**Study Title:** A Phase 2 randomised, single blinded, placebo controlled, cross-over trial of a single dose of live attenuated influenza vaccine in 12-23 month old children (FluSNIFF-toddler)

**Short Title:** LAIV safety in 12-23 month old children (FluSNIFF-toddler)

**IRAS Project ID:** 1012411

**ISRCTN number**: xxxx

**UHS Study Number:** RHM CHI1293

**Date and Version No**: 2.0 14th August 2025


| | |
|---|---|
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| Sponsor: | University Hospital Southampton NHS Foundation Trust |
| Funder: | National Institute Health Research (NIHR), NIHR204677National Immunisation Schedule Evaluation Consortium (NISEC) II. |


Signatures:

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# 1 Contents

# 2 Key Trial Contacts

| | |
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| **Funder(s)** | National Institute for Health and Care Research via NIHR204677 National Immunisation Schedule Evaluation Consortium (NISEC) II |

| | |
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| **Clinical Trials Unit** | Oxford Vaccine Group,<br>University of Oxford,<br>Centre for Clinical Vaccinology and Tropical Medicine (CCVTM),<br>Churchill Hospital,<br>Oxford, OX3 7LE,<br>United Kingdom<br>info@ovg.ox.ac.uk |
| **External Contract Research Organisation (CRO)** | UMed<br>8 Warner Yard<br>London<br>EC1R 5EY<br>UK |
| **Statisticians** | Xinxue Liu<br>Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine (CCVTM),<br>University of Oxford, Churchill Hospital, Oxford, OX3 7LE,<br>xinxue.liu@paediatrics.ox.ac.uk |

| | |
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| **Committees** | **Data Safety Monitoring Board**<br><br>Chair: Dr Simon Nadel, Imperial College London; s.nadel@imperial.ac.uk<br>Statistician: Professor Victoria Cornelius, v.cornelius@imperial.ac.uk<br>Clinical paediatric expert: TBC<br>Open meetings: CI, Sponsor Representatives, PHARMExcel representative.<br><br>**Trial Steering Group**<br><br>Prof Maheshi Ramasamy (NISEC Director). Prof Christine Jones, Prof Paul Heath, Dr Simon Drysdale, Dr Anu Goenka.<br><br>**Study Management Group**<br><br>Co-CIs: S Faust & A Munro<br><br>Co-investigators: X.Liu, Dr P. Moore (GP), R. Cutts (lead study primary care research nurse), Prof S De Lusignan (GP)<br><br>uMed: M Wilson, H. Walsh, L. Batt, A. Jina, E. Klamerus, K. Sundararajan, S. Banik<br><br>UHS: T. Bower, B. Wilson, C. Sayce.<br><br>Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC): E. Button, |
| | Project Management:<br><br>Chloe Sayce (Senior Vaccine Project Manager)<br><br>Thomas Bower and Ben Wilson (Project Managers)<br><br>S Davies-Dear or Mikayala King (Sponsor Representative)<br><br>uMed (Vendor) project managers.<br><br>RSC Project Managers (for site identification). |

# 3 Protocol Summary

**Protocol Title:** A Phase 2 randomised, single blinded, placebo controlled, cross-over trial of a single dose of live attenuated influenza vaccine in 12-23 month old children (FluSNIFF Toddler).

**Rationale:** This study will collect and analyse data on the safety of giving a single dose of live attenuated influenza vaccine (LAIV) to young children aged 12-23 months inclusive. The primary outcome is medically attended wheeze in the first 28 days following vaccine administration.

For this study, wheeze will be defined as a physician-diagnosed wheeze or asthma (practice, home visit or hospital) or an illness for which the child was prescribed medication used to treat wheeze or asthma.

**Objectives and endpoints:**

| Objective | Outcomes |
|---|---|
| • To assess the safety of giving a single dose of LAIV to young children aged 12-23 months inclusive | **Primary** |
| | • Incidence of medically attended, physician-diagnosed wheeze or asthma or an illness for which the child was prescribed asthma medication. |
| | **Secondary** |
| | • All medically attended adverse events |

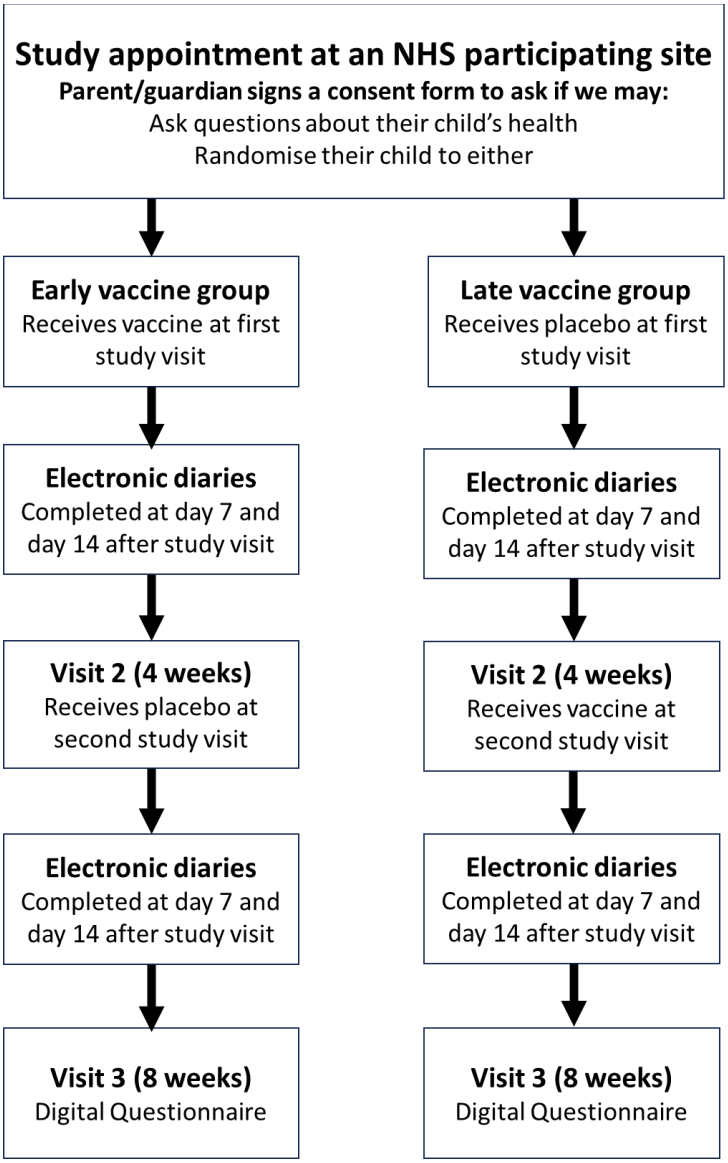
**Brief Summary:** This study is a blinded, cross-over, randomised controlled trial of LAIV compared to placebo nasal spray in children aged 12 to 23 months. The primary outcome is medically attended wheeze in the four weeks following vaccination. To reduce the burden on GPs, study outcomes will be assessed by remote data extraction from electronic health records.

There will be two in-person study visits and one visit by digital questionnaire. At the first visit, participants will be consented, screened and randomised 1:1 to receive either LAIV or placebo nasal spray. Four weeks later at the second visit, basic safety information will be collected, and the participants will receive either vaccine or placebo (whichever they did not receive at the first visit). The final visit will be four weeks later and will be conducted via digital questionnaire to collect safety information. Recruitment will be enriched for children with a history suggestive of increased risk of wheezing, including a personal history in the child of eczema, bronchiolitis or viral induced wheeze.

