FluSNIFF-toddler Site Guide

Season 2 (S2) restart

V3 – 29 JUL 2026

Supersedes V2 24SEPT25. Reflects Protocol V4.0 (3 June 2026) and PIS V1.1 (24 June 2026).

What's changed in this version (summary for returning site staff)

SAE reporting pathway – clarified that entering an SAE directly into the uMed platform does NOT by itself confirm Sponsor/CI notification; sites must actively confirm escalation with uMed for every SAE (Season 1 learning).

Severity grading reference updated to CTCAE v6.0 (2025), with paediatric amendments, per Protocol V4.0.

New Season 1 pause / Season 2 restart context, and CAG approval reference (26/CAG/0037).

New section on the mandatory S2 training webinars (incl. safety mini-module).

LPMS/ETC guidance corrected: the Treatment Cost/ETC follows whichever visit administers Fluenz – Visit 1 for the Early Vaccine (EV) group, Visit 2 for the Late Vaccine (LV) group – not uniformly Day 0.

Contents 2
Introduction 4
Key Contacts 4
For trial support 4
Other contacts 4
Study Overview 4
Season 1 pause and Season 2 restart 5
Roles & Responsibilities 5
Sites 5
uMed 5
Electronic Investigator Site File (eISF) 5
Delegation Log and Training 5
IMP Handling 6
Importance of Maintaining Parent Blinding 6
Why this matters 6
What sites must do 6
Visit Overview 6
Note on Eligibility and Visit 1 7
Visit 1 (Day 0) — step-by-step (site) 7
Visit 2 (Day 28) — step-by-step (site) 7
Visit 3 (Day 56) — no site visit 8
Protocol Deviation Reporting 8
Steps for Sites 8
Safety Reporting 8
How SAEs can come to a site's attention 9
Add an SAE in uMed platform 9
Severity grading – use these definitions when completing the SAE form 9
Causality categories – select the most appropriate 10
Fluenz and Placebo Supplies 10
Prescribing and Administration Pathways (PGD vs PSD) 10
Recording FluSNIFF-toddler Study Data in the Child's NHS Electronic Health Record (EHR) 10
Suggested EHR Entry – LAIV Administration 11
When to Record 11
Parental Access to NHS App: Suggested Message for Sites 11
Instructions for Reporting FluSNIFF Recruitment Activity via LPMS (for Excess Treatment Cost Recovery) 11
What is LPMS? 12
What do you need to do? 12
Season 2 Mandatory Training (New for Season 2) 12
Video Links 13
Platform Demo Videos 13
Instructional vaccine administration video – to maintain blinding of parent 13

Webpage Links 13
Acronyms 13
Appendix: Site Guide Amendment History 15

Introduction

- This study evaluates the safety of live attenuated influenza vaccine (LAIV) in children aged 12–23 months.
- Sponsored by University Hospital Southampton NHS Foundation Trust, supported by NIHR and delivered with uMed.
- Primary outcome: medically attended wheeze within 28 days of vaccination.
- FluSNIFF-toddler opened to recruitment in autumn 2025 (Season 1) and reopened for Season 2 in July 2026 – see “Season 1 pause and Season 2 restart” below for the background.
- 1196 / 3000 participants were recruited in Season 1. The aim is to reach the 3000 total by the end of Season 2.

Key Contacts

For trial support

- Trial site uMed contact phone number: 0800 055 4288
- Trial site uMed contact email: sitesupport@umed.io

Other contacts

- Chief Investigator: Prof Saul Faust (University Hospital Southampton)
- Co-Lead Investigator: Dr Alasdair Munro (University Hospital Southampton)
- Sponsor Contact: Sharon Davies-Dear, UHS
- Project Management: Chloe Sayce (Senior PM), Thomas Bower & Ben Wilson (PMs)
- uMed Contact: Helena Walsh-Stewart (Project Manager) – do not contact Helena directly; for all queries contact sitesupport@umed.io
- RCGP RSC Contact: Eva Klamerus / Elizabeth Button
- FluSNIFF website: https://umed.io/flusniff-toddler/

