Safety of Nasal Influenza Immunisation in Children with Asthma:

The SNIFFLE 4 study

VERSION 2.2, 5 September 2016

SPONSOR: Imperial College Healthcare NHS Trust

FUNDING: Department of Health Policy Research Programme (NVEC039/0031)

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This protocol describes the SNIFFLE 4 study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

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

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

Protocol authorised by:

Name & Role	**Date**	**Signature**

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	*Details of Changes made*
1	*2.1*	***14 Aug 2016*** *Approved by:* ***REC: 2 Sept 16*** ***HRA: pending***	*Paul Turner*	1) Following discussions with PHE and DoH, remove "surveillance nasal swabs" during influenza season, and instead take nasal swabs during the 7 days post vaccination to assess for viral shedding. 2) Update PILs and consents to incorporate nasal swabbing as in (1) above. 3) Update PILs and consents to include IRAS/HRA reference numbers as requested by HRA
2	*2.2*	***5 Sept 2016*** *Approved by:* ***REC: pending*** ***HRA: pending***	*Paul Turner*	1. Clarify consent procedure to be followed for participants who turn 16 years in the 4 weeks following vaccination. 2. Clarify eligibility criteria in line with analysis plan as outlined in section 9. 3. Include further details regarding statistical analysis [section 9.2] 4. Minor clarifications and corrections: i. Correct name/title of PIS 16-17 year olds to PIS 16+years (to remove confusion over which PIS to be used in young people age 18 yrs and ensure consistency with consent forms). ii. Clarify exclusion regarding ICU admission (that this relates to intubation+ventilation) iii. Clarify "hospitalisation" in children age 2-4 years means observation in hospital > 4hrs.

PROTOCOL SYNOPSIS

Title	Safety of Nasal Influenza Immunisation in Children with Asthma
Abbreviated title	SNIFFLE 4 study
Eudra CT registration no.	2016-002352-24
HRA NREC Number	16/WM/0276
Sponsor R&D Number	16SM3348
Clinicaltrials.gov registration no.	NCT02866942
HRA IRAS / UKCRN reference	207822
Primary objective	To assess changes in asthma symptoms / symptom control following LAIV in children with asthma / recurrent wheezing, including children with difficult/severe asthma.
Intervention and key procedures	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). Nasal swab (collected by parent) in the event of flu like illness from January 2017 until end of Influenza season (approx. April 2017)
Safety	Participants will be immunised in the hospital environment, by personnel qualified in the recognition and treatment of anaphylaxis, and observed for at least 20 minutes following a dose. Families will be contacted at 72 hours after immunisation to establish the occurrence of any delayed effects. Completion of validated questionnaire at 4 weeks after LAIV.
Patient group	Children and young people with asthma / recurrent wheezing attending paediatric outpatients, aged 2-18 years old (inclusive). Target recruitment of 840 subjects.
Primary outcome	Change in asthma symptoms and control pre and 4 weeks post LAIV, as assessed by validated questionnaire: • Age 2-4 years: TRACK questionnaire • Age 5-11 years: C-ACT score • Age 12+ years: ACT score
Secondary outcomes	1. Incidence of adverse events (AEs) and serious adverse events (SAEs) following LAIV 2. To document influenza virus shedding in the week following vaccination with LAIV
Sponsor	Imperial College Healthcare NHS Trust
Funding	Department of Health Policy Research Programme (NVEC039/0031)

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GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
BDP	Beclomethasone dipropionate
BDR	Bronchodilator responsiveness
BTS / SIGN	British Thoracic Society / Scottish Intercollegiate Guidelines Network
C-ACT	Childhood Asthma Control Test
CRF	Case report form
DoH	Department of Health (England)
FeNO	Fractional exhaled nitric oxide
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
LAIV	Live Attenuated Influenza Vaccine (Intranasal, live)
LRTA	Leukotriene Receptor Antagonist
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PHE	Public Health England
PSW	Preschool wheeze
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIV	Trivalent Influenza Vaccine (Intramuscular, killed)
TRACK	Test for Respiratory and Asthma Control in Kids
TSC	Trial Study Committee

INVESTIGATORS AND FACILITIES

LEAD STUDY CENTRE AND NATIONAL COORDINATING CENTRE

Imperial College Healthcare NHS Trust / 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

CHIEF INVESTIGATOR

Name	Dr Paul Turner BM BCh FRACP MRCPCH PhD
Position	MRC Clinician Scientist & Hon Consultant in Paediatric Allergy & Immunology
Institution	Imperial College Healthcare NHS Trust / 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

TRIAL STATISTICIAN

Name	Prof 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

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 7754
Fax	020 3312 7571
Email	h.hanna@imperial.ac.uk

CO-INVESTIGATORS

IMPERIAL COLLEGE LONDON

Name	Dr Sejal Saglani
Position	Reader and Hon Consultant in Paediatric Respiratory Medicine
Institution	Imperial College London / Royal Brompton & Harefield NHS Foundation Trust
Address	Royal Brompton Hospital, Sydney Street, London SW3 6NP
Phone	020 7594 3167
Email	s.saglani@imperial.ac.uk

Name	Dr Louise Fleming
Position	Clinical Senior Lecturer and Hon Consultant in Paediatric Respiratory Medicine
Institution	Imperial College London / Royal Brompton & Harefield NHS Foundation Trust
Address	Royal Brompton Hospital, Sydney Street, London SW3 6NP
Phone	020 7352 8121 ext 2938
Email	L.Fleming@rbht.nhs.uk

PUBLIC HEALTH ENGLAND

Name	Professor Elizabeth Miller
Position	Consultant Epidemiologist
Institution	Immunisation Hepatitis and Blood Safety Department, Public Health England
Address	61 Colindale Avenue, London NW9 5EQ
Phone	020 8327 7430
Email	liz.miller@phe.gov.uk

Name	Dr Jo Southern MSc PhD MICR CSci MFPH
Position	Senior Clinical Scientist, Epidemiology
Institution	Immunisation Hepatitis and Blood Safety Department, Public Health England
Address	61 Colindale Avenue, London NW9 5EQ
Phone	020 8327 6021
Email	jo.southern@phe.gov.uk

SITES AND PRINCIPLE INVESTIGATORS

BIRMINGHAM

Name	Dr Prasad Nagakumar & Dr Satish Rao
Position	Consultant in Paediatric Respiratory Medicine
Institution	Birmingham Children's Hospital NHS Foundation Trust
Address	Steelhouse Lane , Birmingham, B4 6NH
Phone	0121 333 8199
Email	Prasad.Nagakumar@bch.nhs.uk / satish.rao@bch.nhs.uk

BRIGHTON

Name	Dr Paul Seddon & Dr Katy Fiddler
Position	Consultant in Paediatric Respiratory Medicine
Institution	Brighton & Sussex University Hospitals NHS Trust
Address	Royal Alexandra Children's Hospital, Eastern Road, Brighton BN2 5BE
Phone	01273 696955
Email	seddop@gmail.com

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

LEEDS

Name	Dr Alexandra Adams
Position	Consultant in Paediatric Respiratory Medicine
Institution	Leeds Children's Hospital
Address	Leeds General Infirmary, Great George Street, Leeds, LS1 3EX
Phone	0113 392 7125
Email	Alexandra.adams2@nhs.net

LEICESTER

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

LIVERPOOL

Name	Dr Ian Sinha
Position	Consultant in Respiratory Medicine
Institution	Alder Hey Children's Hospital NHS Foundation Trust
Address	Eaton Road, West Derby, Liverpool L12 2AP
Phone	0151 228 4811 x2777
Email	Ian.Sinha@alderhey.nhs.uk

LONDON: KING'S COLLEGE HOSPITAL

Name	Dr Atul Gupta
Position	Consultant in Paediatric Respiratory Medicine
Institution	Kings College Hospital NHS Foundation Trust
Address	Denmark Hill, London SE5 9RS
Phone	020 3299 4574
Email	Atulgupta1@nhs.net

LONDON: ROYAL BROMPTON HOSPITAL

Name	Dr Sejal Saglani / Dr Louise Fleming
Position	Hon Consultants in Paediatric Respiratory Medicine
Institution	Imperial College London / Royal Brompton & Harefield NHS Foundation Trust
Address	Royal Brompton Hospital, Sydney Street, London SW3 6NP
Phone	020 7594 3167
Email	s.saglani@imperial.ac.uk / L.Fleming@rbht.nhs.uk

LONDON: ST MARY'S HOSPITAL

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

MANCHESTER

Name	Dr Stephen Hughes & Dr Clare Murray
Position	Consultant Paediatric Immunologist / Consultant in Paed Respiratory Medicine
Institution	Royal Manchester Children's Hospital
Address	Oxford Road, Manchester, M13 9WL
Phone	0161 701 0678
Email	stephen.hughes@cmft.nhs.uk / Clare.murray@manchester.ac.uk

NEWCASTLE

Name	Dr Sam Moss
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 282 0673
Email	Samantha.Moss@nuth.nhs.uk

