmed influenza in both primary and secondary care including against A/H1N1pdm09. The UK results concord with those from several other geographical settings, although a number of studies report relatively lower effectiveness of LAIV against A/H1N1pdm09 infection compared to inactivated influenza vaccine (IIV). The reasons for these apparent differences in effectiveness are currently unclear.

Despite a suspension of the paediatric immunisation programme in 2017/18 mainly due to poor efficacy measures in previous years, the USA Advisory Committee on Immunisation Practice (ACIP) has reinstated its routine programme for the winter of 2018/19.

Several hypotheses are emerging to explain the apparent reduction in A/H1N1pdm09 quadrivalent LAIV effectiveness in the USA last season and their discordance with findings elsewhere including the UK together with the possible lower effectiveness of LAIV against A/H1N1pdm09 compared to IIV. These include one or more of the following:

1. CDC/DoD specific finding – related to chance, methodology, programmatic issues
2. Reduced replicative fitness of the current A/H1N1pdm09 strain.
3. Viral interference/competition between A/H1N1pdm09 vaccine strain and other vaccine viruses in multivalent formulation;
4. Prior vaccination with LAIV or IIV resulting in specific immunological interference with H1N1pdm09 vaccine virus replication;
5. Repeat LAIV vaccination resulting in broader, longer term immunological changes affecting all viruses (mimicking adult response);
6. Combinations of the above

Based upon in vitro studies, the manufacturer of LAIV (MedImmune) have stated that reduced replicative fitness of the A/H1N1pdm09 strain is likely to be the important root cause. However, this factor alone cannot explain the difference in effectiveness observed between the USA and sites elsewhere including the UK. This suggests that there is an important additional factor(s) involved. The US programme has been running for many more years than the UK – and in addition children 6 months to 24 months of age are offered IIV, unlike the UK. These prior vaccine exposures are potential contributory factors, which is currently being analysed by a group at Public Health England from a study conducted in 2017/18 for which Dr Turner was CI.

LAIV shedding studies in children could be an important way to confirm whether impediments to viral replication do indeed explain these observed reductions in VE and what future implications (if any) this might have for the UK paediatric LAIV programme. LAIV virus replication in children will be dependent on virological and host factors. The virus factors include replicative fitness of individual strains and the

susceptibility to inhibition by other replicating strains (ability to compete). Host factors which may influence this include pre-existing specific immunity as a result of prior infection or previous vaccination (with either LAIV or IIV), and innate immune factors including mucosal immunity.

There is significant variability in shedding across viral subtypes in studies done to date, so there is a need to obtain local data in a small pilot observational study which will look in detail at virus shedding by sequential daily virus samples, something not possible on a larger scale. The data generated will inform future LAIV studies in the UK in terms of optimum time of sample collection for viral shedding studies, which are likely to be required on a regular basis, to supplement field studies of vaccine effectiveness. Obtaining additional samples (blood, oral fluids, nasal swabs) which are correlates of vaccine take will allow us to measure the association between type-specific vaccine immunogenicity and virus shedding and will add to existing data from previous seasons on this.

1.2 RESEARCH QUESTION

To measure type-specific vaccine virus shedding by sequential daily virus samples, and assess how this relates to immunogenicity in the 2018/19 vaccination season.

This study will enrol up to 30 children that will allow these factors to be assessed. Both written informed consent from parent/ guardian and written assent from the child will be in place prior to any study procedure. All participants will have a baseline assessment of pre-existing influenza immunity (blood test, oral fluid collection and nasal swabs), followed by a single dose of LAIV. Parents will then be asked to take nasal swabs at home on days 1, 2, 3, 4, 5, 6, 7, 8, with further nasal swab, blood test and oral fluid collection in hospital 4 weeks later, in order to assess for immune responses to LAIV.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To measure kinetics of type-specific vaccine virus shedding in 2018/19 in the eight days following LAIV administration.

2.2 SECONDARY OBJECTIVE

Quantitative analysis of immunogenicity using a range of indicators (including HI and/or MN, and nasal IgA responses), and to measure the association between type-specific vaccine immunogenicity and virus shedding.

3. STUDY DESIGN

Type of Study: Single centre, interventional study of the virus shedding in children receiving LAIV

Number of Subjects: 30

Expected Duration: Influenza vaccine season (estimated to commence September 2018 (exact date depending on availability of the Fluenz vaccine from UK Department of Health).

4. STUDY POPULATION

This is a single group study, no randomisation, in children aged 6-15 years at enrolment.

4.1 RECRUITMENT

Subjects will be recruited from existing paediatric services at St Mary's Hospital, London. Recruitment will be via publicity (posters, flyers), email and postal mailing (with an option for a follow-up contact by post, email or telephone* where there is no response to the initial invite).

*Telephone calling will only take place where the child/family is already under the care of the local clinical team, and the clinician thus has an established relationship with the family.