Study Overview

- Design: Randomised, single-blinded, placebo-controlled, crossover trial.
- Protocol version in effect: V4.0, dated 3 June 2026. Participant Information Sheet (PIS): V1.1, dated 24 June 2026.
- A substantial amendment covering Protocol V4.0, PIS V1.1, CAG approval and DSMB-driven changes was submitted to the HRA on 1 July 2026; decision expected at the end of July/early August 2026. ⚠️ Site-facing documents referencing the amendment will be distributed but cannot be confirmed until HRA approval is confirmed – this Site Guide will be reissued once that happens.
- Sample Size: 3,000 children (total across both seasons).
- Visits: Visit 1 (Day 0, first site visit); Visit 2 (Day 28 -3/+7 days, second site visit); Visit 3 (Day 56, digital follow-up survey by uMed – no site involvement).
- IMP: LAIV (Fluenz, AstraZeneca) 0.2ml intranasal (0.1ml per nostril); Placebo 0.9% saline, 0.2ml intranasal via 1ml syringe and atomiser (0.1ml per nostril).

Season 1 pause and Season 2 restart

FluSNIFF-toddler opened to recruitment in autumn 2025. Due to a delay in site initiation the study opened later than planned, and an earlier-than-anticipated onset of the influenza/RSV season created a risk that the elevated background rate of viral-induced wheeze would confound the primary outcome. On this basis, following consultation with the TSC and DSMB, the Chief Investigators paused new enrollment in November 2025 to protect the scientific validity of the trial.

This was an operational decision, not a safety-triggered pause. A total of 1,196 participants had been randomised at the point of the pause and continued to be followed up as per protocol. The DSMB reviewed all available safety data from these participants, identified no safety signals, and recommended the trial proceed. FluSNIFF-toddler reopened to recruitment in July 2026, with a plan to complete recruitment over the following autumn.

Data from participants enrolled prior to the pause will be carried forward into the primary analysis. The DSMB review thresholds (100 and 500 participants vaccinated) were both met in Season 1; the next formal DSMB review will take place once the trial is fully recruited, unless a safety concern requires an earlier review.

- uMed's involvement in recruitment support for GP practices has been reviewed and approved by the HRA Confidential Advisory Group (CAG reference: 26/CAG/0037, dated 15 June 2026).

Roles & Responsibilities

Sites

- Approve potential participants in uMed platform
- Conduct Visits 1 & 2
- Enter data into uMed platform
- Maintain delegation log
- Report SAEs via uMed platform within 24 hours of being alerted, and **confirm with uMed that Sponsor/CI escalation has occurred for every SAE** – see Safety Reporting section.

uMed

- Participant identification and outreach.
- Digital pre-screening, eConsent, and surveys (Day 7, 14, 28, 56).
- SAE notification alerts, and confirmation of escalation to Sponsor/CI across all SAE reporting pathways.
- eISF maintenance

Electronic Investigator Site File (eISF)

All logs are stored in the eISF which you will be given access to.

Delegation Log and Training

- The delegation log can be found in eISF.
- Training for this study is SIV attendance, which includes targeted GCP training for those without formal training.
- All staff undertaking study tasks must be delegated those tasks on the delegation log.

- New for Season 2: a mandatory training webinar is required for all delegated site staff, including a dedicated safety mini-module – see “Season 2 Mandatory Training” near the end of this guide.

IMP Handling

Storage

- Fluenz – refrigerated 2–8°C, protect from light, not >20 min out of fridge.
- Saline placebo – stored as per NHS stock.

Accountability: logging of batch and expiry date for LAIV only. No tracking required for saline.

Blinding: parents remain blinded; staff unblinded. Ensure parents cannot see which is administered (use positioning and tray cover). Instructional video and Standard Operating Procedure for Administration provided to sites.

Importance of Maintaining Parent Blinding

In the FluSNIFF-toddler trial, the child’s parent/guardian must remain blinded to whether their child receives the live attenuated influenza vaccine (LAIV) or saline placebo at each visit.

Please refer to SOP for Saline Placebo Administration – FluSNIFF-Toddler Trial, Version 2, dated 20 August 2025. Applies to all delegated site staff listed on the Delegation Log.