OXFORD

Name	Dr Andrew Ives
Position	Consultant in Paediatric Respiratory Medicine
Institution	Oxford University Hospitals NHS Foundation Trust
Address	Children's Hospital, John Radcliffe Hospital, Headley Way, OX3 9DU
Phone	01865 234194
Email	andrew.ives@ouh.nhs.uk

SHEFFIELD

Name	Dr Nicola Jay / Dr Sonal Kansra
Position	Consultant Paediatrician / Consultant in Paediatric Respiratory Medicine
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 / 7672
Email	Nicola.jay@sch.nhs.uk / sonal.kansra@sch.nhs.uk

SOUTHAMPTON

Name	Prof Graham Roberts & Dr Mich Erlewyn-Lajeunesse
Position	Professor and Hon Consultant Paediatrician in Paediatric Allergy and Respiratory Medicine / 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 6160 / 023 8120 4335
Email	g.c.roberts@soton.ac.uk / Mich.Lajeunesse@soton.ac.uk

TRIAL STUDY COMMITTEE (TSC)

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 TSC will consist of:

- Dr Paul Turner (CI)
- Prof Liz Miller (Co-investigator)
- Dr Jo Southern (Co-investigator)
- Dr Louise Fleming (Co-investigator)
- Dr Sejal Saglani (Co-investigator)

INDEPENDENT DATA MONITORING COMMITTEE

A 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 TSC. The following membership has been confirmed:

- Dr Glenis Scadding [Chairperson] (Consultant in Rhinology and Allergy, London)
- Prof. Jürgen Schwarze (Edward Clark Chair of Child Life and Health, University of Edinburgh)
- Dr Andrew Riordan (Consultant in Paediatric Immunology and Infectious Diseases, Liverpool)
- Dr Andre Charlett (Director of Statistics Unit, Public Health England)

SPONSOR

Imperial College Healthcare NHS Trust, Sponsor number: 16SM3348

CONTACT:

Name	Joanne Siwoniku
Position	Clinical Trials Manager, Joint Research Compliance Office
Institution	Imperial College London and Imperial College Healthcare NHS Trust
Address	Room 221, Medical School Building, Norfolk Place
City	London
Postcode	W2 1PG
Phone	020 7594 6245
Email	j.siwoniku@imperial.ac.uk

FUNDING AND RESOURCES

Funding has been obtained from the Department of Health Policy Research Programme (NVEC039/0031) awarded to Prof Elizabeth Miller, Public Health England.

1. INTRODUCTION

1.1 BACKGROUND

Data collected during previous pandemic situations, as well as mathematical modelling of mixing patterns and infectivity, have shown that children serve as the most important reservoir for influenza infection and transmission.[1,2]

Vaccinating children may therefore provide the most effective method for interrupting the chain of transmission and so achieving disease control. This was recognised by the Joint Committee for Vaccination and Immunisation (JCVI), who at its meeting in June 2012 recommended the annual vaccination of all children aged 2-16 years of age with the live attenuated influenza vaccine (LAIV). LAIV has been shown to be more effective in this age group than the inactivated trivalent influenza vaccine (TIV) which, though recommended for annual vaccination children with specific risk factors, has variable efficacy in young children depending on the match between vaccine and circulating strains.[3]

The safety of LAIV in non-atopic children has been demonstrated in a number of published studies,[4] and to date over 1 million doses have been given. However, LAIV contains very small amounts of egg protein (ovalbumin) and until recently has been contraindicated in children with egg allergy. The SNIFFLE-1[5] and SNIFFLE-2 studies[6], commissioned by Public Health England, demonstrated the safety of LAIV in children with egg allergy. A total of 1237 doses were administered in 887 children, with no systemic allergic or anaphylactic reactions observed. Administration of LAIV in children with a history of asthma or recurrent wheezing did not affect asthma control.[6] This is important, because USA guidelines currently recommend against the use of LAIV in children with a history of wheezing in the preceding 12 months,[7] although the evidence for this recommendation is poor.[5,6] However, due to the small numbers of children on high-dose inhaled corticosteroids (BTS/SIGN step 4+ treatment), only limited conclusions could be drawn regarding the safety of LAIV in children with "severe asthma" (defined as BTS/SIGN step 4+ therapy).

We now wish to assess the safety of LAIV in children with asthma, including those children with "severe asthma" or "difficult-to-control" symptoms, to increase the safety data in this sub-population.

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[1]JCVI Statement on the Routine Annual Influenza Vaccination Programme – Extension of the Programme to Children, 2012. https://www.gov.uk/government/publications/jcvi-statement-on-the-routine-annual-influenza-vaccination-programme

[2]Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. PLoS Med. 2013 Oct;10(10):e1001527. doi: 10.1371/journal.pmed.1001527.

[3]Heikkinen T, Heinonen S. Effectiveness and Safety of Influenza Vaccination in Children: European Perspective. Vaccine. 2011 Oct 6;29(43):7529-34

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

[5] Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M; on behalf of the SNIFFLE Study Investigators. Safety of live attenuated influenza vaccine in atopic children with egg allergy. J Allergy Clin Immunol. 2015;136:376-81.

[6]Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M; SNIFFLE-2 Study Investigators. Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study. BMJ. 2015; 351:h6291.

[7] Grohskopf, L.A., Olsen, S.J., Sokolow, L.Z., Bresee, J.S., Cox, N.J., Broder, K.R. et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014-15 Influenza Season. MMWR Morb Mortal Wkly Rep. 2014; 63: 691–697

Figure 1a: BTS/SIGN Management steps: Children / young people aged over 12 years:

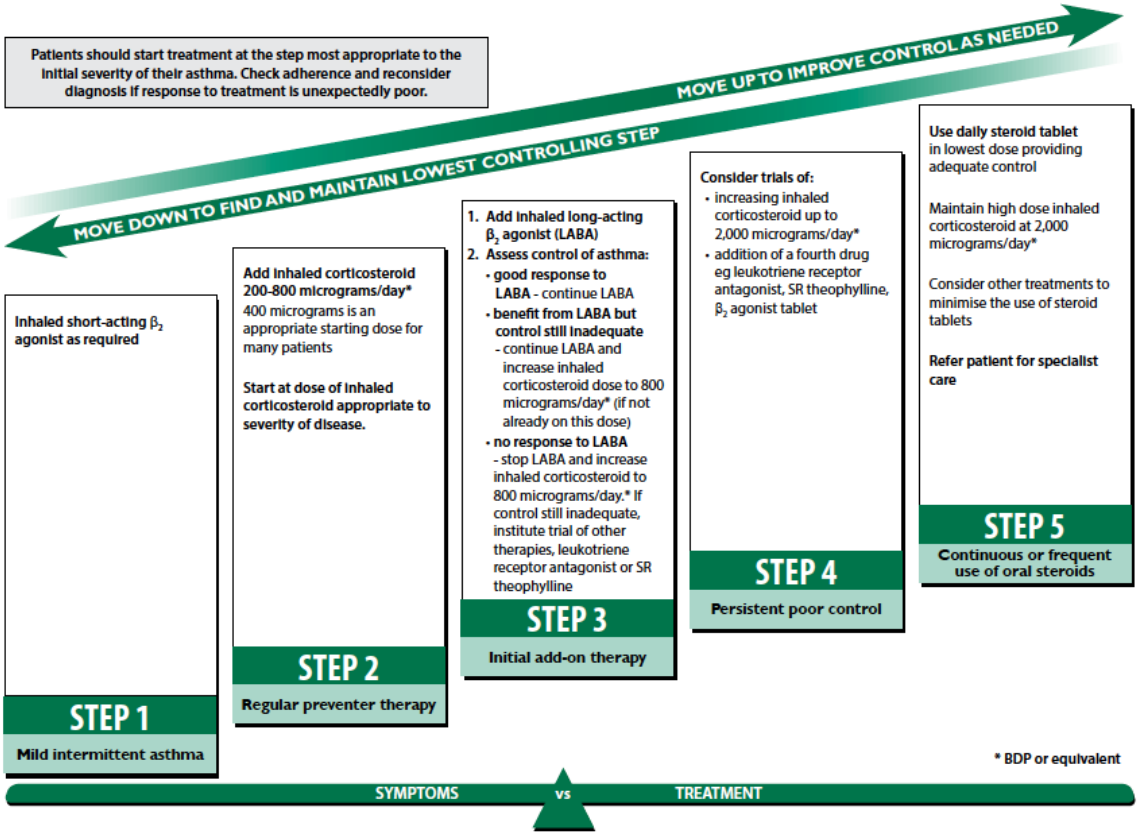


Figure 1b: BTS/SIGN Management steps: Children aged 5-12 years:

