Safety of Nasal Influenza Immunisation in Egg Allergic Children

The SNIFFLE 2 study

VERSION 2.3, 16 November 2014

STATEMENT OF COMPLIANCE

This protocol describes the SNIFFLE 2 study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

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

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

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Title	Safety of Nasal Influenza Immunisation in Egg Allergic Children – follow-on study
Abbreviated title	SNIFFLE 2 study
Eudra CT registration no.	2014-001537-92
Clinical Trials.gov number	NCT02111512
NREC Number	West Midlands – Edgbaston 14/WM/0159
Sponsor R&D Number	RHM CHI 0714
UKCRN Number	17189
Primary objectives	To assess the incidence of allergic reaction to nasal influenza vaccination using a Live Attenuated Influenza Vaccine (LAIV) in egg-allergic children, in order to determine the safety of immunisation of egg-allergic children using LAIV in primary care
Intervention	Single dose of intranasal LAIV (To fulfil a duty of care, influenza vaccine-naïve individuals under 9 years of age AND at high risk for severe influenza infection will be eligible for a second dose 4 weeks later, as per DoH guidelines).
Safety	Participants will be immunised in the hospital environment, by personnel qualified in the recognition and treatment of anaphylaxis, and observed for at least 30 minutes following a dose. Families will be contacted at 72 hours after immunisation to establish the occurrence of any delayed effects. Families of children with asthma/recurrent wheeze will be further contacted at 4 weeks after LAIV immunisation to determine asthma control.
Patient group	Children and young people with a physician-diagnosis of egg allergy between 2 -17 years old. Target recruitment of 730 subjects
Sponsor	University Hospital Southampton NHS Foundation Trust
Funding	Public Health England via National Vaccine Evaluation Consortium Grant, Department of Health Research and Development Directorate grant number 039/0031 to Prof E Miller, PHE Patients enrolled in Scotland will be funded through a grant from Health Protection Scotland

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
ISC	Internal Study Committee
IDMC	Independent Data Monitoring Committee
LAIV	Live Attenuated Influenza Vaccine (Intranasal, live)
SAE	Serious adverse event
SAR	Serious adverse reaction
SPT	Skin Prick test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIV	Trivalent Influenza Vaccine (Intramuscular, killed)
TMG	Trial Management Group
TNSS	Total Nasal Symptom Score

INVESTIGATORS AND FACILITIES

LEAD STUDY CENTRE

University Hospital Southampton NHS Foundation Trust,
Southampton General Hospital, Southampton SO16 6YD
T: 023 80 777 222

NATIONAL COORDINATING CENTRE

Imperial College London
Paediatric Research Unit, 7th Floor QEQM Building, St Mary's Hospital, Praed Street, London W2 1NY
T: 020 3312 7754

STUDY MANAGEMENT

JOINT CHIEF INVESTIGATORS

Name	Dr Mich Erlewyn-Lajeunesse BSc MBBS DM FRCPCH
Position	Consultant Paediatric Immunologist and Hon. Senior Clinical Lecturer
Institution	University Hospital Southampton NHS Foundation Trust
Address	Southampton General Hospital
City	Southampton
Postcode	SO16 6YD
Phone	023 8120 4335 / 0791 758 1269
Email	Mich.Lajeunesse@soton.ac.uk

NB: For regulatory purposes and in compliance with Good Clinical Practice, **Dr Mich Erlewyn-Lajeunesse is the nominated Chief Investigator for the study**.

Name	Dr Paul Turner BM BCh FRACP MRCPCH PhD
Position	MRC Clinician Scientist & Hon Consultant in Paediatric Allergy & Immunology
Institution	Imperial College London
Address	Paediatric Research Unit, 7th Floor QEQM Building, St Mary's Hospital, Praed Street
City	London
Postcode	W2 1NY
Phone	020 3312 7754
Email	p.turner@imperial.ac.uk

STATISTICIAN

Name	Dr Nick Andrews
Position	Deputy Head of the Statistics Unit
Institution	Public Health England
Address	61 Colindale Avenue
City	London
Postcode	NW9 5EQ
Phone	Switchboard 0044 208 200 6868
Email	Nick.Andrews@phe.gov.uk

CO-INVESTIGATORS

PUBLIC HEALTH ENGLAND

Name	Professor Elizabeth Miller
Position	Consultant Epidemiologist
Institution	Immunisation Hepatitis and Blood Safety Department Public Health England
Address	61 Colindale Avenue
City	London
Postcode	NW9 5EQ
Phone	0044 208 327 7430 (direct)
Email	liz.miller@phe.gov.uk

Name	Dr Jo Southern MSc PhD MICR CSci MFPH
Position	Senior Clinical Scientist, Epidemiology
Institution	Centre for Infectious Disease Surveillance and Control (CIDSC) Public Health England
Address	61 Colindale Ave
City	London
Postcode	NW9 5EQ
Phone	020 8327 6084
Email	jo.southern@phe.gov.uk

SITES AND PRINCIPLE INVESTIGATORS

BATH

Name	Dr Natasha Zurick
Position	Consultant Paediatrician
Institution	Royal United Hospital Bath NHS Trust
Address	Children's Centre, Outpatients Department B11, Royal United Hospital, Combe Park, Bath BA1 3NG
Phone	01225 821545
Email	n.zurick@nhs.net

BELFAST, NORTHERN IRELAND

Name	Dr Bernadette O'Connor
Position	Consultant Paediatrician
Institution	Ulster Hospital
Address	Upper Newtownards Road, Dundonald BT16 1RH
Phone	02890 564753
Email	bernadette.oconnor@setrust.hscni.net

BIRMINGHAM: SANDWELL GENERAL HOSPITAL

Name	Dr Nick Makwana
Position	Consultant Paediatrician
Institution	Sandwell & West Birmingham NHS Trust
Address	Lyndon, West Bromwich, B71 4HJ
Phone	0121 553 1831 x 3310
Email	nmakwana@nhs.net

BRISTOL

Name	Dr Huw Thomas
Position	Consultant Paediatrician
Institution	Bristol Royal Hospital for Children
Address	Upper Maudlin Street, Bristol BS2 8BJ
Phone	0117 342 8655
Email	Huw.Thomas@UHBristol.nhs.uk

CAMBRIDGE

Name	Dr Eleanor Minshall
Position	Consultant in Paediatric Allergy
Institution	Cambridge University Hospitals NHS Foundation Trust
Address	Addenbrookes Hospital, Hills Road, Cambridge CB2 0QQ
Phone	01223 596185
Email	eleanor.minshall@addenbrookes.nhs.uk

CAMBRIDGESHIRE COMMUNITY SERVICES NHS TRUST

Name	Dr KP Ramesh
Position	Consultant Paediatrician
Institution	Cambridgeshire Community Services NHS Trust
Address	Children's Unit, Hinchingbrooke Hospital, Hinchingbrooke Park, Huntingdon, Cambridgeshire, PE29 6NT
Phone	01480 416416
Email	KP.ramesh@nhs.net

EDINBURGH

Name	Prof. Jürgen Schwarze, Dr. med., FRCPCH
Position	Edward Clark Chair of Child Life and Health
Institution	Child Life and Health, University of Edinburgh
Address	20 Sylvan Place Edinburgh, Scotland EH9 1UW
Phone	0131 536 0801/0841
Email	jurgen.schwarze@ed.ac.uk

HEREFORD

Name	Dr Iain Darwood
Position	Consultant Paediatrician
Institution	Wye Valley NHS Trust
Address	Hereford County Hospital, Union Walk, Hereford, HR1 2ER
Phone	01432 364123
Email	iain.darwood@wvt.nhs.uk

LEEDS

Name	Dr Donald Hodge (Consultant Paediatrician) & Brenda DeWitt (Specialist Nurse Practitioner in Paediatric Allergy)
Institution	Leeds Children's Hospital
Address	Paediatric Offices, A Floor, Brotherton Wing, Leeds General Infirmary, Great George Street, Leeds, West Yorkshire, LS1 3EX
Phone	0113 392 2840 - Donald Hodge / 0113 392 3832 - Brenda DeWitt
Email	donald.hodge@leedsth.nhs.uk / brenda.dewitt@leedsth.nhs.uk

LEICESTER

Name	Dr Gary Stiefel
Position	Consultant in Paediatric Allergy
Institution	Leicester Royal Infirmary
Address	Infirmary Square Leicester LE1 5WW
Phone	0116 258 6914
Email	Gary.GHS.Stiefel@uhl-tr.nhs.uk

LIVERPOOL

Name	Christine Doyle
Position	Nurse Consultant in Respiratory Medicine & Allergy
Institution	Alder Hey Children's Hospital NHS Foundation Trust
Address	Eaton Road, West Derby, Liverpool L12 2AP
Phone	0151 252 5776
Email	chris.doyle@alderhey.nhs.uk

LONDON: KING'S COLLEGE HOSPITAL

Name	Dr Susan Leech
Position	Consultant in Paediatric Allergy
Institution	Kings College Hospital NHS Foundation Trust
Address	Denmark Hill, London SE5 9RS
Phone	020 3299 1757
Email	sueleech@nhs.net