Why this matters

- The primary outcome is whether a child experiences medically attended wheeze within 28 days of vaccination.
- If parents knew (or suspected) whether their child received the live vaccine or placebo, it could influence how quickly or how often they seek medical care.
- This would introduce bias into the study results, making the data unreliable.

What sites must do

- Always administer the spray in a way that prevents the parent from seeing which product is used.
- Ask parents to look away or focus only on holding their child during administration.
- Use identical wording and tone regardless of whether vaccine or placebo is given.
- Record and report any instance where unblinding occurs as a protocol deviation.
- Per PIS V1.1, parents are told they can find out which spray their child received after the study ends, if they wish – site staff can use this line if parents ask about unblinding during the study.

Visit Overview

Visit	Day	Early Vaccine Group (EV)	Late Vaccine Group (LV)
Visit 1	Day 0	Fluenz	Placebo
Visit 2	Day 28 (-3/+7 days)	Placebo	Fluenz
Visit 3	Day 56	Digital follow-up	Digital follow-up

Note on Eligibility and Visit 1

If a child does not meet the eligibility criteria at Visit 1 due to temporary ill health (e.g. fever, acute respiratory illness, or active wheeze), the appointment may be rescheduled within the recruitment window. In this situation:

- Complete the consent process as usual (see Visit 1, Point 4 below).
- Do not randomise the participant at this visit.
- When the child returns for their rearranged appointment, repeat Visit 1 procedures in full (eligibility check, randomisation, and IMP administration).

Visit 1 (Day 0) — step-by-step (site)

1. Log in & select participant – log into the uMed platform → search for the participant → open their record.
2. Add Visit 1 date – data capture section → Select Visit → Enter Data, enter Visit 1 (Day 0) date. Save entry.
3. Eligibility tab – select Enter Data. Complete the eligibility assessment questions, including age (12–23 months on the day of the first visit), temporary exclusion checks (no moderate/severe acute respiratory illness, no fever >37.8°C, no active wheeze, no investigational vaccine in the last 30 days). Save entry.
4. Consent tab – confirm/countersign ongoing consent: tick box to confirm parent is happy to proceed; tick box to countersign; confirm if additional questions were needed before dosing (Yes/No); add parent's email; save entry.
5. Randomisation – move to the Randomisation tab, select Randomise patient. The system assigns EV (Early Vaccine Group) or LV (Late Vaccine Group).
6. Administer the correct product – if EV, Fluenz (LAIV) today; if LV, Placebo (0.9% saline) today. Dose: 0.2mL intranasal total, 0.1mL per nostril.
7. Provide reminder card – what to expect; digital diary timing (Day 7 & Day 14); contact details for support. uMed handles surveys and follow-up messaging.
8. Record IMP administration (critical) – Data Capture tab → Enter Data → IMP administration at Day 0 visit. If Fluenz: record product, vial/lot number, expiry date, time, vaccinator name. If Placebo: record administration occurred, date, time and vaccinator name (lot/expiry not required). Save entry.

> ⚠️ **Always record "administration occurred = Yes"**
> Whenever the product (LAIV or placebo) was given – even if it's the placebo – record administration occurred = Yes. Do not enter "No" just because it wasn't the active vaccine; this field is about whether an intervention happened, not which one.

Visit 2 (Day 28) — step-by-step (site)

1. Log in & select participant – log into uMed → open participant record.
2. Add Visit 2 date – data capture section, Visit tab → Enter Data → enter Visit 2 (Day 28) date. Save entry.
3. Administer the alternate product – if EV at Visit 1 → Placebo today; if LV at Visit 1 → Fluenz today (same dose: 0.1mL per nostril).

4. Record IMP administration – Data Capture tab → Enter Data → IMP administration Day 28 Visit. Fluenz: enter batch/lot, expiry, etc. Placebo: lot/expiry not required; document administration only. Save entry.

> ⚠️ **Always record "administration occurred = Yes"**
> Whenever the product (LAIV or placebo) was given – even if it's the placebo – record administration occurred = Yes. Do not enter "No" just because it wasn't the active vaccine; this field is about whether an intervention happened, not which one.