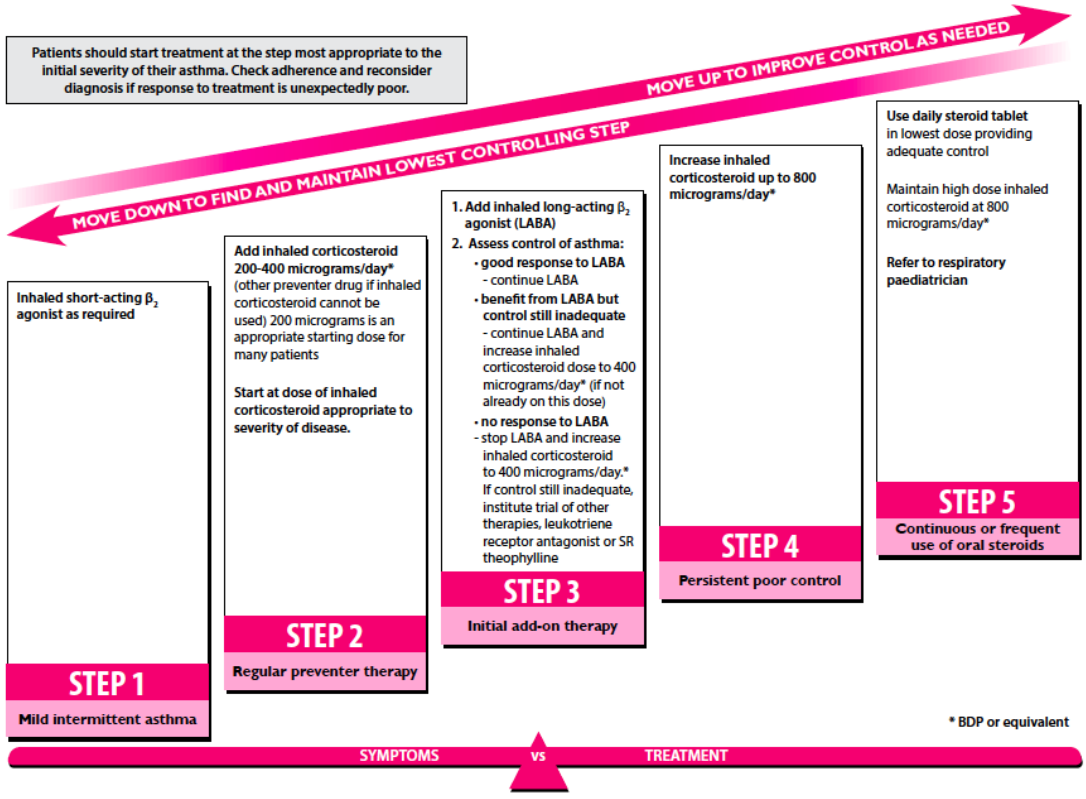
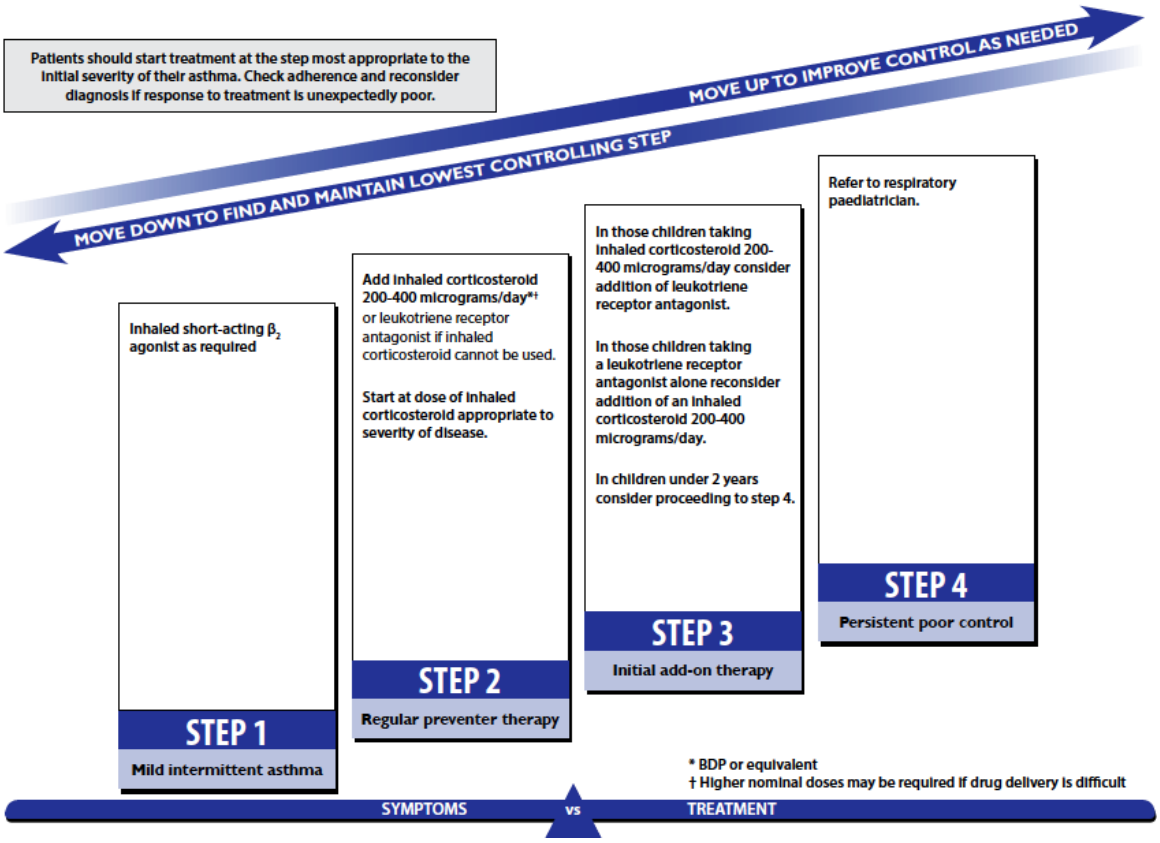


Figure 1c: BTS/SIGN Management steps: Children aged under 5 years:



LAIV results in nasal viral shedding for 7-10 days after administration,[8] an effect more predominant in younger children. It is this which has resulted in the recommendation for LAIV not be administered in the context of a close relative with immunodeficiency, although the viral components in LAIV are attenuated so that the risk of causing infection is negligible.

Data from the USA over recent years has demonstrated reduce vaccine efficacy (VE) for LAIV; this was initially attributed to vaccine lability with inappropriate temperature-controlled handling, and resulted in a change in strains included in the vaccine. However, despite this, VE reported for North America has dropped further, and the vaccine is no longer recommended in the USA.[9] In contrast, VE in the UK and other countries continues to be high, around 60% (slightly greater than the injected influenza vaccine in children) with up to 80% efficacy against influenza B strains.[10] These data continue to support the use of LAIV in children in the UK.

However, it is unclear as to why vaccine efficacy is so different between UK and USA. One hypothesis is that underlying LAIV immunity, induced by previous LAIV vaccination in individuals, can reduce the ability of subsequent vaccine to induce an immune response. It is noteworthy that LAIV has been used in the USA since 2003, a decade earlier than in the UK. In order to obtain data relating to support or refute this hypothesis, we intend to study vaccine shedding in the 10 days following LAIV administration in this study. We will also correlate vaccine shedding with reported adverse events following vaccination, to see if there is an association present.

[8] Block SL, Yogev R, Hayden FG, Ambrose CS, Zeng W, Walker RE. Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5-49 years of age. Vaccine 2008;26(38):4940-6.
Mallory RM, Yi T, Ambrose CS. Shedding of Ann Arbor strain live attenuated influenza vaccine virus in children 6-59 months of age. Vaccine 2011;29(26):4322-7.
[9] http://www.cdc.gov/media/releases/2016/s0622-laiv-flu.html
[10]https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/530756/Influenza_vaccine_effectiveness_in_primary_care_in_children.pdf

1.2 RESEARCH QUESTION

To assess the safety of LAIV (Fluenz®, Astra Zeneca) in children with asthma or a history of recurrent wheezing, age 2-18 years.

1.3 STUDY RATIONALE & JUSTIFICATION

The JCVI has recommended annual influenza vaccination for all children 2-16 years of age. The programme commenced using Fluenz in the 2013/2014 influenza season, was initially restricted to children under 4 years of age for logistic reasons, but is subsequently being expanded over the next few years to include all children under 16 years.

To date, there are only limited data available regarding the safety of LAIV in children with "severe" asthma requiring high dose inhaled corticosteroid therapy (or more intensive treatment). In the SNIFFLE-1 and -2 studies, only 49 children were included requiring BTS Step 4+ treatment. This lack of data is reflected in the current guidance from Department of Health:

> "There is limited safety data on children who are currently taking a high dose of an inhaled steroid – Budesonide >800 mcg/day or equivalent (e.g. Fluticasone >500 mcgs/day) – such children should only be given LAIV on the advice of their specialist."

This study will enrol 840 children with a history of asthma or recurrent wheezing (target 420 at BTS 4+ or greater, the remaining 420 participants at lesser levels of treatment), to obtain further safety data relating to the administration of LAIV in this group of children and thus inform UK guidance with regard to LAIV.