4.2 ELIGIBILITY CRITERIA: CHILDREN TO RECEIVE LAIV

4.2.1 INCLUSION CRITERIA

1. Children age 6 years to 15 years +364 days of age on enrolment
2. Children eligible to receive LAIV in accordance with Green Book advice [https://www.gov.uk/government/organisations/public-health-england/series/immunisation-against-infectious-disease-the-green-book]
3. Written informed consent given by parent/ guardian and assent from child (both must be in place to proceed).

4.2.2 EXCLUSION CRITERIA

1. **Contraindications to LAIV** (notwithstanding allergy to egg protein), which include:
    a. Hypersensitivity to the active ingredients, gelatin or gentamicin (a possible trace residue)
    b. Previous systemic allergic reaction to LAIV
    c. Previous allergic reaction to an influenza vaccine (not LAIV) is a relative contra-indication, which must be discussed with the CI to confirm patient suitability

d. Children/adolescents who are clinically immunodeficient due to conditions or immunosuppressive therapy such as: acute and chronic leukaemias; lymphoma; symptomatic HIV infection; cellular immune deficiencies; and high-dose corticosteroids*.

***High-dose steroids** is defined as a treatment course for at least one month, equivalent to a dose *greater than* 20mg prednisolone per day (any age), or for children under 20kg, a dose *greater than* 1mg/kg/day.

NB: LAIV is not contraindicated for use in individuals with asymptomatic HIV infection; or individuals who are receiving topical/inhaled/low-dose oral systemic corticosteroids or those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency.

e. Children / adolescents younger than 18 years of age receiving salicylate therapy because of the association of Reye's syndrome with salicylates and wild-type influenza infection.
f. Pregnancy (determined by history). Where this cannot be confirmed, a urine pregnancy test will be performed.

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4.3 SUBJECT WITHDRAWAL

Parents/guardians may withdraw their child at any time without giving a reason. In accordance with the current revision of the Declaration of Helsinki and any other applicable regulations, the parents or legal representatives of the child have the right to withdraw the participant from the study at any time and for any reason, without prejudice to his or her future medical care, and are not obliged to give his or her reasons for doing so.

The investigator may withdraw a participant from the study at any time if, in the investigator's clinical judgment, it is in the best interests of the participant's health and well-being. In addition the participant may be withdrawn for any of the following reasons:

- Decision by the Investigator
- Ineligibility (either newly arising during the study, or retrospective having been overlooked at screening)
- Significant protocol deviation
- Participant non-compliance with study requirements
- An adverse event which requires discontinuation of the study treatment, or results in inability to continue to comply with study procedures.

If known, the reason for withdrawal should be recorded in a CRF. If the participant is withdrawn due to an adverse event, the Investigator will arrange for appropriate follow-up through telephone calls (and/or visits if necessary) until the adverse event has resolved or stabilised.

All safety data for any participants withdrawn after receiving the study vaccination will be included in the data analyses, unless specific instruction for their destruction is received from the participant or their parent/guardian. Withdrawn participants will not be replaced.

5. STUDY TREATMENT

5.1 DESCRIPTION

Live Attenuated Intranasal Vaccine (LAIV) Quadrivalent vaccine (Fluenz-Tetra, Astra Zeneca), as provided for use by the Department of Health as part of the UK National Immunisation Schedule

5.2 DOSAGE AND ROUTE OF ADMINISTRATION

0.2 ml (administered as 0.1 ml per nostril). Immunisation will be carried out by nasal administration, as per the SmPC provided.

5.3 DOSE MODIFICATION

No dose modification proposed.

5.4 PREPARATION AND ADMINISTRATION OF STUDY DRUG

FLUENZ IS FOR NASAL USE only.

• DO NOT USE WITH A NEEDLE. Do not inject.

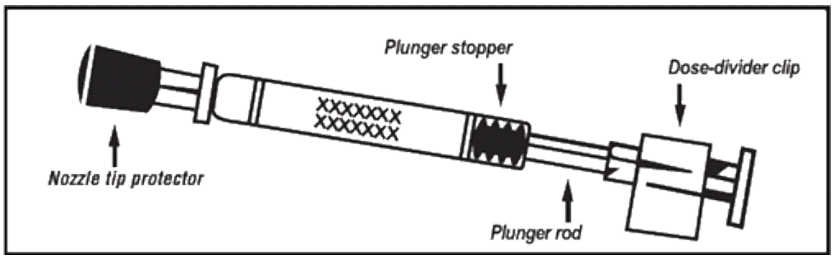
• FLUENZ is administered as a divided dose in both nostrils.

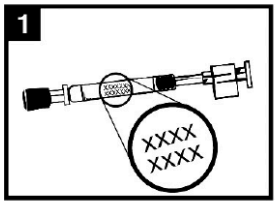
• After administering half of the dose in one nostril, administer the other half of the dose in the other nostril immediately or shortly thereafter.

• The patient can breathe normally while the vaccine is being administered – there is no need to actively inhale or sniff.

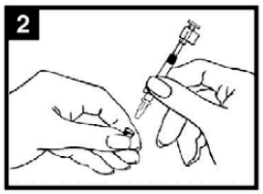
• Refer to the FLUENZ administration diagram (Figure 2) for step-by-step administration instructions.