LONDON: ROYAL FREE HOSPITAL, HAMPSTEAD

Name	Mr James Gardner (Specialist Nurse in Paediatric Allergy) & Dr Rahul Chodhari (Consultant Paediatrician)
Institution	Royal Free London NHS Foundation Trust
Address	Pond Street, LONDON NW3 2QG
Phone	0207 830 2001
Email	jgardner@nhs.net

LONDON: ROYAL LONDON HOSPITAL

Name	Dr Lee Noimark
Position	Consultant in Paediatric Allergy
Institution	Barts Health NHS Trust
Address	7th floor, Royal London Hospital, Whitechapel, London E1 1BB
Phone	07931 734995
Email	lee.noimark@bartshealth.nhs.uk

LONDON: ST GEORGES' HOSPITAL, TOOTING

Name	Prof Paul T Heath
Position	Professor / Consultant Paediatric Infectious Diseases
Institution	Clinical Sciences & Vaccine Institute, St Georges, University of London
Address	Cranmer Terrace London SW17 0RE
Phone	020 87255980
Email	pheath@sgul.ac.uk

LONDON: ST MARY'S HOSPITAL

Name	Paul Turner
Position	MRC Clinician Scientist & Hon Consultant in Paediatric Allergy & Immunology
Institution	Imperial College London
Address	Paediatric Research Unit, 7th Floor QEQM, St Mary's Hospital, Praed Street London W2 1NY
Phone	020 3312 7754
Email	p.turner@imperial.ac.uk

LONDON: ST THOMAS' HOSPITAL

Name	Roisin Fitzsimons
Position	Paediatric Allergy Nurse Consultant
Institution	St Thomas Hospital
Address	Children's Allergy Service, 2nd Floor, B Block, South Wing London SE1 7EH
Phone	02071889783, Bleep 1549 via switch 02071887188
Email	Roisin.Fitzsimons@gstt.nhs.uk

LONDON: UNIVERSITY COLLEGE LONDON HOSPITAL

Name	Dr Jonathan Cohen
Position	Consultant Paediatrician
Institution	University College London Hospitals NHS Foundation Trust
Address	250 Euston Road, London NW1 2PG
Phone	0203 447 9064
Email	Jonathan.cohen@uclh.nhs.uk

LUTON

Name	Dr Anita Modi
Position	Consultant Paediatrician
Institution	Luton and Dunstable Hospital
Address	Lewsey Road, Luton LU4 0DZ
Phone	01582 718 371
Email	Anita.modi@ldh.nhs.uk

MANCHESTER

Name	Dr Stephen Hughes
Position	Consultant Paediatric Immunologist
Institution	Royal Manchester Children's Hospital
Address	Oxford Road, Manchester, M13 9WL
Phone	0161 701 0678
Email	stephen.hughes@cmft.nhs.uk

NEWCASTLE

Name	Dr Louise Michaelis
Position	Consultant in Paediatric Allergy
Institution	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Address	Freeman Hospital, Freeman Road, High Heaton Newcastle upon Tyne NE7 7DN
Phone	0191 233 6161
Email	Louise.Michaelis@nuth.nhs.uk

NORFOLK

Name	Dr John Chapman
Position	Consultant Paediatrician
Institution	James Paget University Hospitals NHS Foundation Trust
Address	Lowestoft Road, Gorleston, Great Yarmouth, Norfolk, NR31 6LA
Phone	01493 452157
Email	John.chapman@jpaget.nhs.uk

OXFORD

Name	Dr Matthew Snape
Position	Consultant in Vaccinology and General Paediatrics
Institution	Oxford Vaccine Group
Address	CCVTM, Churchill Hospital Oxford OX3 7LE
Phone	01865 857405
Email	matthew.snape@paediatrics.ox.ac.uk

PRESTON

Name	Dr Colin Lumsden
Position	Consultant Paediatric Immunologist and Hon. Senior Clinical Lecturer
Institution	Lancashire Teaching Hospitals NHS Foundation Trust
Address	Royal Preston Hospital, Sharoe Green Lane, Fulwood, Preston PR2 9HT
Phone	01772 524280
Email	colin.lumsden@lthtr.nhs.uk

SHEFFIELD

Name	Dr Nicola Jay
Position	Consultant Paediatrician
Institution	Sheffield Children's Hospital NHS Foundation Trust
Address	Clinical Research Facility, D Floor, Stephenson Wing, Sheffield Children's Hospital Sheffield S10 2TH
Phone	0114 271 7559
Email	Nicola.jay@sch.nhs.uk

SHREWSBURY

Name	Martyn Rees
Position	Respiratory and Allergy Nurse Specialist for Children
Institution	Shrewsbury and Telford Hospital NHS Trust
Address	Royal Shrewsbury Hospital, Mytton Oak Road, Shrewsbury, SY3 8XQ
Phone	01743 261636
Email	martin.rees@sath.nhs.uk

SOUTHAMPTON

Name	Dr Mich Erlewyn-Lajeunesse (Joint chief investigator)
Position	Consultant Paediatric Immunologist and Hon. Senior Clinical Lecturer
Institution	University Hospital Southampton NHS Foundation Trust
Address	Southampton General Hospital Southampton SO16 6YD
Phone	023 8120 4335 / 0791 758 1269
Email	Mich.Lajeunesse@soton.ac.uk

WARRINGTON

Name	Dr Richard Briggs
Position	Consultant Paediatrician
Institution	Warrington & Halton Hospitals NHS Foundation Trust
Address	Warrington Hospital, Lovely Lane, Warrington Cheshire WA5 1QG
Phone	01925 662243
Email	richard.briggs@whh.nhs.uk

WINCHESTER

Name	Dr Keith Foote
Position	Consultant Paediatrician
Institution	Hampshire Hospital NHS Foundation Trust
Address	Royal Hampshire County Hospital, Romsey Road, Winchester Hampshire SO22 5DG
Phone	01962 825334
Email	Keith.foote@hhft.nhs.uk

STUDY COORDINATOR AND CLINICAL ENQUIRIES

Name	Ms Heather Hanna
Position	Senior Research Nurse
Institution	Imperial College London
Address	Paediatric Research Unit, 7th Floor QEQM Building, St Mary's Hospital, Praed Street
City	London
Postcode	W2 1NY
Phone	020 3312 7871 / 07500 835518
Fax	020 3312 7571
Email	h.hanna@imperial.ac.uk

INTERNAL STUDY COMMITTEE (ISC)

The ISC will have an independent chair and include a representative of patient organisations. The ISC is the main decision making body, with overall responsibility for ensuring the project's aims are delivered to schedule and within budget. The following membership have been confirmed:

INDEPENDENT (VOTING) MEMBERS:

- Dr Nicola Brathwaite, Consultant in Paediatric Allergy, King's College Hospital (London) (Chairperson)
- Dr Diab Haddad, Consultant in Paediatric Allergy, St Peter's Hospital, Chertsey
- Ms Hazel Gowland, Patient Representative, Anaphylaxis Campaign

DEPENDENT (VOTING) MEMBERS:

- Dr Mich Erlewyn-Lajeunesse, Joint Chief Investigator
- Dr Paul Turner, Joint Chief Investigator
- Prof Liz Miller (Co-investigator)

The dependent members will constitute the Trial Management Group (TMG). The TMG can co-opt other professionals as needed for the smooth running of the trial.

INDEPENDENT DATA MONITORING COMMITTEE

An data monitoring committee (IDMC) will be appointed, consisting of three members independent of the study team. They will review safety data on an on going basis and review severe events reported by PIs. The IDMC will provide advice to the ISC. The following membership has been confirmed:

- Dr Glenis Scadding [Chairperson] (Consultant in Rhinology and Allergy, London)
- Dr Andrew Riordan (Consultant in Paediatric Immunology and Infectious Diseases, Liverpool)
- Dr Giuseppina Rotiroti (Consultant Allergist, Royal Free Hospital NHS Trust)
- Dr Andre Charlett (Director of Statistics Unit, Public Health England)

SPONSOR

University Hospital Southampton NHS Foundation Trust

Sponsor number: RHM CHI 0714

CONTACT:

Name	Mrs Sharon Atwill
Position	Research Governance Officer
Institution	University Hospitals Southampton NHS Foundation Trust
Address	Research and Development Level E, Laboratory & Pathology Block SCBR - Mailpoint 138 Tremona Road
City	Southampton
Postcode	SO16 6YD
Phone	+44-(0)23-8120 5078
Email	sharon.atwill@uhs.nhs.uk

FUNDING AND RESOURCES

1. Public Health England via National Vaccine Evaluation Consortium Grant, Department of Health Research and Development Directorate grant number 039/0031 to Prof E Miller, PHE
2. Patients enrolled in Scotland will be funded through a grant from Health Protection Scotland
3. Patients enrolled in Northern Ireland will be funded through locally-held Public Health funds

INTRODUCTION AND BACKGROUND

BACKGROUND INFORMATION

Egg allergy is one of the most common food allergies in childhood with an estimated prevalence of at least 2% in preschool children (1). Natural tolerance is acquired during childhood so that only about 0.1% of adults have egg allergy (2)

Influenza vaccines contain egg protein as the vaccine virus is cultured in hen's eggs. Individuals who have egg allergy may be at increased risk of reaction to influenza vaccines. In recent years, inactivated influenza vaccines that are egg-free or have a very low ovalbumin content have become available. Table 1 lists the vaccines currently available within the UK. Observational studies have confirmed the safety of the parenteral influenza vaccine in egg-allergic children, including those with a history of previous anaphylaxis to egg protein (3, 4). A recent literature review reported safety data for administration of the parenteral influenza vaccine in over 4000 children with egg allergy (over 3-fold greater than the available data on the use of MMR in egg-allergic children) concluded that "there is now robust evidence that egg-allergic patients, even those with severe allergy, can be safely vaccinated against influenza" (3, 4). These observations only apply to inactivated Trivalent Influenza Vaccine (TIV) delivered by intramuscular injection, and have led to a relaxation of contraindications in the last few years (5, 6). With increased safety data it has become routine to immunise low-risk, egg-allergic children in primary care. It is likely that this will soon extend to children with anaphylaxis to egg in a similar way to the relaxation of the rules surrounding MMR and egg allergy (7).