The study includes an assessment of influenza virus shedding following LAIV. Though efficacy of the vaccine has been maintained in the first few years of LAIV use in the UK, this is not so in the USA where it has been used for the last decade. The unique cohort included in this study provide an opportunity to assess viral shedding in the period immediately after vaccination, through parental collection of nasal swabs at three time points in the week following vaccination, which will be posted in prepaid bags directly to the testing laboratory at PHE Colindale. This will likely be 24 hours, 72 hours and 6 days after vaccination but these time points will be confirmed nearer the start of the study based on international data which is being gathered and published now. There may be a correlation between vaccine shedding and adverse events following vaccination. The data will also help inform as to whether there is a link between vaccine shedding and previous exposure to influenza vaccines including previous LAIV, an issue which might explain the apparent lower efficacy of LAIV in the USA compared to UK and Finland.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess changes in symptoms and symptom control pre- and 4 weeks after LAIV administration in children with asthma / recurrent wheezing, including children with difficult-to-control/severe asthma.

2.2 SECONDARY OBJECTIVE

1. To assess the safety of LAIV in children with a past medical history of asthma or recurrent wheeze, documentation of:
    - AEs occurring up to 72 hours after LAIV in participants.
    - Wheezing / asthma symptoms in subjects given LAIV in the 4 weeks prior to vaccine administration vs the 4 week period after LAIV.
2. To document influenza virus shedding in the week following vaccination with LAIV

3. STUDY DESIGN

Type of Study:	Multicentre, observational study of the safety of LAIV in children with asthma or recurrent wheezing
Number of Subjects:	840 children: 420 on BTS/SIGN STEP 4+ treatment (the remainder on lesser levels of treatment) attending Paediatric Outpatients for routine clinic visits from September-January 2017 (see power calculation below)
Expected Duration:	Recruitment to commence 1st September 2016 Clinical interventions to commence from mid-September 2016 for 5 months.

3.1 STUDY OUTCOMES MEASURES

3.1.1 PRIMARY STUDY OUTCOME

- Change in symptom/disease control assessment through validated questionnaire pre- and 4 weeks after LAIV in children with asthma / recurrent wheezing:
    - In children age 2-4 years inclusive: TRACK score[11] (Appendix 1)
    - In children age 5-11 years: Children's Asthma Control Test (C-ACT) score[12] (Appendix 2a)
    - In children age 12+ years: Asthma Control Test (ACT) score[14] (Appendix 2b)

3.1.2. SECONDARY STUDY OUTCOMES

1. Incidence of adverse events (AE) and serious adverse events (SAEs) in children receiving LAIV:
    - AEs occurring up to 72 hours after LAIV.
    - SAEs unrelated to asthma symptoms with onset up to 72 hours after LAIV
    - Incidence of a 'significant exacerbation' in asthma, defined as:
        i. At least 3 day course of oral steroids following an unscheduled contact with a healthcare professional; OR
        ii. Unscheduled visit to an Emergency department or admission to hospital for treatment of asthma symptoms, requiring systemic corticosteroids[13]
2. Incidence and extent of viral shedding in children and young people receiving LAIV during the 2016/17 influenza season, using quantitative analysis of consecutive nasal swabs obtained up to 10 days following LAIV. These data will be correlated with the incidence of adverse events related to asthma over the same time period.

3.1.3. OTHER STUDY OUTCOMES

Other outcome data collected during the study will include:

- Asthma Control Questionnaire (ACQ) prior to LAIV (see section 8.1.3)
- For participants at the Royal Brompton Hospital site:
    - Paediatric Asthma Quality of Life Questionnaire data (see section 8.3)
    - Inflammatory biomarkers, including Fractional exhaled nitric oxide and assessment of induced sputum.

4. STUDY POPULATION

Subjects will not be randomised in this Phase IV study.

[11] Murphy KR, Zeiger RS, Kosinski M, et al. Test for respiratory and asthma control in kids (TRACK): a caregiver-completed questionnaire for preschool-aged children. J Allergy Clin Immunol. 2009;123(4):833-9.e9.

[12] Jia CE, Zhang HP, Lv Y, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. J Allergy Clin Immunol 2013;131:695-703.

[13] Reddel HK, Taylor DR, Bateman ED, et al.; American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

4.1 RECRUITMENT

Subjects will be recruited through 2 routes:

1. Children currently managed within the existing paediatric services at participating study sites. 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).
2. Children who received the LAIV vaccine in 2014-16 as part of the SNIFFLE studies, who have a diagnosis of asthma or recurrent wheezing and are currently cared for by the clinical team at participating study sites. Families will receive a separate letter of invitation (by post or email), from their clinical team.

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

4.2 ELIGIBILITY CRITERIA: CHILDREN TO RECEIVE LAIV

4.2.1 INCLUSION CRITERIA

1. Aged 2 – 18 years old (inclusive)
2. Physician diagnosis of asthma or recurrent wheezing (by the hospital specialist) **AND**:
   i. In children age 2-4 years: ≥2 exacerbations in the past year requiring oral steroids or observation in-hospital beyond 4 hours duration **OR** receiving regular inhaled corticosteroids.
   ii. In children ≥ 5 years of age, receiving treatment equivalent to at least BTS/SIGN step 2 therapy.
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. In the event of either parent or child being unwilling to give consent/assent as appropriate, enrolment will not proceed.

4.2.2 EXCLUSION CRITERIA

1. **Admission to PICU for invasive ventilation due to a respiratory illness in the preceding 2 years.**
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 *greater than* 20mg prednisolone per day (any age), or for children under 20kg, a dose *greater than* 1mg/kg/day.
      NB: LAIV is not contraindicated for use in individuals with asymptomatic HIV infection; or individuals who are receiving topical/inhaled/low-dose oral systemic corticosteroids or those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency.

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

3. **Contraindications to vaccination on that occasion,** e.g. due to child being acutely unwell:
    a. Febrile ≥38.0°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. Any other significant condition or circumstance which, in the opinion of the investigator, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

*Items 3b-3d are ***relative*** contra-indications: Many children with "difficult-to-control" symptoms may meet fail to meet these criteria on a routine basis. Where these are present, the study centre PIs are able to authorise participation on a case-by-case basis, after assessing the child and their lung function at the time of enrolment.

Recent antihistamine use is not a contra-indication to LAIV administration, but use of any antihistamine in the 96 hours prior to LAIV will be logged on the CRF.

Administration of another live vaccine (e.g. MMR) within the previous 4 weeks is no longer a contra-indication to LAIV administration, according to updated DoH guidelines.

NB: See Summary of Product Characteristics for full details of contra-indications to LAIV.

4.3 SUBJECT WITHDRAWAL

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

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

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

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

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

5. STUDY TREATMENT

5.1 DESCRIPTION

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

5.2 DOSAGE AND ROUTE OF ADMINISTRATION

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

5.3 DOSE MODIFICATION

No dose modification proposed.

5.4 PREPARATION AND ADMINISTRATION OF STUDY DRUG

FLUENZ IS FOR NASAL USE only.

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

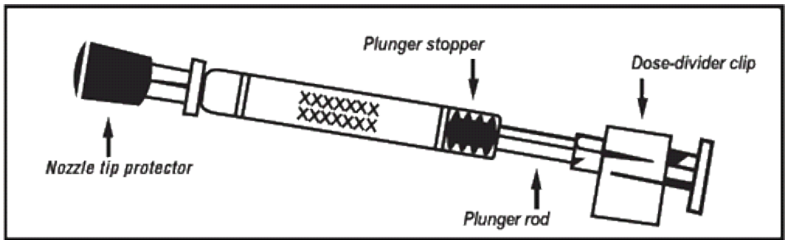
• FLUENZ is administered as a divided dose in both nostrils.

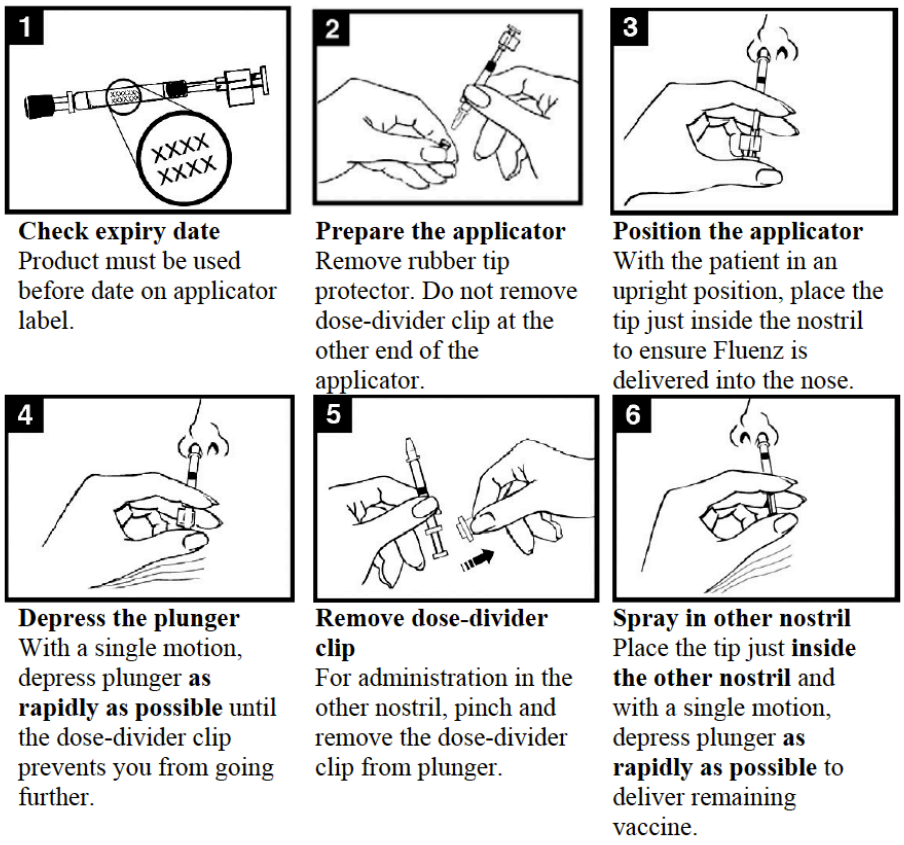
• After administering half of the dose in one nostril, administer the other half of the dose in the other nostril immediately or shortly thereafter.