**Number of Participants:** A total of 3000 children are expected to be randomised.

**Interventions:** All participants will receive live attenuated influenza vaccine (LAIV) (Fluenz, AstraZeneca) during the study. This is a live, attenuated, cold adapted influenza vaccine which is delivered as a nasal spray as 0.1ml solution per nostril. Participants will be randomised to either receive this at the first or second study visit. When not receiving LAIV they will receive 0.1ml per nostril of placebo, administered as normal saline via 1ml syringe and nasal atomiser device. Parents will be blinded to allocation.

**Study flow diagram**



**Abbreviated Schedule of visitations**

| **Early Vaccine Group** | | | |
|---|---|---|---|
| | **D0** | **D28 (-3/+7)** | **D56 (+7)** |
| **In person visit** | X | X | |
| **Digital Questionnaire** | | | X |
| **Consent** | X | X | |
| **Randomisation** | X | | |
| **Vaccination with LAIV** | X | | |
| **Placebo nasal spray** | | X | |
| **Collection of SAEs, and MAAEs** | To be reported at any time up to D56 | | |
| **Late Vaccine Group** | | | |
| | **D0** | **D28 (-3/+7)** | **D56 (+7)** |
| **In person visit** | X | X | |
| **Digital Questionnaire** | | | X |
| **Consent** | X | X | |
| **Randomisation** | X | | |
| **Vaccination with LAIV** | | X | |
| **Placebo nasal spray** | X | | |
| **Collection of SAEs, and MAAEs** | To be reported at any time up to D56 | | |

This trial is being conducted with a company called uMed, a clinical research technology platform, who partners with UK Healthcare Providers to access NHS Electronic Health Record (EHR) data and invite patients to participate in research. uMed has been engaged by the Sponsor to identify, contact, and obtain consent from prospective patients. uMed will collect study outcomes, thereby diminishing the administrative workload of clinical staff, and capture other relevant protocol data. uMed will also support site contracting and setup.

# 4 Lay Summary

The virus that causes influenza (flu) is a common cause of minor illness but is also one of the most important causes of serious lung infections. The people most at risk of serious illness are the elderly, those with weakened immune systems, and very young children. Whilst most children do not suffer from serious illness, young children with flu also spread the virus easily in the wider population, increasing illness in the elderly.

There are vaccines available which can help protect people from developing serious illness from influenza and may also prevent some transmission of the virus. These vaccines are offered to elderly and vulnerable people every autumn in the UK in the form of an injection, as well as to children over the age of two years in the form of a nasal spray. This spray contains a live, but weakened form of the influenza virus which has been modified so it cannot grow in warm conditions, such as in the lungs.

The nasal spray vaccine is a live version of flu that has had the dangerous flu proteins removed (called “attenuation”), so it causes immunity from flu but not serious influenza illness. The vaccine has also been modified to be “cold adapted”, meaning that it can only live in the colder nasal passages in the nose and will not survive if it is inhaled into the lungs. In the UK specialists consider it is safe to the nasal spray vaccine to be given to children 2 years and older with asthma or more serious lung conditions such as cystic fibrosis, to avoid having to use an injection vaccine.

Children less than two years currently cannot receive the nasal spray vaccine. This is because during the original studies of this vaccine, there was not enough evidence to demonstrate that it did not cause wheezing illness in children of this age. Wheezing is a whistling noise in the lungs which suggests that the tubes in the airways are more narrow than usual. Wheezing is commonly seen in older children and adults with asthma, and in younger children with many different respiratory viruses. It could also occur if the airways react to the virus in the vaccine. More evidence is required to demonstrate whether the vaccine is safe enough that we could offer it to children less than two years of age to protect them against serious illness from influenza and prevent spread of the virus from this age group to other, more vulnerable people.

All children in the FluSNIFF-toddler trial will receive the nasal flu vaccine. At the start, 1500 children aged 12 to 23 months will be given the nasal spray influenza vaccine (Fluenz), and 1500 children will receive nasal spray of a placebo. We will then compare how many children in each group were brought to see a doctor who diagnosed wheezing in their chest in the following four weeks. Then, four weeks later, the children will return for their second study visit. If they had LAIV at the first visit, children will

receive the placebo, and if they originally received the placebo children will then receive LAIV. We will again compare rate of wheezing in each group over the following four weeks.

The children's parents will not know whether their child received the vaccine or the placebo, so that this does not influence how likely they will be to visit their doctor.

If there are similar amounts of wheezing detected by doctors in children who have had the LAIV vaccine or the placebo, then then the UK may be able to offer the vaccine to children aged one year and over in the future. As for all vaccines, this decision will be made for the NHS by the Government's Joint Committee of Vaccination and Immunisation.

# 5 Background

Influenza is a significant public health concern globally, with substantial morbidity and mortality rates, especially in vulnerable populations such as children. In the paediatric population, influenza is associated with a high rate of hospital admissions, particularly among young children and those with underlying health conditions. Influenza can lead to severe respiratory illnesses, including pneumonia, and exacerbate existing medical conditions. Children are thought to make a significant contribution to the broader spread of influenza, including to more vulnerable populations (1).

In the United Kingdom, the burden of influenza among children is notable, with considerable implications for paediatric healthcare services and broader public health. Seasonal influenza epidemics result in significant numbers of paediatric hospitalisations and GP consultations each year. The impact extends beyond immediate health concerns, affecting school attendance, parental employment, and the overall well-being of families.

The vaccination program against influenza in the UK aims to reduce this burden by providing immunity to those most at risk and curbing the transmission of the virus within the community. Vaccination is recognized as the most effective method of preventing influenza and its associated complications. The national vaccination program has historically targeted groups considered at high risk, including older adults, individuals with chronic health conditions, healthcare workers, and children from age 2 upwards with the nasal flu vaccine from 2013 (2, 3).

The rationale for extending the vaccination program to children, particularly those under five years of age, is twofold. First, this age group is at a higher risk of influenza-related complications and hospitalizations. Second, vaccinating children can contribute to herd immunity, thereby reducing transmission rates within the community and protecting vulnerable populations that are less responsive to the vaccine, such as the elderly and immunocompromised individuals.

# 6 Study Rationale

The UK Joint Committee on Vaccination and Immunisation (JCVI) have asked the National Immunisation Schedule Evaluation Consortium (NISEC) to undertake a clinical trial of LAIV in children aged 12 - 23 months, investigating only safety outcomes (no blood tests in the main trial cohort), to inform JCVI decision making for the 2026-7 winter influenza season. A new trial focussing on specific safety outcomes in children 12-23 months old is needed as the initial phase 3 trial leading to licensure suggested a possible increased incidence of wheezing post-vaccination in this age group (4). As a result, the vaccine is not currently approved for children under 2 years old. Given the potential

benefits of expanding the vaccination coverage, this study aims to assess the safety profile of LAIV in 1-2-year-old children, addressing the gap in evidence and contributing to informed decision-making regarding vaccine policy and implementation.