Figure 2 FLUENZ Administration

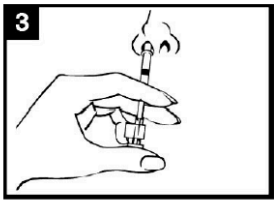




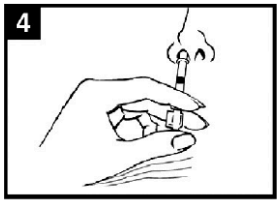
Check expiry date
Product must be used before date on applicator label.



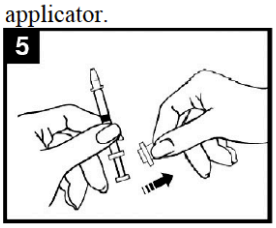
Prepare the applicator
Remove rubber tip protector. Do not remove dose-divider clip at the other end of the applicator.



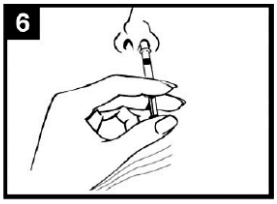
Position the applicator
With the patient in an upright position, place the tip just inside the nostril to ensure Fluenz is delivered into the nose.



Depress the plunger
With a single motion, depress plunger **as rapidly as possible** until the dose-divider clip prevents you from going further.



Remove dose-divider clip
For administration in the other nostril, pinch and remove the dose-divider clip from plunger.



Spray in other nostril
Place the tip just **inside the other nostril** and with a single motion, depress plunger **as rapidly as possible** to deliver remaining vaccine.

Any unused product will be disposed of in accordance with local requirements for medical waste.

5.5 DISPENSING AND PRODUCT ACCOUNTABILITY

Fluenz Tetra (quadrivalent LAIV) is approved by the European Medicines Agency and distribution and administration to selected children will take place during the influenza season 2018-19. Provision of doses of vaccine will be through the Department of Health vaccine supply network as part of the national immunisation programme, with no additional requirements (e.g. cold chain monitoring) beyond that provided by the normal UK vaccine supply system. Vaccine will be delivered via existing systems to on-site pharmacists at study sites (all NHS hospitals). Vaccine doses will be dispensed from hospital stock as standard of care with no additional labelling required, as this is a type A Phase IV study. Doses will be released according to local procedure, using existing hospital systems and logging (rather than CTIMP-specific documentation).

6 STUDY VISITS & PROCEDURES

The study schedule is summarised in the following flow chart and table:

	Visit 1	Days 1,2,3,4,5,6,7,8	Visit 2 - Day 28 (window D21-42)
Written Informed Consent (parent/guardian) Written assent (child)	x x		
Medical assessment	x		
Urine pregnancy test (if pregnancy cannot be excluded by clinical history alone)	x		
Vaccine administration followed by 20 mins observation	x		
Nasal swab and adverse event form	x	x (at home)	x
Oral fluid collection	x		x
Blood test	x [$]		x
2nd dose in children <9 years who meet DoH critieria (see 6.1.3)			(x)

[$]baseline blood sample may be collected up to 2 months before vaccination, if the study participant is having a blood test for another reason and informed consent has been obtained already.

Both study visits will be carried out by members of the research team as per the above schedule, and appointment windows. If any SAE is reported, this will be documented following routine procedures. All clinical information and agreement with parents to be documented in CRFs.

6.1 STUDY VISITS / HOME INTERVENTIONS

6.1.1 VISIT 1 - DAY 0

- Answer any questions the family has about the study having read the PIL.
- Obtain written informed consent from the parent/guardian
- Obtain written assent from child
- Verify inclusion and exclusion criteria with the parent/ guardian (if any notes need to be checked this would be done after consent)
- If the child meets all the inclusion criteria and none of the exclusion criteria, enrol in the study and allocate the next sequential unique participant study number.
- Measure and record body temperature
- *Collect baseline blood sample (up to 25ml). Participants will be offered local anaesthetic cream (to be applied 30mins prior to venepuncture) to minimise discomfort.*[$]
- Take the initial nasal swab, demonstrating to parents how this is done to facilitate compliance with taking the nasal swabs at home in the 8 days following vaccination.
- Administer LAIV according to prescription chart, and record this on CRF and chart, including batch number and expiry.
- Observe for 20 minutes, during which time collect oral fluid sample. Also confirm parent has understood how to take the nasal swabs, including posting back to team.
- Record vaccination details via the medical records system.
- Ask parent/ guardian to notify study team of any serious adverse events/reactions
- Arrange further visit for 3-6 weeks following vaccination.

[$]baseline blood sample may be collected up to 2 months before vaccination, if the study participant is having a blood test for another reason and informed consent has been obtained already.

6.1.2 DAILY HOME SWABS - DAYS 1-8

Parents will be asked to take daily nasal swabs from their child/young person at home, in the week following vaccination, from Day 1 until Day 8 post vaccination. The nasal swab, which looks like a large cotton bud, will be passed into the nostril and moved around for a minute. Parents will be provided with eight test kits, full instructions and Royal-Mail approved postage kits (for Category B specimens) and prepaid envelopes for each child, for posting back to PHE through the normal Royal Mail network.