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

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

Figure 2 FLUENZ Administration





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

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

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

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

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

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

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

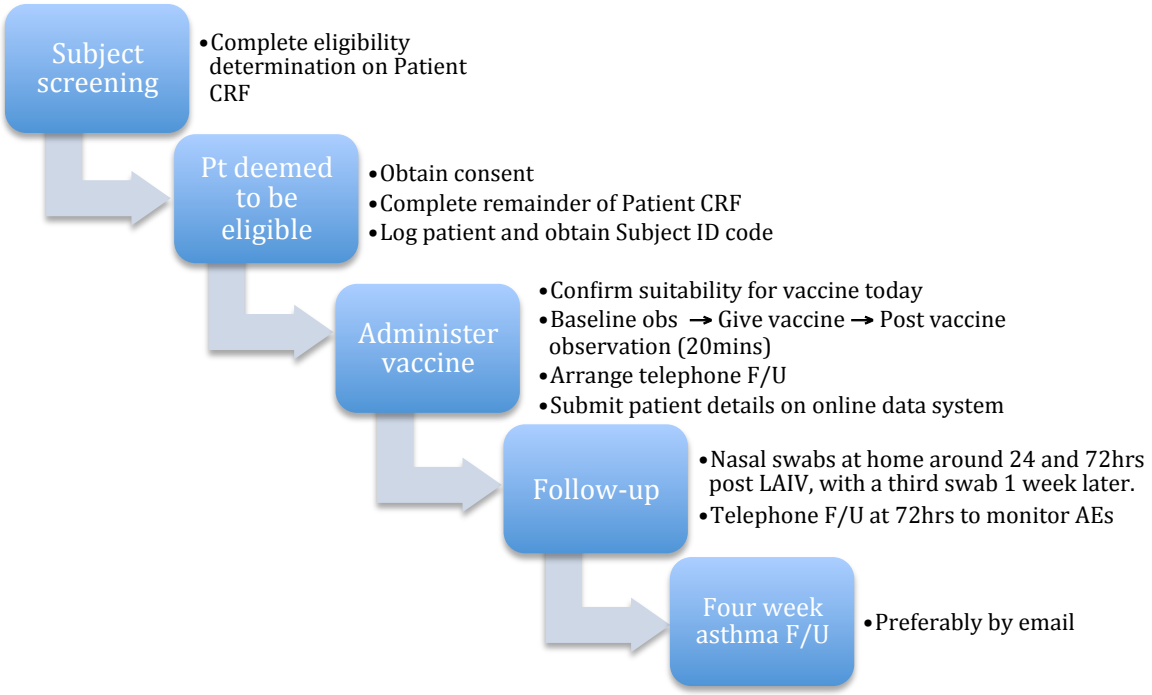
5.5 DISPENSING AND PRODUCT ACCOUNTABILITY

Fluenz Tetra (quadrivalent LAIV) is approved by the European Medicines Agency and distribution and administration to selected children will take place during the influenza season 2016-17. Provision of doses of vaccine will be through the Department of Health vaccine supply network as part of the national immunisation programme, with no additional requirements (e.g. cold chain monitoring) beyond that provided by the normal UK vaccine supply system. Vaccine will be delivered via existing systems to on-site pharmacists at study sites (all NHS hospitals). Doses will then be released according to local procedure, using existing hospital pharmacy systems and logging (rather than CTIMP-specific documentation).

The application for a clinical trials authority will include an exemption for study specific labelling.

6 STUDY VISITS, PROCEDURES SCHEDULE and Patient Flow Diagram

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



	Visit 1	24 hours later	72 hours later	6-7 days later	Follow-up 4 weeks later
Written Informed Consent (parent/ guardian) Written assent (child)	X X				
Medical assessment	X				
Asthma control/symptom questionnaire: • Age 2-4 years: TRACK score (Appendix 1) • Age 5-11 years: C-ACT score (Appendix 2a) • Age 12+ years: ACT score (Appendix 2b)	X				X
Vaccine administration followed by 20 mins observation	X				
Nasal swab at home		X	X	X	
Delayed effects telephone questionnaire at 72hrs			X		
Asthma assessment 4 weeks post LAIV					X
2nd dose in children <9 years who meet DoH critieria (see 6.1.2)					X

6.1 STUDY PROCEDURES

Following consent (see 6.1.2), subjects will be assessed for suitability for vaccine administration. Baseline observations (temperature, heart rate, respiratory rate, oxygen saturations in air and lung function) will be documented on the paper CRF. Asthma control will be assessed as per section 8.1.3.

LAIV will be administered according to the SmPC (see section 5.4) and the child observed for 20 minutes afterwards to confirm no acute adverse event. The observation time will be extended if there is any clinical concern. Vaccine will be administered in a clinical area where facilities exist to manage any adverse reaction, should this occur. Additional surveillance and monitoring will be performed in participants at the Royal Brompton Hospital site (see section 8.6).

Following vaccination, the CRF will be completed and patient details entered on to a secure encrypted server run by Public Health England, confirming vaccine administration and providing the required contact details for follow-up.

6.1.1 POST VACCINATION SCHEDULE

Parents will be asked to take up to 3 nasal swabs from their child/young person at home, in the week following vaccination. The nasal swab, which looks like a large cotton bud, will be passed into the nostril and moved around for a minute. The exact timing of these will be confirmed prior to study commencement, once international efforts to assess vaccine shedding have been reported. However, it is likely these will be at 24 and 72 hours, and at 6-7 days following vaccination. Parents will be provided with three test kits, full instructions and Royal-Mail approved kits (for Category B specimens) will be provided for each child, along with postage-paid envelopes for posting back to PHE through the normal post network.

Parents will be shown the process by their study nurse at the vaccination visit. The swab may be collected up to 24 hours after the stated time.

From 72 hours after LAIV (and up to 7 days later, to allow for weekends), families will be contacted to document any potential adverse events which have occurred since vaccination. This will be done by telephone contact by staff at the study site. A guide for this telephone call is found in Appendix 5. Families will be reminded about the nasal swab at this time.

One month later, families will receive an email invite from Public Health England to complete a brief online questionnaire to assess asthma control. Where families do not have access to email, this can be completed through telephone contact by staff at the local study site (as per the 72 hour follow-up, using the telephone guide in Appendix 6).

6.1.2 SECOND DOSE OF LAIV

Children who meet DoH criteria for specified ‘clinical risk categories’ (Table 1) and are under 9 years of age and have not received prior seasonal influenza vaccination will be offered a second dose of LAIV at least 4 weeks later. We expect very few children to meet this criteria, as most would have received prior influenza vaccination (in SNIFFLE 1, no child 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 1: Clinical risk categories requiring a second dose of LAIV in vaccine-naïve children under age 9 yrs:

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

6.2 CONSENT

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

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

- Many families travel significant distances to specialist allergy/respiratory 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 vaccine to be administered in this study is part of the routine UK National Immunisation Schedule. The study allows children to participate in this programme in a safe environment, utilising a vaccine delivery route (intranasal) which minimises discomfort to the child.
- The proposed consent process has been trialled successfully in the SNIFFLE-2 and -3 studies, with positive feedback from both eligible young people and their families.

Following discussion with the Research Ethics Committee, it has been agreed that **in participants under 16 years at the time of consent** and vaccination, but who will turn 16 years of age prior to the 4 week follow-up assessment, the participant does not need to be formally consented as it can be assumed that in voluntarily answering the questionnaire, the participant provides consent.

However, for participants at the Royal Brompton site undergoing further assessment at the 4 week follow-up (as outlined in section 8.3), formal consent will need to be taken from the young person prior to the assessments being performed.

7 ADVERSE EVENT REPORTING

7.1 DEFINITIONS

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

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

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

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

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that:

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

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

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

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 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 not related to asthma/wheezing will only be collected where onset is within 72 hours of vaccine administration. Those relating to respiratory symptoms will be collected up to one month after LAIV at visit 1.

7.1.1 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 a SAE report form in addition to CRFs. 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 reported within 24 hours of the Site Study Team becoming aware of the event. All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed, to the JRCO (Fax number: 0203 311 0203 or via email to jrco.ctimp.team@imperial.ac.uk).