# 7 Synopsis

| | | | |
|---|---|---|---|
| Trial Title | A phase 2 randomised, single blinded, placebo controlled, cross-over trial of a single dose of live attenuated influenza vaccine (FluSNIFF-toddler) | | |
| Internal ref. no. (or short title) | LAIV safety in 12-23 month old children (FluSNIFF-toddler) | | |
| Trial registration | ISRCTN: xxxx | | |
| Sponsor | University Hospital Southampton NHS Foundation Trust<br>Tremona Road<br>Southampton<br>SO16 6YD | | |
| Funder | National Institute for Health and Care Research via NIHR204677 National Immunisation Schedule Evaluation Consortium (NISEC) II | | |
| Clinical Phase | Phase 2 | | |
| Trial Design | Randomised, single blinded, placebo controlled, cross-over, trial of live, attenuated influenza vaccine in children aged 12 – 23 months | | |
| Trial Participants | Children aged 12 months to 23 months (up to one day before their second birthday) in good health | | |
| Sample Size | 3000 children | | |
| Planned Trial Period | 56 days per participant (following on from the day of randomisation)<br>Total trial period 3 months<br>Global end of study – Last Visit Last Subject | | |
| | Objectives | Outcome Measures | Timepoint(s) |
| Primary | To determine the safety and reactogenicity of LAIV in children | Episode of respiratory wheeze diagnosed by a health practitioner | Day 0 to 28 following vaccination |

<table>
<tr><td></td><td></td><td>requiring medical attention</td><td></td></tr>
<tr><td rowspan="2">Key secondary</td><td rowspan="2">To assess safety of LAIV</td><td>Serious adverse events</td><td>Throughout the study</td></tr>
<tr><td>All medically attended adverse events</td><td>Throughout the study</td></tr>
<tr><td>Intervention(s)<br>• IMP(s)</td><td colspan="3">
<table>
<tr><th>Vaccine</th><th>Dose</th><th>Route of administration</th></tr>
<tr><td>Fluenz nasal spray</td><td>$10^7$FFU of:<br>A/Victoria/4897/2022, A/Thailand/8/2022, B/Austria/1359417/2021<br>(0.2ml)</td><td>Intranasal</td></tr>
<tr><td>0.9% Saline placebo nasal spray</td><td>0.2ml</td><td>Intranasal</td></tr>
</table>
</td></tr>
</table>

# 8 Risks and Benefits

## 8.1 Potential benefits

Participants in the study will receive a vaccine against seasonal influenza which otherwise will not be available to them through the national immunisation programme. Receipt of the vaccine may provide immune protection against the circulating strains of influenza during this autumn/winter season.

## 8.2 Potential risks

### 8.2.1 Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis or other hypersensitivity disorders are known to occur in between 1/1000 and 1/100 recipients of LAIV.
(https://www.medicines.org.uk/emc/product/3296/smpc#about-medicine)

## 8.3 Reactogenicity

More than 1 in 10 people may experience nasal congestion or discharge, reduced appetite or weakness, and up to 1 in 10 people may experience fever, muscle aches or headaches following vaccination with LAIV. The investigation of lower respiratory tract reactogenicity outcomes is the primary reason for this trial.

# 9 Objectives and Outcome Measures

| Objectives | Outcome Measures | Timepoint(s) |
|---|---|---|
| Primary | | |
| To determine the safety and reactogenicity of LAIV in children | Episode of respiratory wheeze requiring medical attention diagnosed by a health practitioner | Day 0 to 28 following vaccination |
| Key secondary | | |
| To assess safety of LAIV | Serious adverse events | Throughout the study |
| | All medically attended adverse events | Throughout the study |

## 9.1 Outcome ascertainment

Outcomes will be collected from routine GP medical records by the digital CRO, uMed. For medically attended wheeze, specific codes referring to a diagnosis of "Viral induced wheeze" and "Asthma" will be used, alongside findings of "Wheeze", and any new prescription for either Salbutamol or Ipratropium Bromide:

- 276191000000107 | Viral wheeze (disorder)
- 195967001 | Asthma (disorder)
- 56018004 | Wheezing (finding)
- 24612001 | Wheeze - rhonchi (finding)
- 372897005 | Salbutamol (substance)
- 372518007 | Ipratropium (substance)

Whilst using codes of a finding of "wheeze" are most specific to the primary outcome, these codes are rarely used in practice and yield insufficient events. GP EPR data from a 3 month period indicates that, "Viral induced wheeze", and "Asthma" are the codes most commonly associated with wheezing. This

yields a population incidence of roughly 2% during a three-month period, in line with the power calculations for the study.

The primary outcome includes all events coded with a finding of “wheeze” together with the addition codes asthma/viral wheeze/salbutamol/ipratropium.

Additional medical attendances at locations other than the child’s primary GP practice (e.g., hospital or other GP locations) will be determined using electronic diaries and solicited at follow up visits.

# 10 Study Design

## 10.1 Trial Design

A randomised, single blinded, placebo controlled, cross-over trial of a LAIV. At day 0 participants will be randomised to either the early vaccine (EV) group, or the late vaccine (LV) group.

### 10.1.1 Setting

Multicentre study conducted through academic and NHS clinical trials sites in primary and secondary care settings.

### 10.1.2 Trial duration

Total duration of each participant will be 56 days from day 0 (the day of randomisation). The total trial period will be approximately 3 months.

### 10.1.3 Study groups

The study will consist of 2 groups of children who have been randomised to either the early vaccine (EV) or late vaccine (LV) arms of the trial.

### 10.1.4 Early Vaccine (EV)

Participants randomised to EV will receive the study intervention of 0.2ml Fluenz nasal spray (0.1ml per nostril) on day 0. At the follow up visit on day 28 they will receive 0.2ml of 0.9% saline placebo nasal spray (0.1ml per nostril). Their final follow up visit will be on 56 post randomisation.

### 10.1.5 Late Vaccine (LV)

Participants randomised to LV will receive 0.2ml of 0.9% saline placebo nasal spray on day 0 (0.1ml per nostril). At the follow up visit on day 28 they will receive the study intervention of 0.2ml Fluenz nasal spray (0.1ml per nostril). Their final follow up visit will be on day 56 post randomisation.

# 11 Participant Identification

## 11.1 Trial Participants

Participants will be children aged 12 months to 23 months. Comorbidities of clinical definition mild/moderate/well controlled will be permitted.

Children with a formal personal medical history of previous wheeze will specifically be invited to take part.

## 11.2 Inclusion Criteria

- Aged between 12 months up until one day before their second birthday.
- Parent/legal guardian is willing and able to give written informed consent for participation in the trial.
- In good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity, specifically including a personal history of eczema, bronchiolitis or viral induced wheeze
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
- Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.

## 11.3 Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Previous receipt of an IM seasonal influenza vaccine
- Receipt of any investigational vaccine other than the study intervention within 30 days before and after each study vaccination.
- Living in close contact with someone with a severely weakened immune system.
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines.
- Children eligible for annual influenza immunisation according to the national NHS programme, including those with any confirmed or suspected immunosuppressive or immunodeficient state; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting ≤14 days).

- History of allergic disease or reactions likely to be exacerbated by any component of study vaccines (e.g. hypersensitivity to gentamicin, gelatin, or other ingredients of Fluenz). Allergy to egg is only a contraindication if the participant has previously had anaphylaxis to egg.
- Any history of anaphylaxis.
- Current diagnosis of or treatment for cancer
- Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness, defined broadly as currently requiring frequent hospital/specialist input or recently resulting in hospital admission, or as determined by the investigator (mild/moderate well controlled comorbidities are allowed).
- History of active or previous auto-immune neurological disorders (e.g. Guillain-Barre syndrome, transverse myelitis).
- Scheduled elective surgery during the trial
- Children receiving salicylate therapy (i.e., aspirin)
- Participants who have received an investigational product, or participated in another research trial involving an investigational product in the past 12 weeks or 5 half-lives after the last IMP dose (whichever is longer) before the first dose of study treatment.
- Parent or guardian has insufficient level of English language to undertake all study requirements in opinion of the Investigators except where translation has been able to be provided and is available.