Parents will be shown the process by their study nurse at the vaccination visit. Parents will receive a daily reminder text/email to take and post the samples. In the event of a missed swab, families will be asked to take the swabs as planned the next day. The final Day 8 swab can be collected up to 24 hours late i.e. on Day 9.

Adverse event information will be collected on a daily basis, using the form parents are asked to complete when they return the daily swabs to Public Health England.

6.1.3 VISIT 2 - DAY 28 (WINDOW DAY 21 TO DAY 42) FOLLOWING VACCINATION

- Confirm continued consent with parent/ guardian and note continuation on GP notes and CRF (if consent withdrawn, complete a withdrawal form documenting this).
- Obtain interim history, specifically any serious adverse events, serious reactions, and visits to hospital – report SAEs according to section 7 below.
- Take nasal swab (same as initial swab)
- Collect oral fluid sample
- Collect a blood sample (up to 25ml). Participants will be offered local anaesthetic cream (to be applied 30mins prior to venepuncture) to minimise discomfort.
- 2nd dose of LAIV were indicated:

  Children who meet DoH criteria for specified 'clinical risk categories' (Table 1) and are under 9 years of age and have not received prior seasonal influenza vaccination will also be offered a second dose of LAIV. We expect very few children to meet this criteria, as most would have received prior influenza vaccination. However, there is a duty of care to our participants and we are therefore including provision for a second dose in this protocol.

Table 1: Clinical risk categories requiring a second dose of LAIV in vaccine-naïve children under age 9 yrs:

Chronic respiratory disease	• Asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. • Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). • Children who have previously been admitted to hospital for lower respiratory tract disease.
Chronic heart disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Chronic neurological disease	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological disease (e.g. polio syndrome sufferers). Clinicians should consider on an individual basis the clinical needs of patients including individuals with cerebral palsy, multiple sclerosis and related or

	similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological or severe learning disability.
Diabetes	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.
Immunosuppression	Immunosuppression due to disease or treatment. Patients undergoing chemotherapy leading to immunosuppression. Asplenia or splenic dysfunction. HIV infection at all stages. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose greater than 20mg prednisolone per day (any age); or for children under 20kg, a dose greater than 1mg per kg per day. It is difficult to define at what level of immunosuppression a patient could be considered to be at a greater risk of the serious consequences of influenza and should be offered influenza vaccination. This decision is best made on an individual basis and left to the patient's clinician. Some immunocompromised patients may have a suboptimal immunological response to the vaccine. NB: LAIV is not contraindicated for use in individuals with asymptomatic HIV infection; or individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency.

6.2 CONSENT

We will endeavour to provide the Patient Information Leaflets prior to visit to hospital, but this may not always be possible. Patients may therefore be consented (according to Good Clinical Practice) without a requirement for a 'cooling-off' period following receipt of the study information leaflets, **where this is specifically requested by the family**. In this case, at least 30 minutes will be allowed for participants and their carers to read the patient information provided and consider the contents.

The reasons for this were highlighted in the PPI discussions during the development of the previous SNIFFLE protocols and include:

- Many families travel significant distances to specialist clinics, often requiring the child to miss school and their parents/carers to miss work. In previous studies by this group, for example SNIFFLE-1, families frequently requested vaccination at the same time as their routine outpatient appointment, to avoid having to make a second trip to hospital.
- The vaccine to be administered in this study is part of the routine UK National Immunisation Schedule. The study allows children to participate in this programme in a safe environment, utilising a vaccine delivery route (intranasal) which minimises discomfort to the child.
- The proposed consent process has been trialled successfully in the SNIFFLE-2 and -3 studies and the Flu-shed study, with positive feedback from both eligible young people and their families.

6.3 COLLECTION AND POSTING OF SAMPLES

6.3.1 COLLECTING SAMPLES

Baseline Nasal swab:

Will be collected by research team staff and stored at -20℃ until processing at Imperial College London.

Nasal swabs:

Parents will be asked to take daily nasal swabs from their child according to the schedule described above. Parents will be provided with eight test kits, each with prepaid returns to the testing laboratory (PHE), for their child and instructions as per appendix 1, as well as being shown the process by their study nurse at the vaccination visit. This will involve putting a swab, which looks like a large cotton bud, into each nostril and moving it around for up to a minute.

Oral fluid samples:

The first oral fluid sample will be collected by the nurse at the day 0 appointment, the second at Visit 2. The procedure involves passing a foam tipped swab across the teeth and gum line for around a minute in an action similar to brushing teeth.

Blood samples

Blood sampling will be performed by Trust-approved phlebotomy staff or the research team in accordance with local protocol. No more than two attempts at venepuncture will be made at any one time. Anaesthetic cream (e.g. EMLA or Ametop) will be offered for use at the intended sampling site to minimise discomfort.