Supplier	Product	Vaccine type	Age indication	Ovalbumin content (ng per dose)
Abbott Healthcare	Influvac	Inactivated	> 6 months	100
	Imuvac	Inactivated	> 6 months	100
Janssen-Cilag	Viroflu	Inactivated	> 6 months (caution in <5yrs)	<50
	Inflexal V	Inactivated	> 6 months (caution in <5yrs)	<50
GSK	Fluarix	Inactivated	> 6 months	<50
Masta	Imuvac	Inactivated	> 6 months	100
	Influvac	Inactivated	> 6 months	100
	Split virion BP	Inactivated	> 6 months	<50
Novartis	Agrippal	Inactivated	> 6 months	<200
	Fluvirin	Inactivated	> 4 years	<1000
	Optaflu	Inactivated	> 18 years	None
Pfizer	Influenza vaccine	Inactivated	> 5 years	<1000
	Enzira	Inactivated	> 5 years	<1000
Sanofi Pasteur MSD	Split virion BP	Inactivated	> 6 months	<50
	Intanza	Inactivated	> 18 years	<24
Astra Zeneca	**FLUENZ**	**Live attenuated**	**2 – 18 years**	**<240**

Table 1: Ovalbumin content in influenza vaccines available in UK. Green book chapter 19: 207-209 (accessible at http://immunisation.dh.gov.uk/category/the-green-book)

A trivalent Live Attenuated Intranasal Vaccine (LAIV), given via the intranasal route, has been available in the United States for several years (8). It has demonstrated efficacy against influenza in children from 2-17 years old (9-12). LAIV is also grown in hens' eggs and contains ovalbumin.

The safety of trivalent LAIV in non-egg-allergic children has been established predominantly in the MI-CP111 trial (13). Table 2 depicts the safety data collected during the first 10 days post vaccination. In this study, all children received both an intranasal spray and an intramuscular injection. The nasal placebo dose (saline) was associated with significant nasal symptoms (parent/subject reported) but on day 0-1 the incidence of this was considerably lower at only 12%. The quadrivalent vaccine has been found to have a similar safety profile [REF].

	Injection Site Reaction	**Runny Nose/ Nasal Congestion**	**Fever >100°F**	**Fever >101°F**	**Fever >102°F**
TIV n=4232	**25%**	**46%**	**12%**	**7%**	**4%**
LAIV n=4243	**21%**	**57%**	**15%**	**8%**	**4%**
	***p*<0.001**	***p*<0.001**	***p*<0.001**	**NS**	**NS**

Table 2: Percentage of children with adverse events on days 0-10 after immunisation with LAIV from Study MI-CP111 (13)

LAIV is contraindicated in children under 2 years old. This is because there has been increased incidence of wheezing in children under 2 years old in the 4 weeks following immunisation (13, 14). This effect is not seen in older children (13, 15, 16), even in those with pre-existing asthma and wheeze (17). Post marketing surveillance data has not reproduced this signal (18). LAIV is not associated with new onset asthma (16).

In the United States, LAIV was initially approved for use in individuals aged 5-49 years in 2003, which was extended to individuals aged 2-49 years in 2007 (19). It has been given to several million people since that time (20). The vaccine has proven to be safe and efficacious, and equivalent to TIV in terms of its safety profile (18, 21-26). There have been no reports of accidental administration in children with egg allergy during this time, although it is likely to have occurred. There are only 7 reported cases of anaphylaxis as an adverse event following administration of LAIV (20, 25). Of these only 5 were thought to be causally related to vaccine administration and none were related to egg allergy (20). The estimated rate of anaphylaxis following LAIV administration is 1 case in 20,000 to 1,000,000 doses (20).

There are currently no published data on the safety of LAIV in egg-allergic children, thus its use in this population (under the terms of its license by regulatory authorities) has been contraindicated. However, a recent safety surveillance study (The SNIFFLE I study) commissioned by Public Health England on behalf of the UK Department of Health assessed the safety of trivalent-LAIV in children with >95% likelihood of clinical egg allergy. A total of 433 doses were administered in 282 children, with no systemic allergic or anaphylactic reactions observed (manuscript currently in submission).

At the current time, the Department of Health is planning to provide quadrivalent LAIV for use as part of the UK National Immunisation Programme for the 2014/15 influenza season. This is because the quadrivalent vaccine includes four rather than three influenza strains, which results in improved immunity (27). The manufacturer has stated that the egg protein content of the two different vaccines (trivalent vs quadrivalent) is the same.

RESEARCH QUESTION

To assess the safety of LAIV (Fluenz®, Astra Zeneca) in children with a physician diagnosis of egg allergy, in order to determine the safety of immunisation of egg-allergic children using LAIV in primary care.

RATIONALE FOR CURRENT STUDY

In July 2012 the Joint Committee on Vaccination and Immunisation (JCVI) proposed an extended annual influenza immunisation programme for children 2 -17 years old using egg-containing LAIV (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf). Contraindications to the administration of LAIV will cause disruption to the roll out of the new vaccine programme and require primary and secondary care resources for the immunisation of egg allergic children using TIV (25). The programme commenced in Autumn 2013 with all children in the UK aged 2 and 3 years invited to participate. This had a significant impact on referrals to specialist allergy services as immunisation was indicated for a large number of egg-allergic children who would previously not have received seasonal flu vaccine.

STUDY JUSTIFICATION

The intranasal LAIV contains under 240ng of ovalbumin, which is delivered to the nasal mucosa. This amount is in the mid-range in terms of the amount of ovalbumin in parenteral influenza vaccine formulations. Estimates of the paediatric ED10 (amount of protein needed to trigger an allergic reaction in at least 10% of children) is around 20mg – i.e. 10^5 x more than that delivered by the vaccine (28, 29). In a recent study by Clark et al, intranasal challenges were performed in peanut-allergic children using a dose of peanut (10µg) approximately 300 times less than the established ED10 for peanut (approximately 3mg peanut protein)(30). Patients experienced mild symptoms of rhinitis only, with no other organ involvement or evidence of systemic reaction.

During the influenza season 2013/14, the SNIFFLE I study reported no systemic or significant local allergic reactions with 433 doses of trivalent-LAIV administered in 282 egg-allergic children. Eight children experienced possible local allergic symptoms following LAIV, all of which were mild, self-limiting and occurred within 30 minutes of LAIV administration. On the basis of these data, the 95% upper confidence interval for occurrence of a significant allergic reaction to LAIV in egg-allergic children is <1.3%, equivalent to under 1 in 77 doses. The current study will increase the power of this safety calculation, to that which might be viewed as being acceptable to permit future use of LAIV in egg-allergic children in the primary care setting.

The existing data strongly suggest that few, if any, egg-allergic children will experience significant symptoms following intranasal LAIV administration. In order to achieve a larger sample size, secondary paediatric centres (in addition to tertiary paediatric allergy clinics) will be included, where there is sufficient expertise and experience to safely manage any allergic reaction.

It is proposed that the negligible risk involved to participants is outweighed not only by the protection against influenza infection following vaccination, but also by the demonstration in a larger cohort of patients that LAIV is safe in egg-allergic children. The success of the introduction of annual influenza vaccination to the UK paediatric immunisation schedule depends on the wide availability and uptake of the vaccine. This study will provide the necessary safety data for vaccine use in those children with egg allergy (up to 5% of the total paediatric population for some ages) which will facilitate the planned extensive use of this vaccine as a public health intervention.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

To assess the incidence of immediate allergic reaction to nasal influenza vaccination with LAIV in egg-allergic children

SECONDARY OBJECTIVES

1) To assess the incidence of immediate allergic reaction to LAIV in the following subgroups:
   a) By age group 2-5, 6-11, 12-17 years
   b) Children with a clinician-assessed history of reaction to egg in the previous 12 months
   c) Children with evidence of >95% likelihood of egg allergy (defined as a serum specific IgE 6.0 IU/mL or above (31) or skin prick test (SPT) 7mm or above to egg (32, 33) within the past 3 months
   d) Children with evidence of >95% likelihood of egg allergy (as defined in c) above) within the past 12 months
   e) children with a previous history of anaphylaxis to egg protein
   f) children who have reacted previously to airborne traces of egg
   g) children who have egg allergy but are tolerant of baked egg
   h) Children who have previously received influenza vaccine
   i) Presence of physician-diagnosed asthma / recurrent wheeze

2) To assess the incidence of delayed symptoms up to 72 hours after nasal influenza vaccination with LAIV in egg-allergic children

3) To assess for a change in asthma control (by validated questionnaire) pre and 4 weeks post LAIV immunisation.