### 11.3.1 Temporary exclusion criteria

If at Visit 1 Screening & Vaccination the volunteer has any of the following, they will not be enrolled that day.

- Acute respiratory illness with or without wheeze (moderate or severe illness with or without fever)

- Fever (oral temperature greater than 37.8°C)

- Active wheezing at the time of dosing/randomisation (including use of bronchodilators within the past 72 hours).

They may be considered for enrolment later in the trial if they recover in sufficient time.

# 12 Trial procedures

See table in appendix A

## 12.1 Recruitment

### 12.1.1 Volunteer Identification

Potentially eligible participants will be identified via participating sites as children registered to GP practices within the age range of 12 to 23 months, and will be contacted via email/text message to inform them about the study and invite them to participate via approved materials.

Children aged 12–23 months will be identified by running a secure, pseudonymised query of participating GP practices' EMIS/TPP systems against the trial's inclusion/exclusion criteria within uMed's ISO-27001-certified AWS London environment. Before any invitations are sent, records will be cross-checked against the NHS National Data Opt-Out register to exclude those who have opted out of research contact. The resulting eligible list will then be approved by the GP practice. Once approved, parents or legal guardians will be sent SMS or email invitations—via uMed's platform— on behalf of their GP practice.

Volunteers may be recruited by use of an advertisement +/- registration form formally approved by the ethics committee and distributed or posted in the following places:

- From General Practitioner databases (including Child Health Information Services (CHIS)) by direct email or via use of uMed system.
- On institutional websites where information will be given and the volunteer information sheet will be downloadable or sent to the volunteer upon request
- In public places, including buses and trains, health centres, GP practice waiting rooms etc. with the agreement of the owner / proprietor
- In newspapers or other literature for circulation
- On radio via announcements
- On a website operated by our group or with the agreement of the owner or operator
- As a post on social media accounts including, but not limited to X, Facebook, Threads or other social media account owned and operated by the study research groups
- By email distribution to a group or list only with the express agreement of the network administrator or with equivalent authorisation
- By email distribution to individuals who have already expressed an interest in taking part in any clinical trial at the databases held at study sites.

- On stalls or stands at exhibitions or fairs
- Via presentations (e.g. presentations at lectures or invited seminars)
- Via PIC sites and other NHS databases local to sites

Volunteers parents/legal guardians will be sent a copy of the participant information sheet in response to requests for further information. Volunteers parents/legal guardians will be given a minimum of 24 hours to review the documentation where possible, prior to attending a screening visit. Sufficient time should be given prior to taking informed consent.

Recruitment will be enriched for participants with a history which might indicated a higher risk of wheezing illnesses, including:

- Personal medical history of wheeze or bronchiolitis
- Personal medical history of eczema

## 12.2 Screening and Eligibility Assessment

### 12.2.1 Informed Consent

The study will obtain **legally valid informed consent from the parent or legal guardian** of each participant in accordance with:

- ICH-GCP E6(R2) section 4.8
- UK SI 2004 No.1031 (as amended), regulations 28–31
- MHRA “Remote and Electronic Consent” guidance (2020)
- HRA “Electronic Consent (eConsent) Guidance” (2018)
- UK GDPR and Data Protection Act 2018 (secure processing & audit trail)

The **primary route** will be fully compliant **electronic consent (eConsent)** delivered via the uMed platform; an equivalent **face-to-face consent** pathway is available on request.

**Step 1 – Digital Pre-screen Survey**

- Parents receive an **SMS or e-mail invite** containing:
    - short study introduction.
    - link to an online pre-screen (≤15 questions).
- If inclusion/exclusion criteria are met, the system displays the full **Participant Information Sheet (PIS)** and advances to eConsent.

**Step 2 – eConsent Workflow**

1. PIS is presented in **plain language**, with expandable "More Info" sections, audio narration and large-print toggle.
2. The parent confirms identity (DOB of child + mobile OTP).
3. Mandatory understanding checks (≤4 quiz questions) guard against incomplete comprehension (GCP 4.8.11).
4. Electronic signature captured (typed name + date/time stamp + IP address).
5. **Tamper-proof PDF** of signed form is auto-e-mailed to the parent and filed in the site eISF; investigator signs the countersignature section at or before first visit.
6. The eConsent platform is **validated, Part-11-style** (audit trail, role-based access, version control) and hosted in the UK.

**Pause / Nurse Call-back**

- At any screen the parent may request to pause for a call back.
- The platform flags a **call-back task** to the study nurse within 24 h; progress is locked until the nurse documents that outstanding questions were answered.
- This satisfies the GCP requirement that the subject (guardian) has "adequate time and opportunity to ask questions" (GCP 4.8.6).

**Optional Face-to-Face Consent at Site**

- Parents may instead choose **in-clinic consent**.
- Site staff give the paper PIS/ICF or display the same PIS on a tablet, answer questions, witness wet or stylus signature, and upload the signed form to the eISF.
- Both routes generate identical consent content; only the mode of signature differs, meeting MHRA/HRA equivalence expectations.

Regulatory Compliance & Record-keeping

- **Audit trail**: every consent-related action (view, pause, sign, withdraw) is date-/time-/user-stamped and exportable for inspection.
- **Version control**: if the PIS/ICF is amended, the system locks further enrolments until the updated version is uploaded and the REC has approved.

- **Data security**: pseudonymised IDs are used; personal identifiers are encrypted at rest and in transit (AES-256, TLS 1.2).
- Copies of all consent documents are retained for **at least 25 years** post-trial (per UK SI 2004 Reg 31A).

The consent process—digital or paper—fulfils all elements of informed consent (content, comprehension, voluntariness, documentation), meeting **GCP, MHRA and REC requirements**.

**Confirmation of Ongoing Consent & Eligibility at First In-Person Visit**

At the participant's first in-person visit (Day 0), the Investigator or delegated site staff will:

1. **Re-confirm Informed Consent**

a. Verify that the parent/legal guardian still consents to their child's participation.

b. Provide an opportunity to ask any further questions, and document continued consent by countersigning the ICF (or updating the eConsent record).

2. **Review Eligibility Criteria**

a. Confirm that all inclusion criteria remain met (e.g., age 12–23 months; parent/guardian able to comply).

b. Re-assess key exclusion criteria (e.g., no acute respiratory illness, no fever > 37.8 °C at Visit 1; no recent receipt of excluded vaccines or investigational products).

c. Any changes that render the child ineligible must be documented, and the child must not be enrolled or randomised.

3. **Document Findings**

a. Record confirmation of ongoing consent and eligibility in the Source Data and on the **Visit 1** e**CRF**.

b. If any uncertainty arises, the child's enrolment is deferred until eligibility and consent are satisfactorily confirmed.

### 12.2.2 Screening

During the eligibility check, if written consent is obtained then the participant's parent/legal guardian will complete a screening questionnaire online to check their eligibility for the study. Time period sensitive criteria will be re-checked in person at visit one.

The eligibility of the child will be reviewed by a suitable member of the clinical team. Decisions to exclude from enrolling in the trial or to withdraw a participant will be at the discretion of the investigator.

As per Section "Temporary exclusion criteria": If a child has an acute respiratory illness (moderate or severe illness with/without fever) or a fever (oral temperature > 37.8°C) at Visit 1 Screening, the child will not be enrolled that day, but may be considered for enrolment at a later date if they recover in sufficient time.