The following blood samples (total volume 25ml, maximum 2.5ml/kg body weight) will be collected, prior to and 3-6 weeks after LAIV vaccination:

- 5ml into a tube for collection of clotted blood (for serum studies)
- 18ml into Lithium Heparin tubes for processing in PBMCs (for CMI)
- 2ml into a PAXgene RNA tube (for global assessment of host response by whole blood transcriptomics)

6.3.2 LABELLING SAMPLES

All samples will be labelled with the participant's unique identification number. Participants will be assigned a 2 digit number (01 etc.). Numbers will be used sequentially in order of enrolment to the study. Labels will also identify the protocol (i.e. FluSHED-2) such that all labels per child will be uniform e.g. FLU2-01. Nurses and or parents will complete the date sample taken alongside this prior to posting, so a swab label should say e.g. FLU-01 Day1 7.10.18, FLU-02 Day2 8.10.18 etc.

6.3.3 POSTING SAMPLES

Appropriate prepaid postage packs will be provided to parents to return **nasal swabs** on the day each is taken. Samples will be sent by Royal Mail to the Influenza Laboratory, Public Health England (PHE Colindale). **Oral fluid samples** will be sent directly to PHE by the research team.

All samples to be sent to PHE will be placed into a NOAX green topped tube containing an absorbent strip and then placed in an approved transport box (along with Sample Postage and Receipt Form CTD014). The box is then placed into a postage bag showing the "UN3373 biological substance, category B" identification diamond sticker, and either dropped at a post office or into a post box for delivery to the Influenza Laboratory, PHE Colindale.

Blood samples: Lithium heparin samples and PAXgene tubes will be transferred to the Lalvani laboratory at Imperial College London within 4 hours of collection. Serum will be separated from clotted blood following centrifugation, aliquoted and stored at -80°C until transfer on dry ice to the Influenza Laboratory, Public Health England (PHE Colindale) for further analysis.

Documentation included will identify the child by subject number and will allow documentation and tracking of the movement of samples between sites and laboratories (ref study SOPs). Logs of samples sent and received will be kept at PHE Colindale, to enable the identification of any lost or delayed samples and to provide a log of where samples are currently stored.

6.4 LABORATORY ASSAYS

Nasal swabs for Immunoglobulin-A analysis

Immunoglobulin-A will be eluted from the pre-vaccine (and where taken in the sub-study, post vaccine) nasal swabs according to local SOP and analysed for anti-Influenza IgA responses by ELISA. The laboratory has developed a high sensitivity assay for the detection of anti-influenza IgA on flocked swabs. These procedures will take place in Professor Shattock's GCLP-certified laboratory at the Section of Virology, Imperial College London.

Post vaccine (shedding) nasal swabs

Material from the post-vaccine nasal swabs will be tested using RT-PCR assays developed and validated for both individual detection and measurement of each of the four viral strains present in the LAIV vaccines used. The assays used will provide quantitative data about the viral load of each of the vaccine strains present in nasal swabs, as previously described (DNA vaccination protects against an influenza challenge in a double-blind randomised placebo-controlled phase 1b clinical trial. [Jones et al 2009.] Strains will be in line with WHO determination as included in guidance at http://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/

Oral fluid

All oral fluid samples will be analysed by ELISA using plates coated with antigens specific for the viruses in the vaccine. This will initially be limited to detection of IgG antibody to A/California/7/2009 (antigenically similar to A/Michigan/45/2015 (H1N1)pdm09-like virus, and include detection of antibody specific for H3N2 virus antigenically like the A/Hong Kong/4801/2014 (H3N2)-like virus, B/Brisbane/60/2008-like virus and a B/Phuket/3073/2013-like virus, once these tests have been developed and validated). The method uses the recombinant HA1 fragment of haemagglutinin from each individual vaccine virus for coating 96 well plates, onto which strain specific antibodies, present in oral fluid samples bind. This bound antibody is initially complexed with biotin-labelled anti-human IgG, followed by its detection using streptavidin-HRP conjugate to enhance detection. Each oral fluid is analysed in triplicate in 1:50 dilution. The results will be reported as T/N ratio (OD sample/OD negative control).

Serological analysis

Analysis of serum samples will be for the presence of haemagglutination inhibition titres to relevant influenza strains (HAI) or Microneutralisation titres according to previously published methods and SOPs, and in compliance with MHRA requirements for GLP.

Haemagglutination inhibition (HAI)

The principle of the HAI test is based on the ability of specific anti-influenza antibodies to inhibit haemagglutination of red blood cells (RBC) by influenza virus HA. Antibody to influenza virus haemagglutinin has been traditionally associated with protection. Historic studies and recent meta-analyses, indicate that influenza infections are significantly reduced in persons who had preexposure haemagglutination-inhibition (HAI) antibody titres >32 or 40.

The sera to be tested have to be previously treated to eliminate the non-specific inhibitors and the anti-species HAIs found in normal human serum. The HAI experiments, including serum pre-treatment, will be performed in accordance to protocols and SOP's established by RVU. Each serum sample is titrated in duplicate with each virus and individual titres will be reported (two for each sample in each analysis).