STUDY DESIGN

TYPE OF STUDY

- Multicentre, observational study of the safety of LAIV in egg allergic children.

NUMBER OF SUBJECTS

- 730 children, on the basis of power calculations (see below).

EXPECTED DURATION OF STUDY

- Recruitment to commence 1st September 2014
- Clinical interventions to commence from mid-September 2014 for 5 months.

OUTCOME MEASURES

PRIMARY OUTCOMES:

- Immediate allergic reaction (occurring within 2 hours of administration)

SECONDARY OUTCOMES:

- Adverse events (of non-allergic aetiology) following administration
- Delayed onset allergic reaction (<72 hours following administration)
- Change in asthma control (by a validated questionnaire) pre and post LAIV

STUDY TREATMENT

DESCRIPTION

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

At the current time, the Department of Health is planning to utilise the LAIV Quadrivalent vaccine (Fluenz Tetra, Astra Zeneca) for the influenza season 2014/15. However, in the event the quadrivalent LAIV is not available, vaccine supply will be with the trivalent LAIV.

DOSAGE AND ROUTE OF ADMINISTRATION

0.2 ml (administered as 0.1 ml per nostril). Immunisation must be carried out by nasal administration.

DOSE MODIFICATION

No dose modification proposed.

PREPARATION AND ADMINISTRATION OF STUDY DRUG

FLUENZ IS FOR NASAL USE only.

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

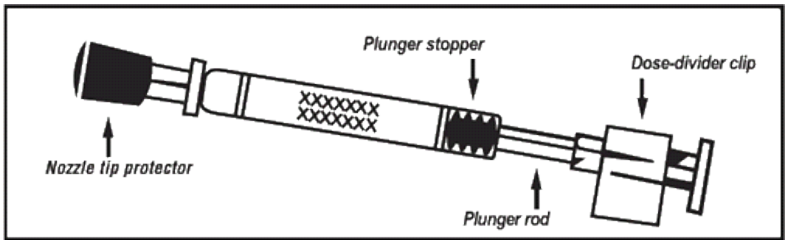
• FLUENZ is administered as a divided dose in both nostrils.

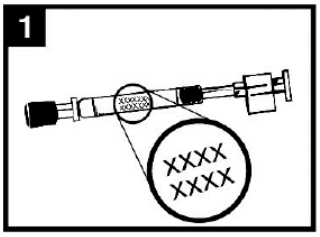
• After administering half of the dose in one nostril, administer the other half of the dose in the other nostril immediately or shortly thereafter.

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

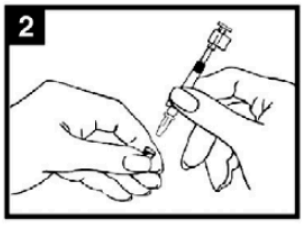
• Refer to the FLUENZ administration diagram (Figure 1) for step-by-step administration instructions.

Figure 1 FLUENZ Administration

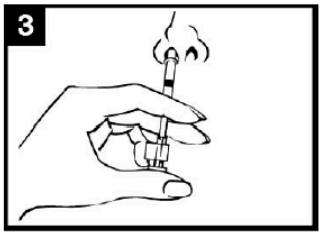




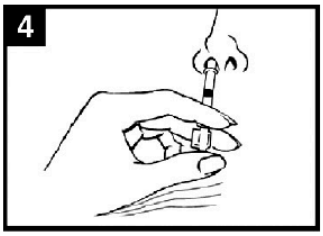
Check expiry date
Product must be used before date on applicator label.



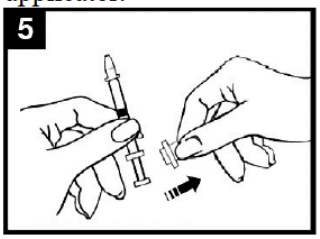
Prepare the applicator
Remove rubber tip protector. Do not remove dose-divider clip at the other end of the applicator.



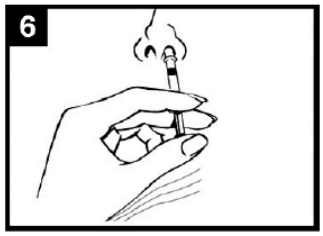
Position the applicator
With the patient in an upright position, place the tip just inside the nostril to ensure Fluenz is delivered into the nose.



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



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



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

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

DISPENSING AND PRODUCT ACCOUNTABILITY

Both formulations of Fluenz (trivalent and quadrivalent LAIV) are approved by the European Medicines Agency and distribution and administration to selected children will take place during the influenza season 2014-15. This is a pragmatic study, designed to ensure rigorous surveillance of Fluenz administration in a population of children with egg allergy. Provision of doses of vaccine will be through the Department of Health vaccine supply network as part of the national immunisation programme, with no additional requirements (e.g. cold chain monitoring) beyond that provided by the normal UK vaccine supply system. Vaccine will be delivered via existing systems to on-site pharmacists at the study sites (all NHS hospital organisations). Doses will then be released according to local procedure, using existing hospital pharmacy systems and logging (rather than CTIMP-specific documentation).

SUBJECT ENROLLMENT

RECRUITMENT

Subjects will be recruited through 2 routes:

1. Egg allergic children currently managed within an existing paediatric outpatient services. Recruitment will be via publicity (posters, flyers), email and postal mailing (with an option for a follow-up contact by post, email or telephone* where there is no response to the initial invite). Children who received the LAIV vaccine in 2013/14 will receive a separate letter of invitation (by post or email) inviting them to participate in this follow-on study.

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

2. New referrals from primary and secondary care for parenteral influenza vaccination in egg allergic children not currently managed within the existing outpatient service. This includes the ability to utilise PIC sites to aid recruitment.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. Aged 2 – 17 years old

2. Physician-diagnosis of egg allergy **WITH** current avoidance of egg in one of the following categories:
   - E0 – avoids all foods containing egg in any form
   - E1 – tolerates egg in baked foods (cakes, biscuits) but not other forms
   - E2 – able to eat lightly cooked egg (e.g. scrambled egg, boiled egg) but reacts to raw egg in uncooked cake mixtures, fresh mayonnaise, ice cream etc.

3. Written informed consent from parent/guardian (or the patient themselves from age 16 years), with assent from children aged 8 years and above wherever possible.

EXCLUSION CRITERIA

1. **Clinical resolution of egg allergy**

2. **Contraindications to LAIV** (notwithstanding allergy to egg protein), which include:
   a. Hypersensitivity to the active ingredients, gelatin or gentamicin (a possible trace residue)
   b. Previous systemic allergic reaction to LAIV
   c. Previous allergic reaction to an influenza vaccine (not LAIV) is a relative contra-indication, which must be discussed with the site PI to confirm patient suitability
   d. Children/adolescents who are clinically immunodeficient due to conditions or immunosuppressive therapy such as: acute and chronic leukaemias; lymphoma; symptomatic HIV infection; cellular immune deficiencies; and high-dose corticosteroids*.

*__High-dose steroids__ is defined as a treatment course for at least one month, equivalent to a dose of prednisolone at 20mg or more per day (any age); or for children under 20kg, a dose of 1mg/kg/day or more.

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

e. Children and adolescents younger than 18 years of age receiving salicylate therapy because of the association of Reye's syndrome with salicylates and wild-type influenza infection.

3. **Contraindication to vaccination on that occasion,** e.g. due to child being acutely unwell:
   a. Febrile ≥38.0^{o}C in last 72 hours
   b. Acute wheeze in last 72 hours requiring treatment beyond that normally prescribed for regular use by the child's treating healthcare professional
   c. Recent admission to hospital in last 2 weeks for acute asthma
   d. Current oral steroid for asthma exacerbation or course completed within last 2 weeks
   e. Recent use (within last 96 hours) of an antihistamine

NB: See Summary of Product Characteristics for full details of contra-indications to LAIV. Note that **Fluenz is not recommended during pregnancy.** Administration of another live vaccine (e.g. MMR) within the previous 4 weeks is no longer a contra-indication to LAIV administratation, according to updated DoH guidelines.

Children requiring oral steroids for their asthma management (ie. BTS Step 5) may be included in the study if they meet the following criteria:

1. Their asthma is stable on their current regimen and has been so for the previous 2 weeks
2. They are reviewed by the centre PI prior to inclusion in the study
3. Their Asthma Control Test score at inclusion is no lower than 20.