Both SAEs and SARs will be reported to the Independent Data Monitoring Committee (IDMC). The IDMC has the authority to recommend termination of the trial because of safety findings. SARs will also be reported to MHRA through the yellow card system.

7.2 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

7.2.1 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 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.

7.2.2 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 (Table 3). **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.

Anaphylaxis will be defined as per the case definition and guidelines as described by the Brighton Collaboration Anaphylaxis Working Group (see appendix 4).

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.

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

Table 3: World Allergy Organisation (WAO) Grading System for allergic reactions to immunotherapy

7.3 REPORTING PROCEDURES

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

7.3.1 NON SERIOUS AR/AES

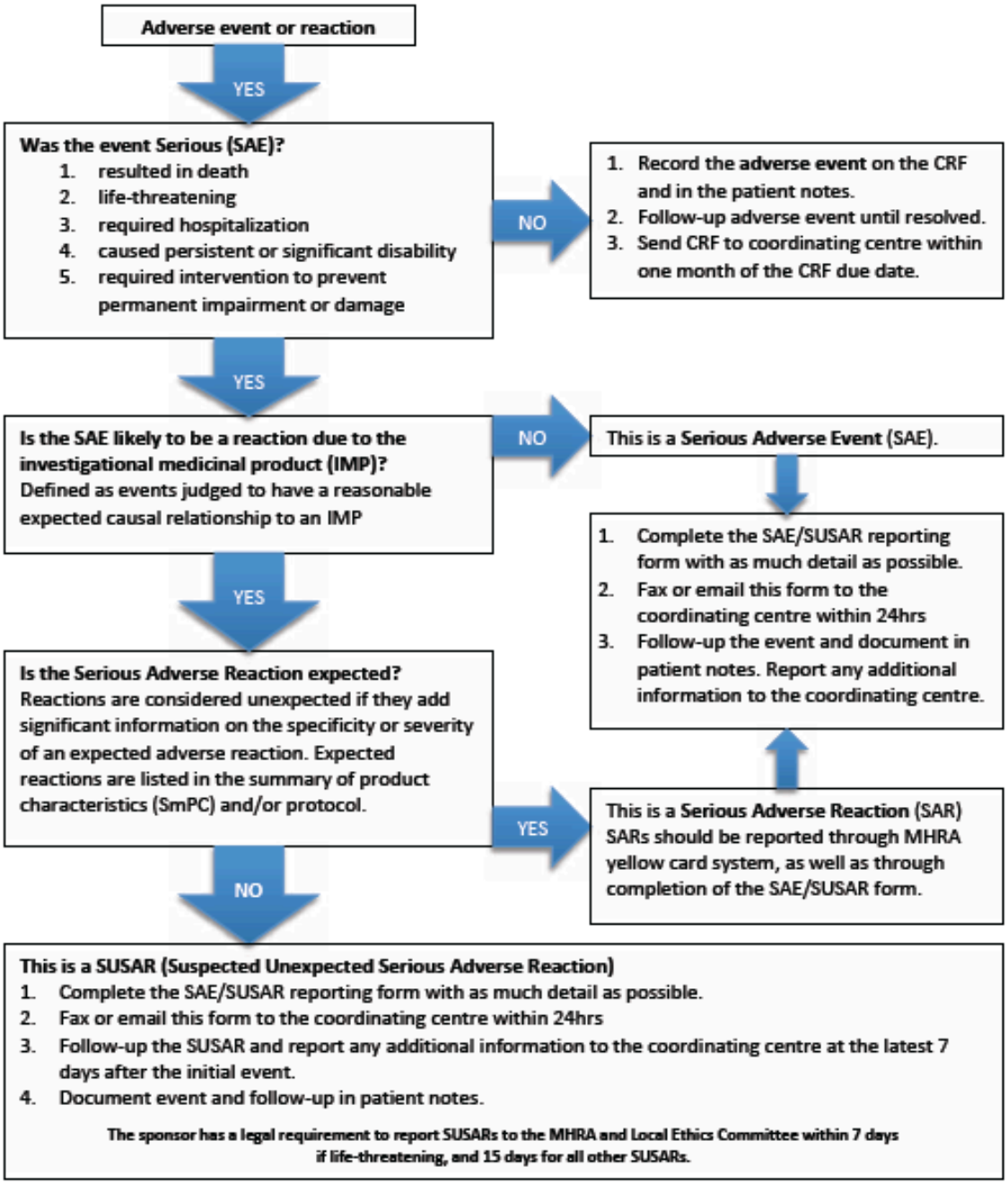
All such events, whether expected or not, should be recorded in the adverse event section of the relevant case report form and reported to the study CI within one month of the form being due.

7.3.2 SERIOUS AR/AES

Fatal or life threatening SAEs and SUSARs should be reported on the same day as the site is made aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should determine the causality of the event. Additional information should be sent to the CI within 5 days if the reaction has not resolved at the time of reporting. Any expected SAR will also be reported via the MHRA yellow card system.

SAEs: An SAE form should be completed and emailed to the study CI immediately, who will in turn inform the JRCO (Fax number: 0203 311 0203 or via email to jrco.ctimp.team@imperial.ac.uk) within 24 hours.

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



Contact details for reporting SAEs and SUSARs:

Study CI:	**Fax 020 3312 7571**	**Email: p.turner@imperial.ac.uk**
Compliance Office:	**Fax: 020 3311 0203**	**Email:** jrco.ctimp.team@imperial.ac.uk

8. ASSESSMENT AND FOLLOW-UP

8.1 CLINICAL ASSESSMENTS

8.1.1 ALLERGY TESTING

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

8.1.2 LUNG FUNCTION TESTING

Where study participants are able to comply, lung function will be performed prior to LAIV using the system in use at each centre and according to local protocol. Data relating to bronchodilator responsiveness (BDR) will be collected if performed for routine clinical assessment. For children with non-severe symptoms, an assessment of peak flow using a peak flow meter will suffice, although formal lung function is preferable.

8.1.2 CLINICAL OBSERVATION / MONITORING OF PATIENTS BY CLINICAL STAFF

Patients will have baseline observations (temperature, heart rate, respiratory rate, oxygen saturations, lung function (FEV1 and/or PEFR)) performed prior to LAIV administration, with clinical respiratory and dermatological assessment at the same time.

Children will be observed for at least 20 minutes after LAIV in a safe environment with appropriate clinical supervision and access to paediatric resuscitation facilities and trained staff, in the event of a severe allergic reaction.

8.1.3 ASTHMA CONTROL ASSESSMENT PRE AND 4 WEEKS POST VACCINATION

Participants' families will be asked to complete a questionnaire to determine their child's asthma symptoms and control, using a validated tool at visit 1:

- In children age 2-4 years: TRACK questionnaire (Appendix 1)
- In children age 5-11 years: C-ACT questionnaire (Appendix 2a)
- In children age 12+ years: ACT questionnaire (Appendix 2b)

As part of the CRF, the questions on the Asthma Control Questionnaire[14] (ACQ, Appendix 3) will also be completed. While the (C-)ACT and TRACK questionnaires assess asthma symptoms over the preceding 4 weeks, the ACQ assesses symptoms and control over the preceding 7 days and also includes lung function;[15] the ACQ may therefore be more representative of asthma control at the time of vaccination. The (C-)ACT will be completed first, before the ACQ.

Families will be asked to complete a further questionnaire 4 weeks after vaccination. In general, this will be done using an online questionnaire. Families will be asked at their first

[14] Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14: 902–907.
[15] Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Validation, measurement properties and interpretation of the Asthma Control Questionnaire in children. Eur Respir J 2010: 36: 1410-1416

visit as to whether they prefer to be contacted by telephone by the 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 6. These data will be recorded on a CRF.

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.

At the Royal Brompton, participants will be invited to return to hospital for the 4 week follow-up (which will, in general, coincide with a routine clinic follow-up appointment). The follow-up questionnaires will be completed at this visit, along with some further repeat assessments (section 8.3).

8.2 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 minutes. A guide for this telephone call is provided in Appendix 5. 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.

8.3 ADDITIONAL CLINICAL ASSESSMENTS (ROYAL BROMPTON SITE ONLY)

Participants at the Royal Brompton Hospital site will undergo further clinical assessments, immediately prior to and 4 weeks after LAIV. Thus, participants at the Royal Brompton will be asked to return 4 weeks later for these repeat assessments. Data will be collected on a supplementary clinical record form.

The planned additional assessments are as follows:

1. **Measurement of fractional exhaled nitric oxide (FeNO)**
   Exhaled nitric oxide is a marker thought to represent inflammation in the airways. This non-invasive technique is approved by NICE for the diagnosis and monitoring of asthma in both children and adults.[16] For most children at this site, FeNO is measured as part of routine clinical care. For school-aged children, exhaled nitric oxide will be measured according to local protocol. For preschool children, exhaled breath will be collected during normal tidal breathing into a bag and nitric oxide measured in the collected gas ("offline" method). This technique has been established as a routine test at the Royal Brompton Hospital.