Microneutralisation (MN)

The Microneutralisation assay will only be performed for the analysis of serological responses to the pandemic H1N1 and H7N9 strains. Protocols have already been set up by the laboratory and various previous data indicate that this assay is more sensitive (i.e. detects more 4-fold increases and generally higher GMTs) than the HAI. However, MN is not routinely used for analysis of seasonal vaccines for several reasons: There is no defined correlate of protection for the MN, whereas such values are defined for HAI and SRH. Secondly, this test is technically more demanding and time consuming than the HAI. Lastly, the cross-reactivity between strains of currently circulating (seasonal) viruses and resulting pre-existing immunity complicates the development of specific and sensitive MN protocols and potentially confuses interpretation of results from vaccine trials.

The Microneutralisation assays for measurement of responses to the A(H1N1)pdm09 component of the LAIV and cross-reactive responses to unrelated subtypes (such as H7N9), including serum pre-treatment, will be performed in 96- well format according to previously described protocols and SOPs developed at RVU. The Microneutralisation analysis will be performed in duplicate (in separate runs on 2 days) for each sample and both titres will be reported for each sample.

Cell Mediated Immunity (CMI)

The T-cell response to influenza virus will be assessed by Fluorescence-immunospot that will quantify the magnitude of cross-reactive IFNg and IL-2 secreting T-cells. Where sufficient cells remain, detailed characterisation of the protective phenotype of cells will be undertaken using flow-cytometry to identify the induction and maintenance of protection-associated CD8+ T-cells.

Global assessment of host response by whole blood transcriptomics on PAXgene RNA

The global host response will be evaluated by whole blood transcriptomic profiling (RNA-Seq) in order to identify predictors of impaired vaccine take by correlating the baseline transcriptomic profile on the day of vaccination with peak immune response at 3-6 weeks. HLA-typing will also be undertaken, where consent is provided, in order to assess how an individuals HLA-type may affect the immune response to the vaccine.

Reporting

The data manager will receive results for assays in form of an Excel table – one signed hard copy and one electronic copy, by email.

6.4.1 HANDLING OF RESIDUAL SAMPLES ON COMPLETION OF TESTING

During the consent process, parents/guardians will be asked for consent to keep their child's residual samples (if any) to be used for further research to improve understanding of vaccines and how they work. Lack of consent to this will not preclude participation in the study. Where consent is given, any residual samples will be archived at -70 ºC or below at PHE Colindale. Residual samples from participants who do not give such consent will be destroyed.

6.5 TRIAL CLOSURE

The expected study duration is ~1 months for any individual participant.

The study will be considered complete following enrolment of the last patient and completion of all study procedures in that patient.

No interim analyses are planned.

6.6 EXPENSES AND PAYMENTS

We will aim to perform study interventions at the same time as an existing clinic appointment. It is therefore not expected that the participants or their families will incur any additional costs requiring reimbursement for the first visit.

We will offer up to £25 towards receipted travel expenses for additional study visits. We will also offer participants a £20 cinema voucher (approximately equivalent to the cost of one adult and one child cinema ticket in London) as a small token of thanks, at the second study visit.

7 ADVERSE EVENT REPORTING

7.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (eg summary of product characteristics (SmPC) for an authorised product*). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward 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, or prolongation of existing inpatients' 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/AR is serious in other situations. Important AE/ARs 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.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

7.1.1 DOCUMENTATION OF ADVERSE EVENTS

For the purposes of this study, parent/carers will be asked to inform the study team of any adverse events occurring up to the time that the Day 8 swab is collected, by completing the relevant section on the daily swab return form. All serious adverse events (SAEs) or reactions (SARs) will be reported on a SAE report form, for 28 days from after LAIV administration, regardless of their severity or relation to study medication or study procedure. The investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

SAEs will be reported within 24 hours of the Site Study Team becoming aware of the event. All SUSARs will be reported by the CI to the relevant Competent Authority, Sponsor, REC and other parties, as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. All SAE information must be recorded on an SAE form and emailed to the JRCO (jrco.ctimp.team@imperial.ac.uk).

SARs will also be reported to MHRA through the yellow card system.

7.2 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

The study site will grade the severity of adverse events experienced by study participants according to the criteria set forth in the NCI-CTCAE Version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

This document provides a common language to describe levels of severity, to analyse and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

All adverse events will be recorded and graded whether they are or are not related to disease progression or treatment. The NCI-CTCAE grades will be the primary source for scoring.

The relation, or attribution, of an adverse event to study participation will be determined by the investigator and recorded on CRF and/or SAE reporting form. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below (Table 2), and with reference to the Reference Safety Information included in section 4.8 of the Summary of Product Characteristics. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made relating to a SUSAR, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Table 2: Assignment of causality for adverse events