5. Remind parent/carer – uMed will push Day 35 & Day 42 surveys; remind them to watch for messages.

Visit 3 (Day 56) — no site visit

Digital follow-up only (uMed survey). No site action required unless uMed flags an SAE or missing critical data.

Protocol Deviation Reporting

When to use this: any time the approved trial protocol is not followed (e.g. missed visit, out-of-window dosing, eligibility not fully met, consent issue, unblinding of parent).

Steps for Sites

1. Locate the Protocol Deviation Form provided to all sites
2. Complete the Form – participant study ID; date of deviation; description of what happened; why it occurred; action taken/corrective measure; signature and date (Investigator or delegated staff).
3. Save as PDF (scan if completed on paper)
4. Notify the Sponsor/Central Team – email a copy to protocoldeviation@umed.io so it is reviewed promptly and tracked centrally; filename should include Site + Participant ID + Date (e.g. Site01_FLSN1023_2025-09-10_ProtocolDeviation.pdf).
5. Maintain Audit Readiness – keep copies of completed forms in eISF (no local duplicates needed); monitors and Sponsor review directly within Florence.

Safety Reporting

- MAAEs: any medically attended event – report until Day 56. No action from sites required beyond recording.
- SAEs: report within 24h of awareness; notified via uMed and submitted via uMed platform.
- SUSARs: Sponsor/uMed report to regulators; PIs informed.
- Exemptions: planned hospitalisations for existing conditions, which have not worsened, are not SAEs. A&E attendances should not routinely be reported as SAEs unless they meet the SAE definition.

⚠️ Season 2 safety pathway fix – please read carefully

During Season 1, SAEs entered directly into the uMed platform by trial sites (bypassing the patient eDiary) did not always trigger the automated alert to uMed and the Sponsor, and some SAEs went unreported as a result.

For Season 2: sites must NOT assume that entering an SAE into the uMed platform has automatically triggered a Sponsor/CI notification. Sites should actively confirm escalation with uMed (via sitesupport@umed.io) for every SAE, regardless of how it came to the site's attention.

uMed will implement automated alerts across all SAE reporting pathways to support compliance with this requirement, but site confirmation remains the safety net.

How SAEs can come to a site's attention

SAEs can be identified via any of the following three routes – the 24-hour reporting clock and the escalation-confirmation requirement above apply regardless of which route applies:

- Direct solicitation at a follow-up visit.
- Participant reports a hospital admission via the eDiary (uMed will notify the site).
- Participant reports directly to uMed via the central telephone number or email on the study card (uMed will notify the site).

Add an SAE in uMed platform

1. Select participant → scroll to AE/SAE → Enter Data.
2. Choose SAE; complete all fields (event term, onset/end dates, seriousness criterion, outcome, action taken, causality, severity).
3. Submit within 24h of site awareness, and confirm with uMed that CI/Sponsor escalation has occurred.

Severity grading – use these definitions when completing the SAE form

Per Protocol V4.0, severity is assessed using the Common Terminology Criteria for Adverse Events (CTCAE v6.0, 2025, with paediatric amendments), summarised in the table below.

Grade	Definition
Grade 0	None.
Grade 1 (Mild)	Transient/mild discomfort <48h; no interference with activity; no intervention required.
Grade 2 (Moderate)	Some limitation in activity; minimal/no medical intervention needed.
Grade 3 (Severe)	Marked limitation; medical intervention/therapy required.
Grade 4 (Potentially life-threatening)	A&E assessment or hospitalisation required.

Causality categories – select the most appropriate

Category	Definition
0 No relationship	No temporal link; clear alternate cause; not a known pattern of response.
1 Unlikely	Unlikely temporal link; alternate cause likely; not a plausible/known pattern.
2 Possible	Reasonable temporal link, or event not readily explained by other factors, or similar pattern seen with vaccines.
3 Probable	Reasonable temporal link and not readily explained by other factors, or known pattern seen with vaccines.
4 Definite	Reasonable temporal link and not explained by other factors and known vaccine response pattern.

Fluenz and Placebo Supplies

Fluenz is provided free of charge and is ordered via UKHSA in the usual way on ImmForm. Any issues with ordering should be escalated to sitesupport@umed.io, who will troubleshoot with UKHSA on behalf of sites.