## 12.3 Randomisation

Computer generated randomisation list will be prepared by the study statistician and will be performed within the electronic case report form at visit one.

## 12.4 Blinding and code-breaking

Participants' parents/legal guardians and analysing statisticians will remain blind to treatment allocation. Clinical staff involved in study delivery will be aware of which vaccine the participant is receiving (arm allocation). To maintain blinding as much as possible from attending healthcare providers during the study, arm allocation will be concealed from other healthcare provider contacts via the electronic case report form and will only be visible to site staff at the time data is being entered during a vaccination visit.

If the clinical condition of a child necessitates unblinding to vaccine or placebo allocation, the local investigator will have unrestricted and immediate access to break the treatment code via the participants electronic case report form if they find it is in the best interest of the trial subject. This will be done if unblinding is thought to be relevant and likely to change clinical management.

## 12.5 Visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the schedule of attendances (see Appendix A). Each visit is assigned a time-point and a window period, within which the visit will be conducted. If a participant cannot attend a visit, where possible, this will be re-arranged to an in-person visit within the time window. The final visit will be conducted via a digital questionnaire administered by uMed. If the questionnaire has not been completed following additional prompts by the uMed nursing delegate, then the local study team will be contacted to attempt reach out to the participant's family.

### 12.5.1 Vaccination

Volunteers will be considered enrolled to the trial at the point of randomisation. All vaccines will be administered nasally according to specific SOPs (Equivalent to NHS guidelines for administration of LAIV).

### 12.5.2 Diary reports

Participants' parents/legal guardians will receive a digital diary request at 7 and 14 days after each in-person study visit during the trial, issued via uMed. This will ask them whether their child has attended a healthcare provider since their last visit or diary entry. If they answer yes, they will be directed to further questions regarding the location and nature of this contact with a healthcare provider.

Participants will not be provided with a 24-hour telephone number to contact the study team for medical advice, as this would significantly impact the primary outcome measure which is dependent on the participant's family conducting their normal healthcare seeking behaviour. Participants will be advised to seek their normal routes of healthcare advice via NHS provision of they have any medical concerns regarding their child, whether or not they are considered related to the study. This information will be captured via the digital diary.

Participants will be provided with a 24h telephone number and email address to report hospital admissions to the study.

### 12.5.3 Safety review

Due to the rapid recruitment and short study period, there are no planned safety reviews whilst the study is ongoing. Safety reviews can be conducted on an ad-hoc basis as requested by the DSMB.

### 12.5.4 Subsequent visits

Follow-up visits will take place as per the schedule of attendances described in Appendix A. Participants will be assessed for medical attendances, interim history and review of diary cards at these time points as detailed in the schedule of attendances.

## 12.6 Early Discontinuation/Withdrawal of Participants

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a participants' parents/legal guardian has the right to withdraw them from the study at any time and for any reason, and are not obliged to give their reasons for doing so. The Investigator may withdraw the participant at any time in the interests of the participants' health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation

- Participant non-compliance with study requirements
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. The DSMB or DSMB chair may recommend withdrawal of participants.

In cases of subject withdrawal, long-term safety data collection may continue as appropriate if subjects have received one or more vaccine doses, unless they decline any further follow-up.

# 13 Trial Interventions

## 13.1 Investigational Medicinal Product(s) (IMP) Description

Fluenz is a live attenuated nasal spray vaccine against influenza, containing three strains of reassortant influenza virus complying with the WHO recommendation (Northern Hemisphere) and EU decision for the annual season for 2025/2026. Products will be used as supplied by the UK Health Security Agency to NHS sites for routine use. The nasal spray is a colourless to pale yellow suspension which may be clear to opalescent, and small white particles may be present. The ovalbumin content of Fluenz is less than 0.024 micrograms per 0.2 ml dose.

#### *13.1.1.1 Dosage, scheduling and packaging*

Dose of the vaccine is as described above, with 2 doses of 0.1ml administered per nostril by intranasal spray. There will be no additional labelling of these vaccines beyond their licensed packaging.

### 13.1.2 Placebo description

The placebo is authorised solution of 0.9% saline. stored as routine NHS stock at the study site. Authorised saline is any routine NHS stock vial or ampule of 0.9% saline available at trial sites.

### 13.1.3 Blinding of IMPs

As the investigators are unblinded there will be no blinding of IMPs, however specific instructions will be given to sites to ensure the participant's parent/legal guardian are unable to see which of vaccine or placebo is being given to their child. Specific site training will explain how vaccine/placebo should be handled and the positioning of parent/carer and child to avoid unblinding of the parent/carer.

### 13.1.4 Storage of IMP

Vaccine and placebo will be stored in accordance with manufacturers' recommendations with routine NHS stock at trial sites.

All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms. To allow for participants to receive the vaccine in a short time period, additional clinic locations may be used. In this instance vaccines will be transported in accordance with local SOP's and approvals as required. No study-specific tracking or documentation of placebo 0.9% saline is required.

#### *13.1.4.1 Fluenz*

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the nasal applicator in the outer carton in order to protect from light. Before use, the vaccine may be taken out of the refrigerator once for a maximum period of 12 hours at a temperature not above 25°C. Stability data indicate that the vaccine components are stable for 12 hours when stored at temperatures from 8°C to 25°C. At the end of this period, Fluenz should be used immediately or discarded. NHS guidelines recommend Fluenz not be kept out of the refrigerator longer than 20 minutes prior to administration.

#### *13.1.4.2 Placebo*

Storage as per normal storage instructions for the sites routine stock of vials or ampules of 0.9% normal saline.

### 13.1.5 Compliance with Trial Treatment

All vaccinations will be administered by the research team and recorded in the CRF. The study medication will be at no time in the possession of the participant and compliance will not, therefore, be an issue. At the end of the study period the date of administration of LAIV will be recorded in the child's GP medical records.

### 13.1.6 Accountability of the Trial Treatment

Accountability of the IMPs will be conducted in accordance with the IMP Handling Manual and IMP Management Plan.

### 13.1.7 Concomitant Medication

As set out by the exclusion criteria, volunteers may not enter the study if they have received: any investigational product within 30 days prior to enrolment or if receipt is planned during the study period, or if there is any use of immunosuppressant medication within 6 months prior to enrolment

or if receipt is planned at any time during the study period (except topical steroids and short course of low dose steroids < 14 day). Volunteers will be excluded in case of prior receipt of any other IMP within 12 weeks or 5 half-lives after the last IMP dose (whichever is longer) before the first dose of study treatment.

## 13.2 Other Interventions

There are no additional investigations other than those specified in this protocol.

# 14 Safety Reporting

## 14.1 Safety reporting window

Safety reporting for the trial will commence once the first participant is consented; and will end after the last participant has attended their final study visit for MAAEs and SAEs.

For individual participants the reporting period begins when consent is confirmed, in person, at the V1 visit, and ends after their final study visit.

All adverse events (AEs) that result in a participants' withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if consent is provided).