SUBJECT WITHDRAWAL

The primary outcome in this study involves a single visit to a hospital for administration of the intranasal vaccine. Subsequent withdrawal will affect only the assessment of delayed symptoms, a secondary outcome measure, which will be collected by telephone.

TRIAL CLOSURE

The study will be considered complete following enrolment of the last patient and completion of the study procedures in that patient, or at the end of the influenza season 2014-15. Upon review by the ISC, recruitment may be extended if target recruitment is achieved prior to end of the influenza season and additional funding is available.

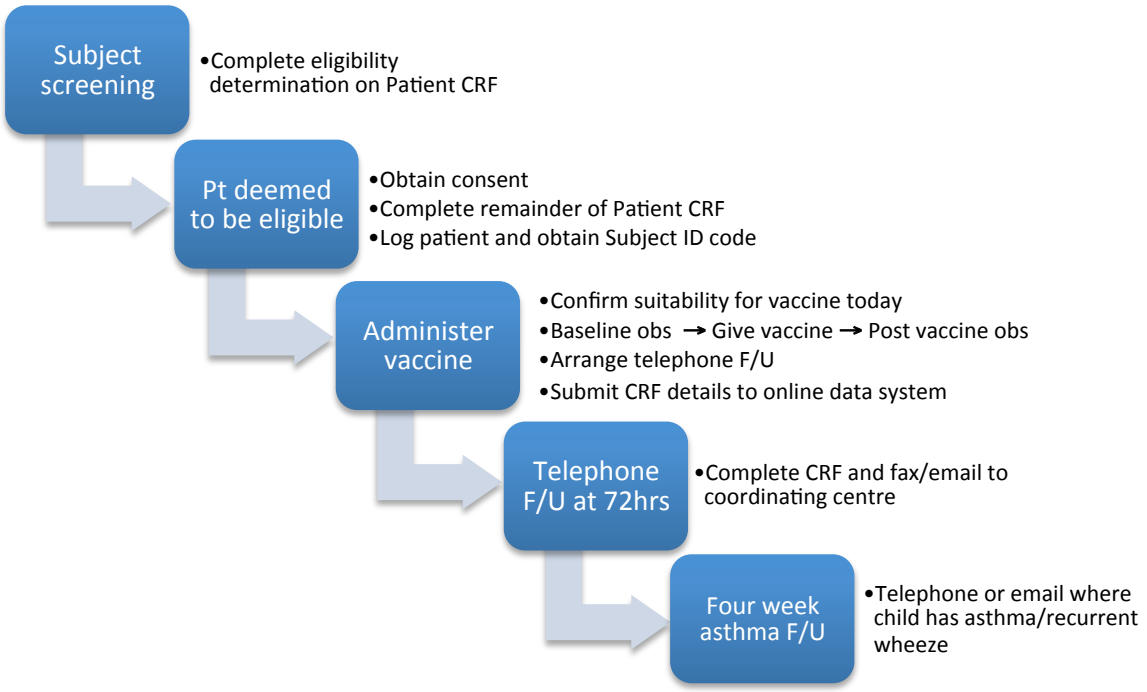
The study will be placed on hold and, upon review of study data and discussion with the IDMC, may be terminated early if any of the following occur:

- One patient suffers an allergic reaction that warrants admission to the ICU and use of mechanical ventilation
- Death of a participant during the study period, from any cause
- Two similar SUSARs (Suspected Unexpected Serious Adverse Reactions) or the repetition of one SUSAR

A teleconference will be scheduled within 72 hours if any of the aforementioned situations occur. This conference will be attended by the members of the IDMC and the ISC. At this teleconference the clinical relevance of the findings will be determined and recommendations may be made by the IDMC which may include:

- requesting further information
- modifying the protocol
- stopping enrolment
- institute more frequent monitoring guidelines
- termination of study

STUDY VISITS, PROCEDURES SCHEDULE and Patient Flow Diagram



	Visit 1	Phone follow up at 72 hours	Follow-up (by phone or email) after 4 weeks
Written Informed Consent (parent/ guardian) Written assent (child)	X X		
Medical assessment	X		
Asthma control questionnaire	X		
Vaccine administration followed by 30 mins observation	X		
Delayed effects telephone questionnaire at 72hrs		X	
Asthma control questionnaire at 4 weeks post LAIV in children with asthma/recurrent wheeze			X

Children who meet Department of Health criteria for specified 'clinical risk categories' (Table 3) and are under 9 years of age and have not received prior seasonal influenza vaccination in previous years will be offered a second dose of LAIV at least 4 weeks later. We expect very few children to meet the criteria for a second dose, as most would have received prior influenza vaccination. For example, using these criteria, no child enrolled in SNIFFLE 1 would have required a second dose. However, there is a duty of care to our participants and we are therefore including provision for a second dose in this protocol. Data pertaining to second visits will be collected on a separate CRF, but not used in the primary analysis.

Table 3: Clinical risk categories requiring a second dose of LAIV in vaccine-naïve children under age 9 years:

Chronic respiratory disease	• Asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. • Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). • Children who have previously been admitted to hospital for lower respiratory tract disease.
Chronic heart disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Chronic neurological disease	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological disease (e.g. polio syndrome sufferers). Clinicians should consider on an individual basis the clinical needs of patients including individuals with cerebral palsy, multiple sclerosis and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological or severe learning disability.
Diabetes	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.
Immunosuppression	Immunosuppression due to disease or treatment. Patients undergoing chemotherapy leading to immunosuppression. Asplenia or splenic dysfunction. HIV infection at all stages. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age); or for children under 20kg, a dose of 1mg or more per kg per day. It is difficult to define at what level of immunosuppression a patient could be considered to be at a greater risk of the serious consequences of influenza and should be offered influenza vaccination. This decision is best made on an individual basis and left to the patient's clinician. Some immunocompromised patients may have a suboptimal immunological response to the vaccine. NB: LAIV is not contraindicated for use in individuals with asymptomatic HIV infection; or individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency.

CONSENT

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

- Many families travel significant distances to specialist allergy clinics, often requiring the child to miss school and their parents/carers to miss work. In SNIFFLE 1, families frequently requested vaccination at the same time as their routine outpatient appointment, to avoid having to make a second trip to hospital. Many families declined to return to hospital for vaccination at a separate visit, and were thus left unvaccinated and at risk of infection. .
- The intervention in this study is part of the routine UK National Immunisation Schedule. The study allows egg-children to participate in this programme in a safe environment, utilising a vaccine delivery route (intranasal) which minimises discomfort to the child. No procedures outside the normal vaccination process are planned.

TELEPHONE FOLLOW UP VISIT

Participants' families will be contacted by the local research team at least 72 hours after LAIV administration (and within 7 days, to allow for weekends), to determine whether their child has experienced any delayed symptoms which might be attributable to the vaccine. This telephone consultation will take approximately 2 minutes. A guide for this telephone call is provided in Appendix 2. These data will be recorded on the CRF. Following this, the CRF will be deemed complete and forwarded to the coordinating centre.

If after three attempts (on three separate days) the local study team is unable to contact the family, the child will be deemed lost to follow up and this will be documented on the CRF, which will then be closed.

ASTHMA CONTROL ASSESSMENT AFTER 4 WEEKS POST VACCINATION

Where the participant has a physician diagnosis of asthma or recurrent wheeze, the participants' families will be contacted 4 weeks after LAIV administration to determine their child's asthma control, using the same validated tool as at visit 1. Families will be asked at visit 1 as to whether they prefer to be contacted by telephone by the local study team, or receive an email request with a link to a secure, online survey. Either way, the survey will take 2-3 minutes to complete. A guide for the telephone call is provided in Appendix 3. These data will be recorded on a CRF, which will then be forwarded to the coordinating centre

If the family fails to respond to the email request, the local study team will attempt to contact the family by telephone. If, after three attempts (on three separate days), the local study team is unable to contact the family, the child will be deemed lost to follow up and this will be documented on the CRF, which will then be closed.

CLINICAL ASSESSMENTS

SKIN PRICK TESTING

Existing data relating to skin prick testing to egg (where performed in routine clinical practice, according to BSACI guidelines (http://www.bsaci.org/Guidelines/Skin_Prick_Testing.pdf) and/or allergy blood tests (serum specific IgE to egg) will be collected from medical records, where available, to confirm sensitisation to egg.

No allergy testing will be performed as part of this protocol.

CLINICAL OBSERVATION / MONITORING OF PATIENTS BY CLINICAL STAFF

Patients will have baseline observations (temperature, heart rate, respiratory rate, oxygen saturations) performed prior to LAIV administration, with clinical respiratory and dermatological assessment at the same time.