In respect of referencing doses ordered for the trial, the Purchase Order/Customer Reference field can be used when raising an order in ImmForm to state how many doses are being ordered for the FluSNIFF trial.

For Placebo, sites should use their own 1ml syringes and 0.9% saline stock. Atomisers are provided by the Sponsor. Costs are covered for stock.

Note: Sites should check how much remaining stock of atomisers they have prior to going live.

Prescribing and Administration Pathways (PGD vs PSD)

For the FluSNIFF study, the investigational product (Fluenz, LAIV, and placebo) can be administered at sites via Patient Specific Direction (PSD):

- The IMP may be prescribed on an individual basis.
- This requires a prescription or written instruction from an authorised prescriber (doctor, dentist, or non-medical prescriber).
- The named prescriber must be recorded in the Delegation Log and assume responsibility for authorising each administration.
- A PSD Proforma is provided by the Sponsor.

Recording FluSNIFF-toddler Study Data in the Child's NHS Electronic Health Record (EHR)

Study participation and immunisation record should only be entered in the EHR on Day 57 or after, to avoid potential study bias.

Item	Record in EHR?	Notes
Study participation	Delayed	Record at Day 60. Recording at enrolment may bias the primary outcome assessment (may make clinical staff more likely to record medically attended wheeze).
Intranasal vaccine administration	Delayed	Record at Day 60 only, as parents may be able to see the EHR online.
Placebo administration	Delayed	Record at Day 60 only, as parents may be able to see the EHR online.
Adverse Events/SAEs	Yes, if clinically significant	If assessed/treated in routine care, it will be captured.
Randomisation group	Never	Clinical information (vaccine and placebo administered dates) recorded on EHR at Day 60.
PSD	Delayed	At Day 60 this is uploaded to EHR.

Suggested EHR Entry – LAIV Administration

When LAIV (Fluenz Tetra) is administered as part of the study, use the following entry in the EHR on or after Day 57 from enrolment:

Suggested wording
"Intranasal influenza vaccine (Fluenz Tetra) administered as per approved FluSNIFF clinical study protocol on X date. Intranasal placebo was administered on X date."
Avoid naming "FluSNIFF" or stating the child is in a clinical trial in the EPR.
Do not enter any data that could indicate when placebo or vaccine was given.

When to Record

The date of LAIV and placebo administration should be entered into the NHS record at the end of participant participation (Day 56 or after).

Parental Access to NHS App: Suggested Message for Sites

If a parent queries missing data in the NHS App, staff may use this explanation:

Suggested wording
"Some parts of the study are blinded so we don't add all information to the medical record straight away. Once the study is completed, any relevant information — such as the flu vaccine given — will be added to the record."

Instructions for Reporting FluSNIFF Recruitment Activity via LPMS (for Excess Treatment Cost Recovery)

As part of NIHR portfolio studies such as FluSNIFF, sites need to record study activity in the Local Portfolio Management System (LPMS). This allows the NIHR Clinical Research Network (CRN)/Research Delivery Network (RDN) to track activity and support recovery of Excess Treatment Costs (ETCs).

What is LPMS?

- LPMS is the system used in primary care (and other NHS sites) to record research activity.
- Common platforms are EDGE or CPMS-linked systems, depending on your region.
- It feeds recruitment and activity data to the national CRN portfolio and is the route by which sites can recover ETCs.

What do you need to do?

1. Check your site's LPMS access – if unfamiliar with LPMS, contact your local RDN support team (https://rdn.nihr.ac.uk/about-us/delivery-organisations). They can confirm whether your site uses EDGE or another LPMS system and set up access if needed.
2. Log FluSNIFF activity in LPMS – each patient recruited/randomised should be entered against the FluSNIFF CPMS ID (69981). Ensure both Visit 1 (Day 0) and Visit 2 (Day 28) are logged, as this confirms the treatment delivery activity underpinning ETC recovery.
3. Flag ETC activity – see the corrected guidance below.
4. If you are unsure – reach out to your local RDN contact for guidance on accessing LPMS, entering FluSNIFF patients correctly, and ensuring ETCs are attributed to your site.