## 14.2 Adverse Event Definitions

| | |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| **Adverse Reaction (AR)** | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.<br>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.<br>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| **Adverse Events of Special Interest (AESI)** | Adverse events identified as being of particular relevance to the IMP's. These will also reported as an SAE, if meeting SAE criteria (e.g. hospitalisation) |
| **Serious Adverse Event (SAE)** | A serious adverse event is any untoward medical occurrence that:<br>• Results in death<br>• Is life-threatening |

| | |
|---|---|
| | • Requires inpatient hospitalisation or prolongation of existing hospitalisation<br>• Results in persistent or significant disability/incapacity<br><br>Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.<br><br>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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. |
| **Serious Adverse Reaction (SAR)** | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:<br><br>• In the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product<br>• In the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question |

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

## 14.3 Assessment results outside of normal parameters as AEs and SAEs

### 14.3.1 Clinical

Abnormal clinical findings from medical history or examination will be assessed as to their clinical significance throughout the trial. If an abnormal finding is deemed to be clinically significant, the participant will be informed and appropriate medical care arranged with the permission of the participant's parent/legal guardian.

## 14.4 Assessment of severity

The severity of medically attended and serious adverse events will be assessed according to scales based on FDA toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, listed in Table 1 below.

*Table 1. Severity grading for local and systemic AEs*

| GRADE 0 | None |
|---|---|
| **GRADE 1** | Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required |
| **GRADE 2** | Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required |
| **GRADE 3** | Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required. |
| **GRADE 4** | Potentially Life-threatening: Requires assessment in A&E or hospitalisation |

## 14.5 Assessment of Causality

For every MAAE or SAE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the local PI with CI oversight. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy. Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality assessment will be assigned by the reporting investigator, immediately. Causality assessment will be recorded on the eCRF.

If a participant experiences a medically attended adverse event considered possibly, probably, or definitely related to the IMP administration, then the investigator or delegated clinician should

arrange a site visit for safety monitoring assessments where clinically indicated. Investigations and assessment should be performed as felt necessary by the investigator.

*Table 2. Guidelines for assessing the relationship of vaccine administration to an AE.*

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

## 14.6 Procedures for Reporting Adverse Events

### 14.6.1 Medically attended AEs

A medically attended AE, is defined as any adverse event for which the participants' parents/legal guardians seeks medical attention for them either at hospital or from primary care. Participants' parents/legal guardians will be asked to record any medically attended AEs on their electronic diary. Medically attended AEs occurring up to 56 days post randomisation, will be directly solicited and reviewed at each study visit.

## 14.7 Reporting Procedures for Serious Adverse Events

Study sites can be alerted to SAEs via three mechanisms:

- Direct solicitation at follow-up visits.

- Participant reports hospital admission in eDiary (uMed will then notify trial site).
- Participant directly reports SAE to uMed via central telephone number or email on study card (uMed will then notify trial site).

Once the site had been notified of an SAE, the site investigator is required to complete the SAE CRF to notify the Chief investigator or delegate. This may require the investigator to contact the participant's parent/legal guardian to gather information regarding the nature of the SAE. If report of the SAE has come via uMed, they will also notify the CI/delegate of its occurrence so they are aware of a pending report.

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported promptly once the local Investigator/study team becomes aware of their occurrence. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor's representative) or delegate within 24 hours of the Investigator being aware of the suspected SAE. The DSMB will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the chair of DSMB will be notified immediately (within 24 hours) of the CI/sponsor being aware of their occurrence. SAEs which are related to a respiratory event will also be reported promptly to the DSMB. SAE will not normally be reported immediately to the ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial participants, at the discretion of the Chief Investigator and/or DSMB. In addition to the expedited reporting above, the Investigator shall include all SAE in the annual Development Safety Update Report (DSUR) report.

### 14.7.1 Events exempt from immediate reporting as SAEs

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event. A&E attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

## 14.8 Expectedness

### 14.8.1 SAEs

There are no expected serious adverse reactions. All SARs identified as probably, possibly or definitely related will therefore be treated as unexpected and reported as SUSARs.

### 14.8.2 AESIs

There are no AESIs of special interest as wheeze is a primary study outcome and any hospitalisations will be collected as SAEs.

## 14.9 SUSAR Reporting

Under direction of the Chief Investigator, all SUSARs will be reported by uMed with support from the sponsor to the relevant Competent Authority 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 CI, 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.

Principal Investigators will be informed of all SUSARs.

## 14.10 Development Safety Update Reports

A Development Safety Update Report (DSUR) will be prepared by the Sponsor to cover a one year reporting period in line with current UK legislation requirements and the approved safety management plan. This will be submitted to the Competent Authority, Ethics Committee and HRA within 60 calendar days of the defined Data Lock Point (DLP).

## 14.11 Interim and End of Study reviews

An interim DSMB review (see also section 17.1.2) will be held at 7 days post 100 participants vaccinated, and 14 days post 500 participants vaccinated. Both reviews will be held whilst recruitment continues.

For the second DSMB review after 500 participants have completed their day 14 diary, this will provide >80% power to detect a RR of 6 for medically attended wheeze, assuming the wheeze rate is 0.9% for the placebo. If the DSMB find that there is a significant increase in medically attended wheeze in the vaccine arm, the study can be halted for further discussion and investigation.

The safety profile will be assessed on an on-going basis by the Investigators. The CI and relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise.

The DSMB will review safety data accumulated when the study is fully recruited. The DSMB may also be consulted should safety concerns arise at any point.

## 14.12 Safety Holding Rules

The study will be paused if, at any point following the review of the first 500 participants:

- The baseline hospitalisation risk significantly exceeds 2.5%, which is the hospitalisation rate in the previous phase III trial (4), **AND**

- The RR of hospitalisation in the vaccine arm vs the placebo arm becomes greater to a statistically significant degree ($p<0.05$)

Or

- Any death or any life-threatening SAE considered related to the IMP (i.e. that cannot reasonably be attributed to a cause other than vaccination).

The study can be paused upon advice of the DSMB, Chief Investigator, Study Sponsor, regulatory authority, Ethical Committee(s), for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the participants or the reliability of the data.

If the trial is halted due to safety concerns, the trial can only be re-started after regulatory authority approval via a substantial amendment.

# 15 Statistics

## 15.1 Sample size

The primary objective of this study is to determine the relative risk of medially attended wheezing in 28 days following LAIV vaccination compared with placebo. The null and alternate hypotheses are:

$H_0$ : Proportion of wheezing $_{LAIV}$ = Proportion of wheezing $_{Placebo}$

$H_1$ : Proportion of wheezing $_{LAIV}$ ≠ Proportion of wheezing $_{Placebo}$

Where the proportion of wheezing is calculated as the number of participants with respiratory wheezing diagnosed by a health practitioner requiring medical attention within 28 days following receiving LAIV or a placebo. We chose 28 days as this is the common interval to observe intermediate reactions following vaccination. The study was a cross-over design, i.e. participants randomised to LAIV or placebo at Day0 will receive placebo or LAIV at Day28, respectively. Although there is no data on the ideal washout period, it is biologically reasonable to assume that the impact of LAIV will last shorter than 28 days. The data from a previous publication comparing medically significant wheeze rates between LAIV and inactivated vaccine groups reported 44 vs 20 cases in the first 28 days following vaccination, and 11 vs 14 cases between 29-42 days post-vaccination, further supporting our assumption. Therefore, we will use both Day 0-28 and Day 28-56 periods in the primary analysis in the primary analysis.

The sample size calculation is based on the below assumptions:

1. The proportion of medially attended wheezing is 0.9% following placebo in 28 days following vaccination;
2. The relative risk of interest is 2;

3. Study power of 80%;
4. Type I error of 0.05 two-sided;

Based on the above sample size, the study will need to recruit 2800 effective participants. Given the study endpoint will be extracted based on electronic medical records, we expect the attrition rate will be low. The total sample size will be 3000.