[16] Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath NICE diagnostics guidance [DG12] Published date: April 2014.

2. **Induced Sputum**
   This is also a routine clinical test in the severe asthma clinic. Hypertonic saline will be given via a nebuliser and the child asked to cough any phlegm into a universal container. In preschool children, the sputum sample can be obtained using a combination of chest physiotherapy and suction. The procedure will only be undertaken where children are clinical well (and thus eligible for LAIV). The sample will be assessed in the laboratory for inflammatory cells and any excess stored at -80°C for analysis of inflammatory cytokines. Where consent is provided, any residual sample will be stored for future research.

3. **Paediatric Asthma Quality of Life Questionnaire (PAQLQ)**
   Children aged 7+ years and their caregiver will be asked to complete the PAQLQ, a validated assessment of health-related quality of life in asthma.[17]

8.4 NASAL SWABBING AND SAMPLE MANAGEMENT

8.4.1 COLLECTION OF NASAL SWAB

Parents will be asked to collect up to 3 nasal swabs in the week following LAIV administration. This will involve putting a swab, which looks like a large cotton bud, into the nostril and moving it around for up to a minute.

8.4.2 LABELLING, DESPATCH, AND STORAGE OF SAMPLES

Each participant will be assigned a unique identifying number during the enrolment process, according to the Standard Operating Protocol in respect of participant identification for the study. The participant number will be linked to a pre-generated sample barcode for every clinical sample taken, which can be scanned at the testing laboratory.

Samples will be sent to the receiving laboratory at the Virus Reference Division, PHE Colindale by Royal Mail using approved packaging which will be supplied to each family. A brief paper form will be completed by parents to confirm date of sampling. All samples will be logged locally, to enable the identification of any lost or delayed samples and provide a log of where samples are currently stored.

Samples arriving at the receiving laboratory at the Virus Reference Division, PHE Colindale without accompanying paperwork will be initially processed (given that consent has already been obtained) but any results embargoed until confirmatory paperwork has been received from the family.

Samples will be initially processed from the administrative perspective and stored until formal processing in batches. Not all swabs received will undergo viral detection and quantification: swabs will be selected from representative cohorts of individuals, by previous

[17] Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res 1996; 5: 35 -46.

influenza vaccination status: no previous vaccination, previous LAIV only, previous injected influenza vaccine only. This will allow an assessment of the impact of previous LAIV receipt on viral shedding, something necessary to determine the effect of prior influenza immunisation on viral shedding. Any swabs not included in the viral quantification will be handled as per section 8.4.3.

8.4.3 HANDLING OF RESIDUAL SAMPLES ON COMPLETION OF TESTING

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

8.5 LOSS TO FOLLOW-UP

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

8.6 TRIAL CLOSURE

The study will be considered complete following enrolment of the last patient and completion of the study procedures in that patient. Upon review by the TSC, recruitment may be extended if target recruitment is achieved prior to end of the vaccination period for influenza 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 or asthma episode 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 TSC. 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

9. STATISTICS AND DATA ANALYSIS

9.1 DEFINITIONS

For the purpose of analyses, severity will be defined as follows:

- **Age 2-4 years (preschool wheezers, PSW):**
  - Step 3/4 BTS management: ≥400mcg beclomethasone dipropionate /day or 200mcg/FP, AND LRTA (either continuous or intermittent or previous failed trial)

    OR
  - ≥2 exacerbations in the past year requiring oral steroids or observation in-hospital beyond 4 hours duration

- **Age 5+ years:**
  - Requiring Step 4+ management according to BTS Guidelines

A 'significant exacerbation' in asthma is defined as:

i. At least 3 day course of oral steroids following an unscheduled contact with a healthcare professional; OR

ii. Unscheduled visit to an Emergency department or admission to hospital for treatment of asthma symptoms, requiring systemic corticosteroids

9.2 SAMPLE SIZE ESTIMATION

Sample size is based on the primary objective of comparing the proportion of participants who experience a significant change in asthma control, as measured by a change in at least 3 points *and* from >=20 on the (C-)ACT (good control) to <20 (sub-optimal control) in each group (BTS ≤3 vs BTS 4/5), or vice versa. In the SNIFFLE-2 study, such a change (one way or the other) was seen in about 20% of children (10% worse, 10% better).

A sample of 400 children in each group will provide sufficient power (5% significance level, 80% power) to detect an improvement in 10% vs deterioration in 17.5%, allowing for 10% attrition. In SNIFFLE-2, follow-up at four weeks was 89%. If the proportion of participants with a change in ACT score is less than this, with only 5% improving and 10% getting worse, a sample size of about 420 would provide a similar level of power. This would represent a conservative assumption in the proportions changing. For comparing the average change pre to post vaccination in ACT score between the severe and non-severe groups, the standard deviation of change from SNIFFLE-2 was used (about 3 units). With a sample size of 400 in each group the detectable difference is 0.6 units between the groups (80% power, 5% significance).

Assuming that about 1% of participants experience a significant deterioration in asthma control (as defined in 3.1.2 above), then the 95% CI for a significant deterioration will be from 0.027% to 2.54%. If 0/400 are observed the upper 95% CI is 0.92%.

POPULATION TO BE ANALYSED

CHILDREN AGED 2-18 YEARS (INCLUSIVE) WITH A PHYSICIAN-DIAGNOSIS OF ASTHMA OR RECURRENT WHEEZING, REQUIRING REGULAR MAINTENANCE THERAPY OR, IF

AGE 2-4 YEARS, ≥2 EXACERBATIONS IN THE PAST YEAR AS DEFINED IN SECTION 9.1 . 9.3 STATISTICAL ANALYSIS PLAN

In brief, a per-protocol analysis will be completed for all individuals with at least one safety measurement. Proportions with AEs will be estimated with 95% CIs.

For the primary outcome, the change in TRACK or ACT score pre- and 4 weeks post LAIV will be assessed by McNemar's test for paired data. The minimum important difference (MID) for the ACT score is around 2 points in children[18] and 3 points in adults,[19] and 10 points for TRACK.[20] For the purpose of this analysis, a change in ACT of at least 3 points, or 10 points for TRACK will be determined to be a significant change, where this results in an ACT score below 20 or TRACK score below 80 points.

For secondary outcomes, the incidence of reactions to LAIV (both immediate and delayed) and significant exacerbation in asthma will be estimated with 95% confidence intervals. Comparison to historical rates will be by Fisher's exact test.

Sub-group analyses will be performed using the following criteria:

- Age: 2-4, 5-11, 12-17 years
- Severity of respiratory symptoms: "severe" vs "non-severe"
- Children who have previously received influenza vaccine
- Children receiving high dose inhaled corticosteroids (≥800 mcg/day beclomethasone dipropionate, or equivalent)[21] vs those who are not. This cut-off will be applied to all participants age 6+ years.

Definition of high daily dose of various inhaled corticosteroids in relation to patient age

Inhaled corticosteroid	Threshold daily dose in µg considered as high	
	Age 6–12 years	Age >12 years
Beclomethasone dipropionate	≥800 (DPI or CFC MDI) ≥320 (HFA MDI)	≥2000 (DPI or CFC MDI) ≥1000 (HFA MDI)
Budesonide	≥800 (MDI or DPI)	≥1600 (MDI or DPI)
Ciclesonide	≥160 (HFA MDI)	≥320 (HFA MDI)
Fluticasone propionate	≥500 (HFA MDI or DPI)	≥1000 (HFA MDI or DPI)
Mometasone furoate	≥500 (DPI)	≥800 (DPI)
Triamcinolone acetonide	≥1200	≥2000

Notes: 1) Designation of high doses is provided from manufacturers' recommendations where possible. 2) As chlorofluorocarbon (CFC) preparations are being taken from the market, medication inserts for hydrofluoroalkane (HFA) preparations should be carefully reviewed by the clinician for the equivalent correct dosage. DPI: dry powder inhaler; MDI: metered-dose inhaler.

[18] Voorend-van Bergen S, Vaessen-Verberne AA, Landstra AM, Brackel HJ, van den Berg NJ, Caudri D, de Jongste JC, Merkus PJ, Pijnenburg MW. Monitoring childhood asthma: web-based diaries and the asthma control test. J Allergy Clin Immunol. 2014 Jun;133(6):1599-605.e2.

[19] Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol. 2009 Oct;124(4):719-23.e1.

[20] Zeiger RS, Mellon M, Chipps B, Murphy KR, Schatz M, Kosinski M, Lampl K, Ramachandran S. Test for Respiratory and Asthma Control in Kids (TRACK): clinically meaningful changes in score. J Allergy Clin Immunol. 2011 Nov;128(5):983-8.

[21] Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014 Feb;43(2):343-73.

A further analysis will also be taken to generate Receiver Operating Characteristic (ROC) curves to determine if a cut-off of high specificity and sensitivity can be determined for the (C-)ACT and ACQ in predicting which children are likely to experience a significant exacerbation in asthma following LAIV. The ACQ is only validated for children age 6 and over: thus, this analysis will be performed using both the complete dataset and also after excluding children under age 6 years.