⚠️ Corrected: which visit carries the ETC

Previous guidance said the ETC applies to "the first administration of Fluenz/placebo (Day 0)" – this was imprecise. Per the study's SoECAT, the Treatment Cost (£22.92 per participant) attaches specifically to whichever visit administers Fluenz (the active vaccine), not to Day 0 universally.

Early Vaccine (EV) group: Fluenz is given at Visit 1, so the ETC-relevant visit is Visit 1.
Late Vaccine (LV) group: Fluenz is given at Visit 2, so the ETC-relevant visit is Visit 2 – not Visit 1.

Both visits should still be logged in LPMS for every participant regardless of arm, but when flagging ETC activity specifically, sites should attribute it to the Fluenz-administration visit for that participant's arm.

No additional invoicing is required by the site; the RDN manages recovery centrally. Accurate LPMS reporting ensures your site is reimbursed appropriately and that national reporting of recruitment to FluSNIFF is correct – it also avoids sites bearing treatment costs themselves.

Season 2 Mandatory Training (New for Season 2)

All delegated site staff must complete a mandatory training webinar for Season 2, including a dedicated safety mini-module, before resuming study activity.

Friday 7th August 11am - 12pm - FluSNIFF - Season 2 - Site Initiation Visit (SIV) | Meeting-Join | Microsoft Teams

Monday 10th August 3pm-4pm - FluSNIFF - Season 2 - Site Initiation Visit (SIV) | Meeting-Join | Microsoft Teams

Tuesday 11th August 10am-11am - FluSNIFF - Season 2 - Site Initiation Visit (SIV) | Meeting-Join | Microsoft Teams

Wednesday 12th August 1pm-2pm - FluSNIFF - Season 2 - Site Initiation Visit (SIV) | Meeting-Join | Microsoft Teams

Video Links

Platform Demo Videos

- Landing Page – https://vimeo.com/1119571190/7fcebf40a8
- Preparing for the First Appointment – https://vimeo.com/1119571247/88cbffd1bc
- First Appointment – https://vimeo.com/1119571290/cf82ea7dd4
- Follow Up Appointment – https://vimeo.com/1119571393/578dd09933

Instructional vaccine administration video – to maintain blinding of parent

https://vimeo.com/1119816383/96065bf140

> ⚠️ **Note for Sites**
> In the instructional video, the vaccinator is shown wearing a wristwatch. This is not reflective of required clinical practice. All staff administering IMP must adhere to “bare below the elbows” standards for infection prevention and control.

Webpage Links

- uMed platform – https://mystudy.umed.io/

Acronyms

Acronym	Meaning
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
AcoRD	Attributing the Costs of Health and Social Care Research & Development
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CPMS	Central Portfolio Management System
CRN	Clinical Research Network
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
EDGE	Local Portfolio Management System used by some NHS regions
eCRF	Electronic Case Report Form

Acronym	Meaning
eISF	Electronic Investigator Site File
ETC	Excess Treatment Costs
EV	Early Vaccine group
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
LAIV	Live Attenuated Influenza Vaccine
LPMS	Local Portfolio Management System
LV	Late Vaccine group
MAAE	Medically Attended Adverse Event
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health and Care Research
NISEC	National Immunisation Schedule Evaluation Consortium
ODS	Organisation Data Service
PGD	Patient Group Direction
PI	Principal Investigator
PIS	Participant Information Sheet
PSD	Patient Specific Direction
REC	Research Ethics Committee
RDN	Research Delivery Network
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIV	Site Initiation Visit
SoECAT	Schedule of Events Cost Attribution Template
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UHS	University Hospital Southampton

Acronym	Meaning
UKHSA	UK Health Security Agency

Appendix: Site Guide Amendment History

Version	Date	Summary of changes
V2	24 SEPT 2025	Season 1 site guide.
V3 (this version)	29 JUL 2026	Season 2 restart: SAE reporting pathway fix, CTCAE v6.0 severity grading, Season 1 pause/S2 restart context, CAG approval reference, ODS code/ImmForm collection at onboarding, S2 mandatory training webinars links, ETC/LPMS visit attribution.