## 15.2 Description of statistical methods

The primary analysis population will be participants who are randomised and received LAIV or placebo at Day 0 and Day 28. The proportion of participants with a diagnosis of medically attended wheezing between Day 0 to Day 28 and between Day 28 and Day 56, along with the associated 95% confidence intervals will be presented. When calculating the proportion, the numerator will be the number of participants randomised and received LAIV or placebo at the start of each period**.** The analysis will be conducted according to the vaccine received. The difference in proportions between the two arms will be analysed using Pearson's chi-squared test after combining the data from both periods. The corresponding 95% CI will be derived using a standard method. The risk of wheezing following LAIV will be estimated by a mixed-effects model with the study vaccine received at the start of each period, study period (months) and sequence as fixed effects and participant ID as a random effect to account for within-subject variability. The Kaplan-Meier curve will be used to visualise the time to medically attend wheeze. Participants who withdrew from the study will be censored in the analysis at the time of withdrawal. Non-diagnosed participants will be censored in the analysis at 28 days following vaccination in both periods.

Carryover effects were assessed by testing for the interaction between vaccine and sequence, and if significant, the comparison between the two groups will be done for the two periods separately. We will also test the interaction between the study period (by months) and the vaccine to understand if any increased risk observed following LAIV is affected by the background wheezing risk.

## 15.3 Interim analyses

There will no formal interim analysis.

## 15.4 Missing data

The level and pattern of the missing data in the baseline variables and outcomes will be reported. The potential causes of any missing data will be investigated and documented as far as possible. Any missing data will be dealt with using methods appropriate to the conjectured missing mechanism and level of missing.

# 16 Data Management and quality assurance

The Chief Investigator will be responsible for all data that accrues from the study. The sponsor will act as data controller, University of Oxford will act as a data processor under appropriate agreements.

## 16.1 Access to Data & Data Protection

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

## 16.2 Data Recording

uMed securely collects clinical, patient-reported, and study data in compliance with GCP and regulatory standards. Data is obtained from the following primary sources:

- EHR Data: Extracted from UK general practices (EMIS and TPP systems)
- ePRO/eDiary/eConsent Data: Captured directly from patients via digital surveys for informed consent, subjective outcomes and other patient reported data as required by the Protocol
- Other Study Data: Collected from sites through digital Case Report Forms (CRFs) for protocol-specific activities

All data is stored and managed within uMed's secure cloud infrastructure on Amazon Web Services (AWS) in the London region (UK). Patient-identifiable data remains within this controlled environment. Data management includes strict governance, access control, audit logging, and filtering for National Data Opt-Out and exclusion criteria. Source data files are retained in their original form for traceability and auditability. Data handling adheres to GDPR and relevant local regulations, with access restricted to authorized personnel.

All participant reported adverse event data will be entered onto electronic diary cards (e-diaries) for a maximum of 28 days following administration of the IMP. The eDiary provides a full audit trial of edits and will be reviewed at time-points as indicated in the schedule of events. Any adverse event continuing beyond the period of the diary will be copied into the eCRF as required for safety review.

The participants will be identified by a unique trial specific number and code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file, with the exception of the electronic diaries, for which consent will be obtained to store the participant email

address for quality control purposes. Only site research staff, sponsor staff, monitors (as delegated by sponsor) and University of Oxford data managers have access to view the email address.

## 16.3 Record keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Investigators will permit authorised representatives of the Sponsor(s) and Host institution, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Identifiable information such as contact details will be stored for a minimum of 25 years from the end of the study. This includes storage of consent forms. Storage of these data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required. Considerations at the time of this review will include the value of retaining this information for participant safety (e.g. to inform participants of unexpected safety signals emerging from post-licensing surveillance), as a resource for the participants (e.g. if they wish to check which vaccines they have received in the study) and any regulatory requirements. Financial information will be stored for 7 years. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, a record of this consent will be recorded, retained and stored securely and separately from the research data.

## 16.4 Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected via the uMed Platform. Source documents are the NHS electronic medical records. Source documents are original documents, data, and records from which the participant CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, diaries, electronic medical records and correspondence.

To prevent withdrawal of a participant due to relocation, if there is a nearby participating site and with the consent of the participant, copies of relevant participant research records (such as ICF, paper source documents) will be transferred to the local site using secure email addresses such as nhs.net or by password protected sheets. The electronic research data stored by uMed will also be transferred to the new site. The original records will be retained by the recruiting site.

### 16.5 Data Quality and monitoring

Due to the large volume of electronically collected research data, uMed will adopt a risk-based approach to source data verification. Critical safety and primary endpoint data will undergo complete verification, whereas non-critical data will be selectively verified using random sampling. This approach is aligned with regulatory guidance and ensures efficient, high-quality data monitoring consistent with GCP requirements. This is detailed further in uMed's Data Management Plan.

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with uMed and, for study analysis, Oxford Vaccine Group (University of Oxford) data management SOPs. If additional, study specific processes are required, an approved Data Management Plan will be implemented

## 17 Trial committees

#### 17.1.1 Trial Steering Committee

A Trial Steering Committee will be formed to oversee the study, and advise the Study Management Committee on key issues of study conduct, including, but not limited to, study pauses due to safety concerns on the advice of the DSMB.

#### 17.1.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be convened. The DSMB will evaluate frequency of events, safety and efficacy data as specified in the DSMB charter. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons to the Trial Steering Committee.

The DSMB will review SAEs deemed possibly, probably or definitively related to study interventions. The DSMB will be notified within 24 hours of the CI/Sponsor being aware of their occurrence. The DSMB can recommend placing the study or specific arms of the study on hold if deemed necessary following a study intervention-related SAE.

DSMB formal reviews after 100 and 500 participants and at the end of the trial are detailed in section 14.11.

### 17.1.3 Study Management Group

The trial management group consists of chief investigators and project manager from the sponsor team, representatives from the Oxford Royal College of GPs viral surveillance network, and representatives from uMed.

# 18 Protocol Deviations

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be documented in a protocol deviation form according to SOP R&D/Gen/Admin/009 and filed in the trial master file.

These will be managed as per Sponsor (UHS) SOP R&D/Gen/Admin/009.

# 19 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

# 20 Ethical And Regulatory Considerations

## 20.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

## 20.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

## 20.3 Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject (i.e. as an Urgent Safety Measure).

## 20.4 Other Ethical Considerations

Study team members are not eligible for participation in the study. Family members of the study team are not barred from inclusion in the trial.

## 20.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

## 20.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to ISRCTN database within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

## 20.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of personal data of participants will be minimised by making use of a unique participant study number (uMed ID) only on all study documents and any electronic database(s), with the exception of informed consent forms, participant ID log and electronic diaries. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. A separate confidential file containing identifiable information will be

stored in a secured location in accordance with the current data protection legislation. Photographs of vaccination sites if required (with the participants' written, informed consent), will not include the participants' face and will be identified by the date, trial code and subject's unique identifier. Once developed, photographs will be stored as confidential records, as above. This material may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

# 21 Finance And Insurance

## 21.1 Funding

The study is funded by National Institute Health Research (NIHR), supported by the Vaccine Task Force and DHSC.

## 21.2 Insurance

The Sponsor has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment that is provided.

## 21.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

# 22 Publication Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Data from the study may also be used as part of a thesis for a PhD or MD.