7.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

7.3.1 NON SERIOUS AR/AES

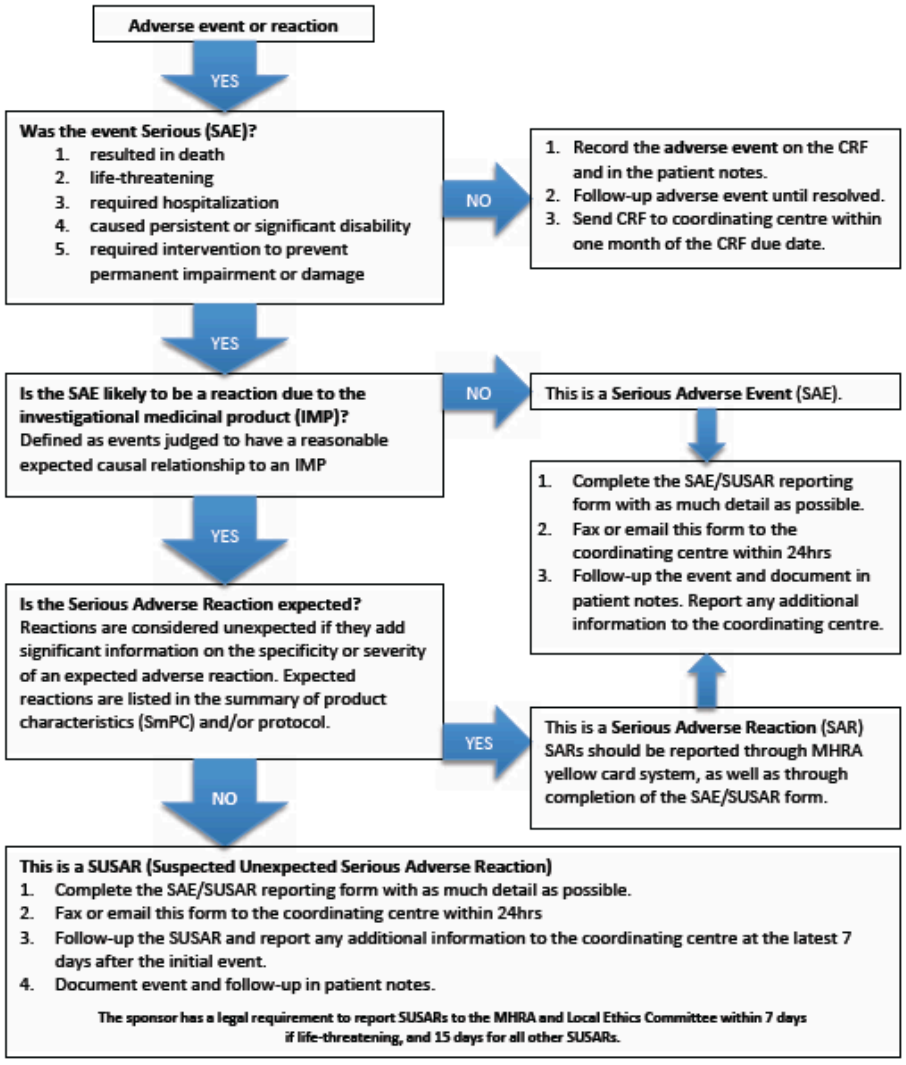
All such events, whether expected or not, should be recorded on the daily swab return forms completed by parents. Non-serious AR/AEs will be collected only where they occur within 8 days of vaccination. Adverse events will then be collated and reported to the study CI within one month of occurrence.

7.3.2 SERIOUS AR/AES

All SAEs and SUSARs should be reported on the day of occurrence, where these occur within 28 days of vaccination. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent to the CI within 5 days if the reaction has not resolved at the time of reporting. Any expected SAR will also be reported via the MHRA yellow card system.

SAEs: An SAE/SUSAR form should be completed and emailed to the study CI immediately, who will in turn inform the JRCO (email to jrco.ctimp.team@imperial.ac.uk) within 24 hours.

SUSARs:. All SUSARs will be reported by the CI to the relevant Competent Authority (MHRA) and to the REC and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.



Contact details for reporting SAEs and SUSARs:

Email: jrco.ctimp.team@imperial.ac.uk

8. DATA MANAGEMENT

8.1 DATA COLLECTION

The following data will be collected:

- Patient demographics
- Current health to establish safety of immunisation
- Vaccination history:
  - previous exposure to influenza vaccine
  - previous reactions to vaccines
- Past medical history:
  - Medical indication for influenza vaccination or routine
  - Current Medication

8.2 DATA RECORDS

Paper records will be maintained at St Mary's Hospital (Imperial College Healthcare NHS Trust) of all participants enrolled in the study. Data will be collected by paper CRF. The clinical data will then be transferred to Public Health England via a UK government 'GSI gateway' secure server, which will include the patient's study number, date of birth, gender and initials, but no other identifiable information. Specific consent to share this patient identifiable information with Public Health England will be included on the study consent form.

These data will be entered into a study specific database according to local SOPs at PHE, Colindale, and linked to laboratory data as this becomes available. Clinical data will be verified electronically by a second study team member at St Mary's Hospital (Imperial College Healthcare NHS Trust), in order to monitor for completion errors or omissions.

Study data will be kept for 10 years following the child's 18th birthday, and then disposed of securely. Local paperwork will be kept as part of the patient notes/CRF as per local policy.

9. STATISTICS AND DATA ANALYSIS

Full details will be given in the statistical analysis plan produced by the Immunisation Department Statistician.