Patients will be observed for at least 30 minutes after administration of LAIV, for symptoms of local or systemic allergic reaction. Symptoms (Total Nasal Symptom Score, TNSS) will be recorded at 10 and 30 minutes after vaccine administration, as follows:

<table>
<tr><th colspan="2">Total nasal symptom score (TNSS)</th></tr>
<tr><td>Rhinorrhoea</td><td rowspan="4">FOR EACH SYMPTOM, SCORE:

0 = no sign/symptom evident

1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)

2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)

3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living)</td></tr>
<tr><td>Nasal congestion</td></tr>
<tr><td>Nasal itch</td></tr>
<tr><td>Sneezing</td></tr>
</table>

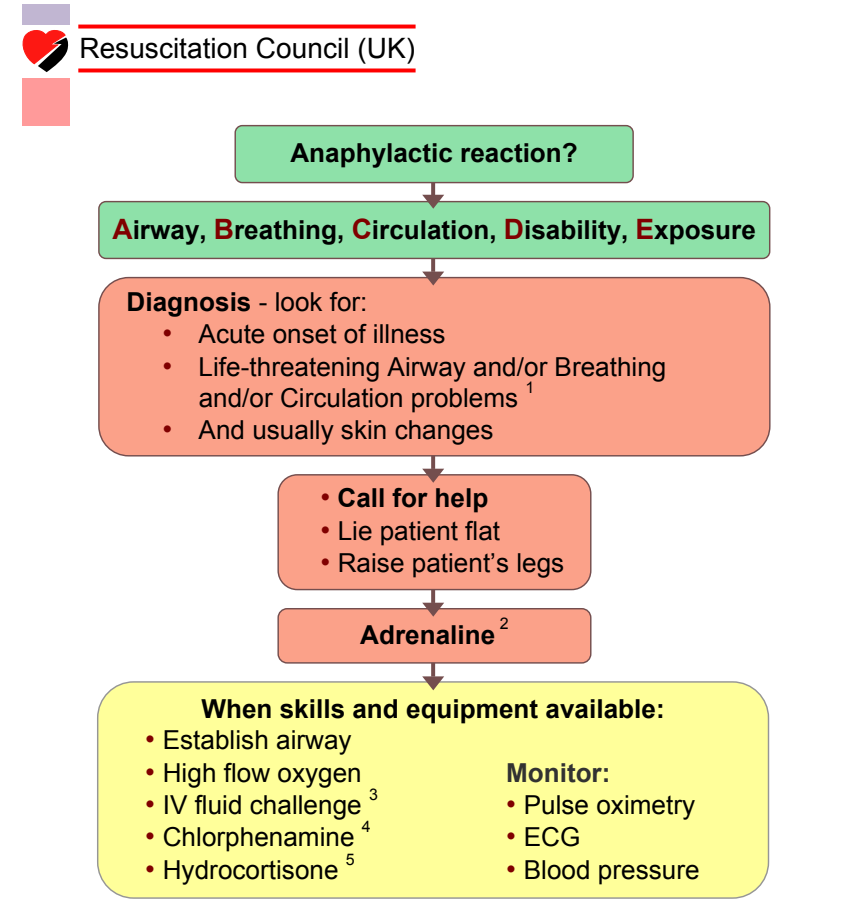
US Department of Health and Human Services Food and Drug Administration, Allergic Rhinitis: Clinical Development Programs for Drug Products; 2000.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf

Children will be observed in safe environment with appropriate clinical supervision and access to paediatric resuscitation facilities and trained staff, in the event of an anaphylactic reaction.

In the SNIFFLE study (2013/14 season), 8 children experienced possible local allergic symptoms following LAIV, all of which were mild and self-limiting. Symptoms commenced within 30 minutes of LAIV administration in all cases. Children will therefore be observed for 30 minutes, and if no symptoms are observed, discharged from the vaccine clinic. However, further clinical observations will be collected in the event of a clinical reaction, as per local policy.

TREATMENT OF ALLERGIC REACTIONS

Any allergic reaction happening during the observation period following vaccine administration will be managed according to local policy. For the purpose of this protocol, we would suggest that mild (non-anaphylactic) symptoms should be treated with a long-acting, non-sedating oral antihistamine such as cetirizine (at doses listed in cBNF). Symptoms of anaphylaxis will be treated according to UK Resuscitation Council guidelines (reproduced below).



1 Life-threatening problems:

Airway:	swelling, hoarseness, stridor
Breathing:	rapid breathing, wheeze, fatigue, cyanosis, SpO_2 < 92%, confusion
Circulation:	pale, clammy, low blood pressure, faintness, drowsy/coma

2 Adrenaline *(give IM unless experienced with IV adrenaline)*
IM doses of 1:1000 adrenaline (repeat after 5 min if no better)

• Adult	500 micrograms IM (0.5 mL)
• Child more than 12 years:	500 micrograms IM (0.5 mL)
• Child 6 -12 years:	300 micrograms IM (0.3 mL)
• Child less than 6 years:	150 micrograms IM (0.15 mL)

Adrenaline IV to be given **only by experienced specialists**
Titrate: Adults 50 micrograms; Children 1 microgram/kg

3 IV fluid challenge:
Adult - 500 – 1000 mL
Child - crystalloid 20 mL/kg

Stop IV colloid
if this might be the cause
of anaphylaxis

	4 Chlorphenamine (IM or slow IV)	5 Hydrocortisone (IM or slow IV)
Adult or child more than 12 years	10 mg	200 mg
Child 6 - 12 years	5 mg	100 mg
Child 6 months to 6 years	2.5 mg	50 mg
Child less than 6 months	250 micrograms/kg	25 mg

ADVERSE EVENT REPORTING

DEFINITIONS

An **adverse event** is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation, including occurrences that are not necessarily caused by or related to the administration of the medicinal product under investigation. An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

A **serious adverse event** (SAE) is defined as any adverse event that suggests a significant hazard. This includes but is not limited to any of the following:

1. Death: Any death that occurs during the study must be reported whether considered treatment related or not.

2. A life-threatening event: Any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred.

3. Inpatient hospitalization or prolongation of existing hospitalization.

4. Persistent or significant disability.

5. An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

An **adverse reaction** is a AE attributable to the medicinal product under investigation, in this case the Fluenz vaccine. If the adverse reaction meets the above criteria (1-6) then it is termed a **Serious Adverse Reaction** (SAR). Where the SAR is considered 'unexpected' i.e. its nature or severity is not consistent with the investigator's protocol, these events will be termed **serious unexpected severe adverse reactions** (SUSARS).

The adverse event or reaction can be described as 'expected' if it caused symptoms and/or signs that could be reasonably described as a consequence of an allergic reaction or following vaccination. Symptoms of an allergic reaction are defined as any described within this protocol, or those in the view of the investigator that are an expected consequence of vaccination.

Any symptoms requiring treatment for anaphylaxis (adrenaline, steroids, salbutamol) **will be classified as a SERIOUS ADVERSE REACTION** and must be documented on both the CRF as well as through completion of a SAE form. The local investigator should also make a notification to the MHRA should also be made through the yellow card scheme (https://yellowcard.mhra.gov.uk/).

For the purpose of this study, SARs and SAEs will only be collected where onset is within 72 hours of vaccine administration.

DOCUMENTATION OF ADVERSE EVENTS

Safety data will be recorded on a specifically designed case report form (CRF). All serious adverse events (SAEs) or reactions (SARs) will be reported on an SAE report in addition to CRFs. Safety data will be reviewed after three months by the Independent Data Monitoring Committee (IDMC). The IDMC has the authority to recommend termination of the trial because of safety findings.

Throughout the study, the investigator will record all adverse events on the appropriate CRF regardless of their severity or relation to study medication or study procedure. The investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. SAEs will be recorded on the SAE report form and reported to the ISC within 24 hours. SARs will also be reported to MHRA through the yellow card system.

GRADING AND ATTRIBUTION OF ADVERSE EVENTS

NON-ALLERGIC REACTIONS

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

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

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

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

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

The relation, or attribution, of an adverse event to study participation will be determined by the investigator and recorded on CRF and/or SAE reporting form. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below (Table 2). If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made relating to a SUSAR, the MHRA will be informed of both points of view.

Table 2: Assignment of causality for adverse events

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

GRADING AND ATTRIBUTION OF ADVERSE EVENTS: ALLERGIC REACTION

Allergic reactions to LAIV will be determined using the World Allergy Organisation (WAO) criteria for allergic reactions to immunotherapy, reproduced below. **For the purpose of this study**, mild symptoms of an allergic reaction (ie. non-anaphylactic symptoms) will be classified as non-serious adverse event, and should be documented on the CRF.

Any symptoms requiring treatment for anaphylaxis (adrenaline, steroids, salbutamol) **will be classified as a SERIOUS ADVERSE REACTION** and will be documented on both the CRF and a SAE form. The local investigator should also make a notification to the MHRA through the MHRA yellow card scheme.

On receipt of CRF / SAE forms, allergic reactions will be further classified by the ISC using World Allergy Organisation (WAO) criteria, which can be mapped to these grades and can be used to inform as to the appropriate NTI-CTCAE grade (Table 3).

Anaphylaxis will be defined as per the case definition and guidelines as described by the Brighton Collaboration Anaphylaxis Working Group (34) (see appendix 1).

WORLD ALLERGY ORGANISATION (WAO) GRADING SYSTEM FOR ALLERGIC REACTIONS TO IMMUNOTHERAPY

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present* **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth† **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/ or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/sign(s) of more than 1 organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV_1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (eg, 40% PEF or FEV_1 drop NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death

SERIOUS ADVERSE EVENT REPORTING

Serious adverse events and reactions must be reported to the PIs within 24 hours. An SAE/SUSAR form should be completed and faxed to the study coordination centre for all SAEs within 24 hours. This will then be communicated to the IDMC Chair, ISC chair and study sponsor. In the event of serious adverse reaction (expected), reporting should also include using the yellow card system.