# 23 Development of a New Product/Process Or The Generation Of Intellectual Property

Ownership of IP generated by employees of the Trust vests in the Trust. The Trust will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

# 24 Archiving

Study data may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the site. All essential documents will be retained for a minimum of 25 years after the study has finished with 5 yearly reviews. The need to store study data for longer in relation

to licensing of the vaccine will be subject to ongoing review. For effective vaccines that may be licensed, we may store research data securely at the site at least 25 years after the end of the study, subject to adjustments in clinical trials regulations. Where relevant participants' bank details will be stored for 7 years in line with the site financial policy. De-identified research data maybe be stored indefinitely, but with 5 yearly review.

General archiving procedures will be conducted in compliance to SOP R&D/Gen/Admin/022 SOP for the Archiving of Clinical Trial Data.

# 25 Sub-study – Pending Funding and Amendment

**This section outlines plans for a future amendment for a sub-study if funding can be secured.**

**This sub-study will take place at hospital sites only.**

## 25.1 Sub-study Summary

The sub-study involves additional activity for a small subset of children enrolled in the main trial across three hospital sites. Approximately 30 to 40 children who enrol will have additional investigations performed at the visit immediately before receiving their nasal influenza vaccine, and at the visit four weeks after this. These investigations will involve insertion of a SAM-Strip to investigate mucosal immunity, and venesection for blood to investigate humoral (and where-possible, T-cell mediated) immunity.

Parents/legal guardians will remain blinded to which visit their child will receive the vaccine or placebo and will not be informed of how the timing of the investigations relate to their randomised allocation.

There will be one additional in-person visit for participants who are randomised to the late vaccine group, as they will need to attend their final follow up visit to have investigations performed four weeks after receiving their nasal influenza vaccine.

All other study activities will be performed according to the main protocol.

## 25.2 Objectives and outcome measures

| Objectives | Outcome Measures | Timepoint(s) |
|---|---|---|
| Primary | | |
| To determine the mucosal and humoral immunogenicity of Fluenz in children aged 12 – 23 months | Mucosal and plasma influenza antibodies | Day 0 and 28 following vaccination |
| Key secondary | | |
| To assess cellular immunogenicity of Fluenz in children aged 12 – 23 months | T cell responses to influenza | Day 0 and 28 following vaccination |

## 25.3 Study Design

### 25.3.1 Trial design

Participants will be randomised as per the main protocol. Additional blood tests and mucosal immunity samples (via SAM-Strips) will be performed in both groups.

### 25.3.2 Population

The sub-study population will be drawn from the main study population within participating hospital sites. The same inclusion and exclusion criteria will apply.

### 25.3.3 Setting

Three NHS hospital sites located in Southampton, St George's hospital and Bristol.

### 25.3.4 Study groups

The study will consist of 2 groups of children who have been randomised to either the early vaccine (EV) or late vaccine (LV) arms of the trial, as per the main protocol.

### 25.3.5 Interventions

Additional samples will be collected from both groups. These will consist of blood tests and SAM-strips collected on both the day of vaccination immediately prior to receiving the nasal influenza vaccine, and at the subsequent visit four weeks post vaccination.

## 25.4 Sub-study Schedule of Visitations

| **Early Vaccine Group** | | | |
|---|---|---|---|
| | **D0** | **D28 (-3/+7)** | **D56 (+7)** |
| **In person visit** | X | X | |
| **Telephone contact** | | | X |
| **Consent** | X | X | |
| **Randomisation** | X | | |
| **Vaccination with LAIV** | X | | |
| **Placebo nasal spray** | | X | |
| **Blood tests** | X | X | |
| **SAM-Strips** | X | X | |
| **Collection of SAEs, AESIs and MAAEs** | To be reported at any time up to D56 | | |
| **Late Vaccine Group** | | | |
| | **D0** | **D28 (-3/+7)** | **D56 (+7)** |
| **In person visit** | X | X | X |
| **Telephone contact** | | | |
| **Consent** | X | X | |
| **Randomisation** | X | | |
| **Vaccination with LAIV** | | X | |
| **Placebo nasal spray** | X | | |
| **Blood tests** | | X | X |
| **SAM-Strips** | | X | X |
| **Collection of SAEs, AESIs and MAAEs** | To be reported at any time up to D56 | | |

# 26 References

1. Worby CJ, Chaves SS, Wallinga J, Lipsitch M, Finelli L, Goldstein E. On the relative role of different age groups in influenza epidemics. Epidemics. 2015;13:10–6.
2. Kassianos G, MacDonald P, Aloysius I, Reynolds A. Implementation of the United Kingdom's childhood influenza national vaccination programme: A review of clinical impact and lessons learned over six influenza seasons. Vaccine. 2020;38(36):5747–58.
3. JCVI. Joint Committee on Vaccinations and Immunisation. JCVI statement on the annual influenza vaccination programme – extension of the programme to children. 2012 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf.
4. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356(7):685–96.

# 27 Appendix A

## 27.1 Schedule of visits for the Early Vaccine (EV) cohort

| Early Vaccine Group | | | |
|---|---|---|---|
| | **D0** | **D28 (-3/+7)** | **D56 (+7)** |
| **In person visit** | X | X | |
| **Digital Questionnaire** | | | X |
| **Consent** | X | X | |
| **Collection of demographic data** | X | | |
| **Medical History** | X | | |
| **Concomitant medications** | X | X | X |
| **Weight** | X | | |
| **Randomisation** | X | | |
| **Vaccination with LAIV** | X | | |
| **Placebo nasal spray** | | X | |
| **e-Diary information provided** | X | | |
| **Study card provided** | X | | |
| **Diary Review** | | X | |
| **Collection of SAEs and MAAEs** | To be reported at any time up to D56 | | |

## 27.2 Schedule of visits for the Late Vaccine (LV) cohort

| Late Vaccine Group | | | |
|---|---|---|---|
| | **D0** | **D28 (-3/+7)** | **D56 (+7)** |
| **In person visit** | X | X | |
| **Digital Questionnaire** | | | X |
| **Consent** | X | X | |
| **Collection of demographic data** | | | |
| **Medical History** | X | | |
| **Concomitant medications** | X | X | X |
| **Weight** | X | | |
| **Randomisation** | X | | |
| **Vaccination** | | X | |
| **Placebo nasal spray** | X | | |
| **e-Diary information provided** | | X | |
| **Study card provided** | X | | |
| **Diary Review** | | | X |
| **Collection of SAEs, AESIs and MAAEs** | To be reported at any time up to D56 | | |

# 28 Appendix B: Amendment History

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| 1 | 1.1 | 14th Aug 2025 | Alasdair Munro | • Clarified global end of trial defined as LVLS (section 7).<br>• Amended exclusion criteria to include receipt of salicylate therapy, and receipt of an IMP within 12 weeks or five half-lives of the IMP (whichever is longer) prior to the first study dose (section 11.3).<br>• The ability for investigators to immediately unblind a participant, where considered necessary, has been clarified (section 12.4).<br>• Introduction of a DSMB review at 7 days post 100 participants vaccinated and 14 days post 500 participants vaccinated (section 14.11)<br>• Introduction of holding rules for baseline hospitalization rate >2.5% and significant increased hospitalizations in vaccination group ($p<0.05$), OR a fatal/life threatening SAE considered associated with the IMP (section 14.12)<br>• Clarified that in the event the study is paused for safety concerns, that a substantial amendment would be required prior to restarting (section 14.12).<br>• Recommended site visit for safety assessment where clinically indicated for review of medically attended adverse events thought possibly related to the IMP (section 14.5). |

| | | | | |
|---|---|---|---|---|
| | | | | • Amend references to placebo to clarify this is routine NHS stock normal saline stored at study sites. |