Primary analysis: As this is a small pilot study analysis of the measured outcomes is descriptive. Proportions with detectable shedding on each day by strain will be given with 95% confidence intervals as will area under the curve be given with 95% CIs. The median day of peak shedding will be calculated by strain as well as the range. Quantitative results for each individual who sheds will be plotted.

Secondary analysis: Antibody responses will summarised as geometric means and geometric mean ratios with 95% confidence intervals as well as proportions above assay thresholds (with 95% CIs). The relationship with shedding by strain assessed by plotting AUC against antibody titre (within those that do shed) and calculating the R-squared value as well as the regression coefficient in a linear regression model on logged data. This will require at least 10 shedding individuals. The relationship with any shedding will be assessed by calculating the geometric mean ratio (with 95% CI) in titres between those who do and do not shed.

Additional analyses: Relationships between shedding of each strain (cross tabulations showing those who shed both, one, neither). Comparisons to shedding to previous studies will be informal and based on comparing the point estimates 95% confidence intervals.

9.1 STUDY OUTCOMES MEASURES

9.1.1 PRIMARY STUDY OUTCOME

Kinetics of type-specific vaccine virus shedding in 2018/19 in the eight days following LAIV administration, specifically:

- Kinetics of shedding, for each individual strain based on the daily quantitative results in pfu/ml.
- Day of peak shedding, for each individual strain
- Days of detectable shedding for each strain
- Area under the curve (AUC) between days 0 and 8 calculated as average pfu/ml per day on logged data (with a minimum limit set at 1pfu (0 on the log scale)).

9.1.2. SECONDARY STUDY OUTCOMES

Quantitative analysis of immunogenicity using a range of indicators, including:

1. MN and HAI titres at each time point (day 0, 28) as well as ratios day 28/day0 and proportions above thresholds and seroconverting.
2. Equivalent data with matching HAI (oral fluid) samples
3. Nasal IgA responses to LAIV taken at the same time

…to measure the association between type-specific vaccine immunogenicity and virus shedding.

9.1.3. OTHER STUDY OUTCOMES

Relationships between shedding of each strain (cross tabulations showing those who shed both, one, neither).

To compare how type-specific vaccine virus shedding in 2018/19 differs from previous studies in 2016/17/18 (conducted by this group, Eudract 2013-003592-35, 2016-002352-24, 2017-000952-24) following change in the A/H1N1pdm09 vaccine virus strain.

In an exploratory analysis, to cell-mediated immunity (CMI) will be correlated to the above primary and secondary endpoints, where available.

9.2 SAMPLE SIZE ESTIMATION

This is a small pilot study to assess virus shedding by sequential daily virus samples in children following LAIV administration, something not possible on a larger scale. The study is not powered for significance testing, but is designed to measure the timing of shedding and relationships between shedding and immunogenicity outcomes. Based on shedding rates in previous studies, and assuming more time points will detect more shedding then a sample size of 20-30 participants should provide approximately 4-15 individuals shedding each strain for whom the kinetics of shedding can be assessed. This, in combination with data on larger numbers with samples at days 1,3 and 6 will help determine the optimum timing of sampling.

9.3 LOSS TO FOLLOW-UP

All data for any participants withdrawn after receiving the study vaccination will be included in the data analyses, unless specific instruction for their destruction is received from the participant or their parent/guardian. Withdrawn participants will not be replaced (allowance for modest attrition is built into the sample size calculation).

10 ADMINISTRATIVE AND REGULATORY ISSUES

10.1 CLINICAL TRIALS AUTHORISATION

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA, Eudra CT registration no. 2018-002470-42. The study is also registered at Clinicaltrials.gov, reference: NCT03735147.

10.2 ETHICS APPROVAL

The Chief Investigator has obtained the required approvals from the London - Riverside Research Ethics Committee (reference 18/LO/1317). The study will be submitted for HRA approval for conduct at Imperial College NHS Trust. 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.

10.3 INFORMED CONSENT AND PARTICIPANT ASSENT

Consent to enter the study must be sought for each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed consent from the parent/legal guardian should be obtained. In children over 8 years of age, participant assent will also be sought. The right of the parent/guardian to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

10.4 CONFIDENTIALITY

Participants' identification data will be required for the registration process. Both Imperial College Healthcare NHS Trust / Imperial College London and Public Health England are registered under the Data Protection Act. The Chief Investigator will preserve the confidentiality of participants taking part in the study under the Data Protection Act.

10.5 INDEMNITY

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

10.6 SPONSOR

Imperial College London will act as the main Sponsor for this study.

10.7 FUNDING

Funding has been secured from the NIHR HPRU in Respiratory Infections at Imperial College London, with additional funding for mechanistic assessments from the Medical Research Council.

10.8 AUDITS

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

10.9 MONITORING

The JRCO Clinical Trial Monitor will be responsible for monitoring this study throughout its duration, including site initiation visit and close out visit. The monitor will conduct a risk assessment and compile a monitoring plan accordingly. After each monitoring visit the monitoring report will be sent to the chief investigator and any action point that needs to be completed will be done so by the study team.

11 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Paul Turner (CI).

12 PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Steering Committee consisting of the study PI and co-investigators.