In the case of suspected unexpected serious adverse reactions (SUSARS), the staff at the site should:

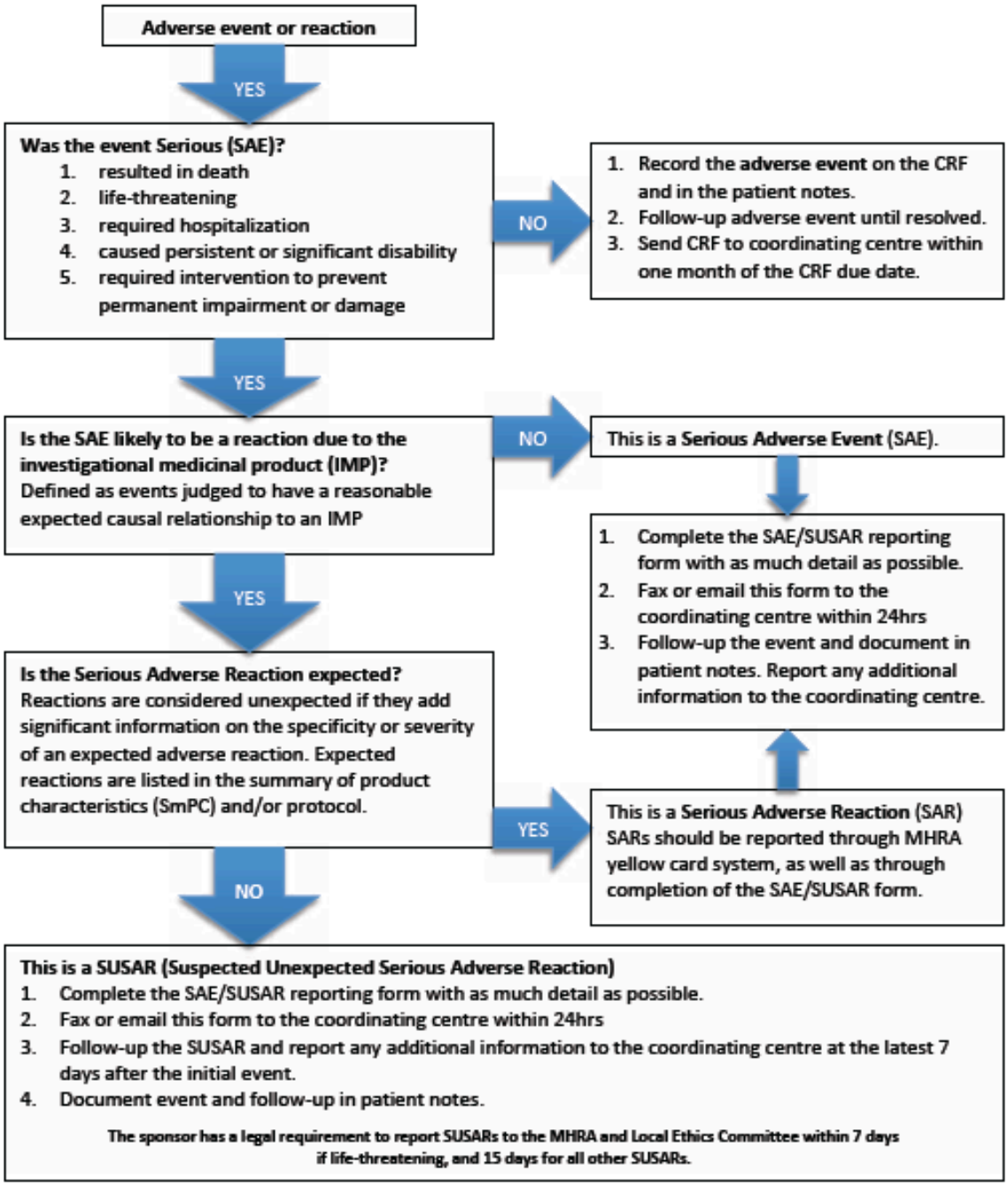
Complete the SAE case report form & send it immediately (within 24 hours, preferably by email or fax), signed and dated to the study coordination centre together with relevant treatment forms and anonymous copies of all relevant investigations.

Or

Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines: fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by local requirements including the appropriate local Research & Development Office.

SUMMARY AND CONTACT DETAILS FOR REPORTING SAE AND SUSARS



Contact details for reporting SAEs and SUSARs:

Fax: 020 3312 7571, attention Dr Paul Turner

Email: p.turner@imperial.ac.uk

STATISTICAL METHODS

SAMPLE SIZE ESTIMATION

Sample size is considered with respect to a historical comparison and also based on the precision around an estimate of 0%.

The SNIFFLE 1 study reported no systemic allergic reactions with 433 doses of LAIV administered to 282 egg-allergic children. On the basis of these data, the 95% upper confidence interval for occurrence of a significant allergic reaction to LAIV in egg-allergic children is <0.85%.

If, in a sample size of 730, there are no systemic or significant local allergic reactions, then this would provide confidence (at the 95% CI) that the true rate of allergic reaction to LAIV in egg-allergic children within the population is no more than 0.5%.

POPULATION TO BE ANALYSED

Children aged 2-17 years old with a physician-diagnosis of egg allergy as defined above.

STATISTICAL ANALYSIS PLAN

The incidence of reactions to LAIV (both immediate and delayed) will be estimated with 95% confidence intervals. Comparison to historical rates will be by Fisher's exact test. For the subgroup analyses, incidence of reactions will be compared between different cohorts (e.g. children with and without prior anaphylaxis to egg protein. Statistical differences will be determined using Fisher's exact test for proportions or using non-parametric tests for graded reactions. Sub-group analyses will be performed using the following criteria:

- Likelihood of clinical egg allergy (<95% and >95% likelihood)
- Severity of egg allergy
- Severe egg allergy – i.e. prior anaphylaxis to egg protein
- Baked egg tolerant
- Previous respiratory reactions to airborne egg
- Presence of physician-diagnosed asthma / recurrent wheeze
- Age: 2-5, 6-11, 12-17 years
- Children who have previously received influenza vaccine

INTERIM ANALYSIS

An interim analysis to assess the safety profile will be conducted after 100 participants have been recruited and received LAIV, the results of which will be reported to the IDMC Chair.

DATA MANAGEMENT

DATA COLLECTION

The following data will be collected:

- Patient demographics
- Current health to establish safety of immunisation
- Vaccination history:
  - previous exposure to influenza vaccine
  - previous reactions to vaccines
- Egg allergy:
  - Previous anaphylaxis? Tolerates baked egg? Respiratory symptoms to aerosolised egg?
  - Most severe reaction to egg: grading (WAO criteria)
  - Timing of most recent reaction
  - Recent diagnostic criteria: Skin test / serum specific IgE
  - Current egg avoidance
- Past medical history:
  - Medical indication for influenza vaccination or routine
  - Asthma: stable, uncontrolled
  - Active Allergic rhinitis
  - Current Medication including drug allergies
  - Other atopy: allergic rhinitis, eczema, other food allergies

Data will initially be submitted by a secure online data management system already used within Public Health England for vaccine surveillance. This data will be de-identified and accessible to the study team. Paper records kept locally at the study sites which will be identified by a study number.

DATA STORAGE

Paper records will be kept locally at the study sites which will be identified by a study number, within patient notes. De-identified patient data will be stored at the Immunisation Department, Public Health England and submitted to the study team using an online data management system.

De-identified study data will be kept for the statutory period and then disposed of securely. Local paperwork will be kept as part of the patient notes/CRF as per local policy.

ADMINISTRATIVE ASPECTS

ETHICAL COMPLIANCE

Approval will be sought from the West Midlands – Edgbaston National Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Study Coordination Centre will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions

INFORMED CONSENT AND PARTICIPANT ASSENT

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

CONFIDENTIALITY

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Email addresses for families will be entered into a secure encrypted online database managed by UK Department of Health through Public Health England. The email addresses will be destroyed at the termination of the study.

PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. No unauthorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the ISC and approved by the ethics committee it cannot be implemented. All significant protocol deviations will be recorded and reported.

MODIFICATIONS OF THE PROTOCOL

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the ISC and the ethics committee. Only amendments that are required for patient safety may be implemented prior to ethics approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, The PIs should be notified of this action within 24 hours and the ethics committee should be informed within 10 working days.

FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

The CIs declare no financial interests or conflicts of interest relating to this study.

USE OF DATA AND PUBLICATIONS POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigators, Statistician and Trial Coordinator, but not local PIs unless they have contributed to the writing of the manuscript. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

REFERENCES

1. Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. Allergy. 2001;56(5):403-11.

2. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. JAllergy ClinImmunol. 2007;120(6):1413-7.

3. Gagnon R, Primeau MN, Roches AD, Lemire C, Kagan R, Carr S, et al. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. JAllergy ClinImmunol. 2010.

4. Des Roches A, Paradis L, Gagnon R, Lemire C, Begin P, Carr S, et al. Egg-allergic patients can be safely vaccinated against influenza. J Allergy Clin Immunol. 2012;130(5):1213-6 e1.

5. Erlewyn-Lajeunesse M, Brathwaite N, Lucas JS, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. BMJ. 2009;339:b3680.

6. Erlewyn-Lajeunesse M, Lucas JS, Warner JO. Influenza immunization in egg allergy: an update for the 2011-2012 season. Clin Exp Allergy. 2011;41(10):1367-70.

7. Clark AT, Skypala I, Leech SC, Ewan PW, Dugue P, Brathwaite N, et al. British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. Clin Exp Allergy. 2010;40(8):1116-29.

8. Esposito S, Montinaro V, Groppali E, Tenconi R, Semino M, Principi N. Live attenuated intranasal influenza vaccine. Human vaccines & immunotherapeutics. 2012;8(1):76-80.

9. Ambrose CS, Wu X, Knuf M, Wutzler P. The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: a meta-analysis of 8 randomized controlled studies. Vaccine. 2012;30(5):886-92.

10. Belshe RB, Toback SL, Yi T, Ambrose CS. Efficacy of live attenuated influenza vaccine in children 6 months to 17 years of age. Influenza and other respiratory viruses. 2010;4(3):141-5.

11. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. The Lancet infectious diseases. 2012;12(1):36-44.

12. Rhorer J, Ambrose CS, Dickinson S, Hamilton H, Oleka NA, Malinoski FJ, et al. Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials. Vaccine. 2009;27(7):1101-10.

13. Belshe RB, Ambrose CS, Yi T. Safety and efficacy of live attenuated influenza vaccine in children 2-7 years of age. Vaccine. 2008;26 Suppl 4:D10-6.

14. 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. The New England journal of medicine. 2007;356(7):685-96.

15. Ambrose CS, Dubovsky F, Yi T, Belshe RB, Ashkenazi S. The safety and efficacy of live attenuated influenza vaccine in young children with asthma or prior wheezing. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2012;31(10):2549-57.

16. Gaglani MJ, Piedra PA, Riggs M, Herschler G, Fewlass C, Glezen WP. Safety of the intranasal, trivalent, live attenuated influenza vaccine (LAIV) in children with intermittent wheezing in an open-label field trial. The Pediatric infectious disease journal. 2008;27(5):444-52.

17. Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. The Pediatric infectious disease journal. 2006;25(10):860-9.

18. Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine. 2011;29(31):4947-52.

19. Toback SL, Ambrose CS, Eaton A, Hansen J, Aukes L, Lewis N, et al. A postlicensure evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 24-59 months of age. Vaccine. 2013;31(14):1812-8.

20. Izurieta HS, Haber P, Wise RP, Iskander J, Pratt D, Mink C, et al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. JAMA. 2005;294(21):2720-5.

21. Ambrose CS, Yi T, Falloon J. An integrated, multistudy analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2-17 years. Influenza and other respiratory viruses. 2011;5(6):389-97.

22. Baxter R, Toback SL, Sifakis F, Hansen J, Bartlett J, Aukes L, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age. Vaccine. 2012;30(19):2989-98.

23. Kelso JM. Safety of influenza vaccines. Current opinion in allergy and clinical immunology. 2012;12(4):383-8.

24. Tennis P, Toback SL, Andrews EB, McQuay LJ, Ambrose CS. A US postmarketing evaluation of the frequency and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years: 2009-2010 season. Vaccine. 2012;30(42):6099-102.

25. Vasu N, Ghaffari G, Craig ET, Craig TJ. Adverse events associated with intranasal influenza vaccine in the United States. TherAdvRespirDis. 2008;2(4):193-8.

26. Vesikari T. Emerging data on the safety and efficacy of influenza vaccines in children. The Pediatric infectious disease journal. 2008;27(11 Suppl):S159-61.

27. Toback SL, Levin MJ, Block SL, Belshe RB, Ambrose CS, Falloon J. Quadrivalent Ann Arbor strain live-attenuated influenza vaccine. Expert review of vaccines. 2012;11(11):1293-303.

28. Blom WM, Vlieg-Boerstra BJ, Kruizinga AG, van der Heide S, Houben GF, Dubois AE. Threshold dose distributions for 5 major allergenic foods in children. J Allergy Clin Immunol. 2013;131(1):172-9.

29. Eller E, Hansen TK, Bindslev-Jensen C. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2012;108(5):332-6.

30. Clark A, Mangat J, King Y, Islam S, Anagnostou K, Foley L, et al. Thermographic imaging during nasal peanut challenge may be useful in the diagnosis of peanut allergy. Allergy. 2012;67(4):574-6.

31. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997;100(4):444-51.

32. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2004;15(5):435-41.

33. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy. 2000;30(11):1540-6.

34. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

APPENDIX 1: BRIGHTON COLLABORATION CASE DEFINITION OF ANAPHYLAXIS[35]

Anaphylaxis is a clinical syndrome characterized by:

- sudden onset AND
- rapid progression of signs and symptoms AND
- involving multiple (≥2) organ systems, as follows:

Level 1 of diagnostic certainty • ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion AND • ≥1 major dermatological criterion
Level 2 of diagnostic certainty • ≥1 major cardiovascular AND ≥1 major respiratory criterion OR • ≥1 major cardiovascular OR respiratory criterion AND • ≥1 minor criterion involving ≥1 different system (*other than* cardiovascular or respiratory systems) OR • (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion)
Level 3 of diagnostic certainty • ≥1 minor cardiovascular OR respiratory criterion AND • ≥1 minor criterion from each of ≥2 different systems/categories

Note that all levels of diagnostic certainty **require the involvement the cardiovascular and/or respiratory systems**.

Organ System	Major Criteria	Minor Criteria
Skin or mucosal	• generalized urticaria (hives) or erythema • angioedema, localized or generalized • generalized pruritus with skin rash	• generalized pruritus without skin rash • generalized prickle sensation • localized injection site urticaria • red and itchy eyes
Cardiovascular	• measured hypotension OR • shock (at least 3 of the following): ▪ tachycardia ▪ capillary refill time (CRT) >3 sec ▪ reduced central pulse volume ▪ decreased level or loss of consciousness	• Reduced peripheral circulation (at least 2 of: • Tachycardia • CRT >3 sec without hypotension • Decreased level of consciousness
Respiratory	• Bilateral wheeze (bronchospasm) • Stridor • Swelling of upper airways • Respiratory distress (at least 2 of tachypnoea; use of accessory respiratory muscles; recession; cyanosis; grunting)	• Persistent dry cough • Hoarse voice • Difficulty breathing without wheeze or stridor • Sensation of throat closure
Gastrointestinal		• Diarrhoea • Abdominal pain • Nausea • Vomiting
Laboratory		Mast cell tryptase > upper normal limit

NB: For the purposes of this study, local rhinitis and oropharyngeal symptoms will be classed as LOCAL symptoms and not indicative of a systemic allergy response.

APPENDIX 2: TOPIC GUIDE FOR 72HR TELEPHONE FOLLOW-UP

Participants' families will be contacted by the local research team at least 72 hours after LAIV administration (and within 7 days, to allow for weekends), to determine whether their child has experienced any delayed symptoms which might be attributable to the vaccine. This telephone consultation will take approximately 2-3 minutes. If after three attempts (on three separate days) the local study team is unable to contact the family, the child will be deemed lost to follow up.

Guide to telephone interview:

1. Confirm interviewee's identity

2. Introduce yourself:

   "I am <name>, from the SNIFFLE-2 Study. We arranged to speak briefly today to find how <participant's name> is going after his/her 'flu vaccine on <date>"

3. "*Have you noticed any health problems since the vaccine?"*

4. For each symptom reported:
   - *When did this start?*
   - *How long did this last?*
   - *Did you do anything as a result?*

APPENDIX 3: TOPIC GUIDE FOR TELEPHONE FOLLOW-UP AT 4 WEEKS

** For patients with asthma/recurrent wheeze only **

Participants' families will be contacted by the local research team between 4-5 weeks after LAIV administration, to determine whether their child has experienced any change in their lower respiratory symptoms which might be attributable to the vaccine. This telephone consultation will take approximately 2-3 minutes. If after three attempts (on three separate days) the local study team is unable to contact the family, the child will be deemed lost to follow up.

Guide to telephone interview:

1. Confirm interviewee's identity

2. Introduce yourself:

   "I am <name> from the SNIFFLE-2 Study. Your child <participant's name> had the 'flu vaccine with us one month ago, and we arranged to speak to find out if you had needed to do anything different with his asthma/wheezing"

3. Complete appropriate Asthma Control Questionnaire over the telephone

   (see separate questionnaires)

4. Finally, ask the following questions:

   i) Since the vaccine, have you had to take <participant's name> to see a Doctor because of his/her breathing?
   ii) (If YES) – did you have to take them to hospital?
   iii) (If YES) – did <participant's name> have to stay in hospital overnight?