Data analysis will be undertaken by PHE Immunisation Department Statistician and members of the Clinical Trial Team where appropriate.

The results of the study will be submitted for peer-reviewed journal publication(s). If requested, anonymised data will be provided to the vaccine manufacturers, and comparative analysis of results may be performed.

No interim analyses are planned.

10 DATA MANAGEMENT

10.1 DATA COLLECTION

The following data will be collected:

- Patient demographics
- Current health to establish safety of immunisation
- Vaccination history:
  - previous exposure to influenza vaccine
  - previous reactions to vaccines
- Past medical history:
  - Medical indication for influenza vaccination or routine
  - Asthma status
  - Active Allergic rhinitis
  - Current Medication
  - Other atopy: allergic rhinitis, eczema, other food allergies

Data will be collected by paper CRF and then transferred to Public Health England, with participants identified by study number. Patient identifiable information (e.g. names, email addresses) will be transferred to Public Health England via a GSI gateway secure server. This is necessary to facilitate the swabbing phase of the study. Specific consent to share patient identifiable information with Public Health England will be included on the study consent form.

10.2 DATA RECORDS

Paper records will be maintained at local sites for all participants enrolled in the study. CRFs will be completed at each visit, reviewed by the coordinating centre and then sent to PHE Colindale. A database will be constructed at PHE Colindale to record the information collected in the CRFs. As the data are being entered, the CRFs will be monitored for completion errors or omissions. When such a problem is identified the card will be photocopied and the field for correction marked. Any corrections necessary will be made by the study team according to GCP and returned to PHE Colindale, where the database will be updated accordingly and the photocopy filed with the original CRF.

Information from CRFs will be entered at PHE Colindale into an Access database. Data will be entered twice by different members of staff into identical Access study databases which will be compared using an Access programme which compares the data in the two databases and identifies data entry errors. These will then be corrected.

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

11 ADMINISTRATIVE AND REGULATORY ISSUES

11.1 CLINICAL TRIALS AUTHORISATION

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA, Eudra CT registration no. 2016-002352-24. The study is also registered at Clinicaltrials.gov, reference: NCT02866942.

11.2 ETHICS APPROVAL

The Chief Investigator has obtained the required approvals from the West Mildands-Edgbaston Research Ethics Committee. The study will be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letters 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.

11.3 INFORMED CONSENT AND PARTICIPANT ASSENT

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

11.4 CONFIDENTIALITY

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

11.5 INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

11.6 SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

11.7 FUNDING

Funding has been secured from the Department of Health Policy Research Programme (NVEC039/0031) awarded to Prof Elizabeth Miller, Public Health England.

11.8 AUDITS

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

11.9 MONITORING

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

12 STUDY MANAGEMENT

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

13 PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Steering Committee and the Department of Health. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Where the journal's policy allows, all site PIs will be listed as collaborators for any publications generated from the study.

Members of 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.

APPENDIX 1: TRACK QUESTIONNAIRE

TRACK™ Test for Respiratory and Asthma Control in Kids

Who should use TRACK?

This simple test can help determine if your child's breathing problems are not under control.

The test was designed for children who

- Are under 5 years of age **AND**
- Have a history of 2 or more episodes of wheezing, shortness of breath, or cough lasting more than 24 hours **AND**
- Have been previously prescribed bronchodilator medicines, also known as quick-relief medications (eg, albuterol, Ventolin®, Proventil®, Maxair®, ProAir®, or Xopenex®), for respiratory problems **OR** have been diagnosed with asthma

For kids under 5 years of age

How to take TRACK

Step 1: Make a check mark in the box below each of your selected answers.

Step 2: Write the number of your answer in the score box provided to the right of each question.

Step 3: Add up the numbers in the individual score boxes to obtain your child's total score.

Step 4: Take the test to your child's health care provider to talk about your child's total TRACK score.

Score

1 During the past 4 weeks, how often was your child bothered by breathing problems, such as wheezing, coughing, or shortness of breath?

Not at all	Once or twice	Once every week	2 or 3 times a week	4 or more times a week
☐ 20	☐ 15	☐ 10	☐ 5	☐ 0

2 During the past 4 weeks, how often did your child's breathing problems (wheezing, coughing, shortness of breath) wake him or her up at night?

Not at all	Once or twice	Once every week	2 or 3 times a week	4 or more times a week
☐ 20	☐ 15	☐ 10	☐ 5	☐ 0

3 During the past 4 weeks, to what extent did your child's breathing problems, such as wheezing, coughing, or shortness of breath, interfere with his or her ability to play, go to school, or engage in usual activities that a child should be doing at his or her age?

Not at all	Slightly	Moderately	Quite a lot	Extremely
☐ 20	☐ 15	☐ 10	☐ 5	☐ 0

4 During the past 3 months, how often did you need to treat your child's breathing problems (wheezing, coughing, shortness of breath) with quick-relief medications (albuterol, Ventolin®, Proventil®, Maxair®, ProAir®, Xopenex®, or Primatene® Mist)?

Not at all	Once or twice	Once every week	2 or 3 times a week	4 or more times a week
☐ 20	☐ 15	☐ 10	☐ 5	☐ 0

5 During the past 12 months, how often did your child need to take oral corticosteroids (prednisone, prednisolone, Orapred®, Prelone®, or Decadron®) for breathing problems not controlled by other medications?

Never	Once	Twice	3 times	4 or more times
☐ 20	☐ 15	☐ 10	☐ 5	☐ 0

Total

Please see reverse side for an explanation of what your child's total TRACK score means.

APPENDIX 2A: ASTHMA CONTROL TEST – FOR CHILDREN AGE 5-11 YEARS

CHILDHOOD ASTHMA CONTROL TEST

For children age 5-12 years of age

How to take the Childhood Asthma Control Test:

1. Let your child respond to the first four questions (1 to 4), by **CIRCLING THEIR ANSWER**. If your child needs help reading or understanding the question, you may help, but let your child select the response.

2. Complete the remaining three questions (5 to 7) on your own by **CIRCLING YOUR ANSWER**. Try not to let your child's responses influence your answers. There are no right or wrong answers.

1. How is your asthma today?

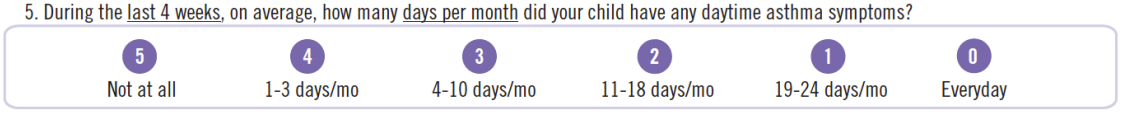
2. How much of a problem is your asthma when you run, exercise or play sports?

3. Do you cough because of your asthma?

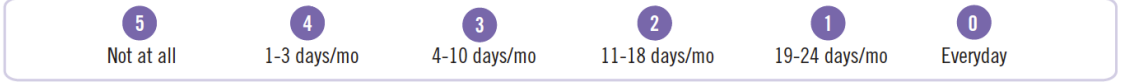
4. Do you wake up during the night because of your asthma?

Please complete the following questions on your own.

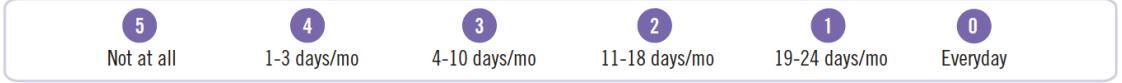
5. During the last 4 weeks, on average, how many days per month did your child have any daytime asthma symptoms?



6. During the last 4 weeks, on average, how many days per month did your child wheeze during the day because of asthma?



7. During the last 4 weeks, on average, how many days per month did your child wake up during the night because of asthma?



APPENDIX 2B: ASTHMA CONTROL TEST – YOUNG PEOPLE AGE 12+ YEARS

ASTHMA CONTROL TEST

For young people over 12 years of age

Why take the Asthma Control Test™?

The Asthma Control Test™ will provide you with a snapshot of how well your asthma has been controlled over the last four weeks, giving you a simple score out of 25. Asthma symptoms can vary from month to month, so it is worth keeping the test handy to see if your score changes. You can also share your results with your doctor or asthma nurse to help explain just how your asthma affects you.

Are you in control of your asthma? Or is your asthma in control of you? Here's how to find out

Step 1: Read each question below carefully, circle your score and write it in the box.
Step 2: Add up each of your five scores to get your total Asthma Control Test™ score.
Step 3: Use the score guide to learn how well you are controlling your asthma.

Q1	During the **past 4 weeks,** how often did your asthma prevent you from getting as much done at work, school or home?	All of the time 1	Most of the time 2	Some of the time 3	A little of the time 4	None of the time 5	Score:
Q2	During the **past 4 weeks,** how often have you had shortness of breath?	More than once a day 1	Once a day 2	3-6 times a week 3	1-2 times a week 4	Not at all 5	Score:
Q3	During the **past 4 weeks,** how often did your asthma symptoms (wheezing, coughing, chest tightness, shortness of breath) wake you up at night or earlier than usual in the morning?	4 or more times a week 1	2-3 nights a week 2	Once a week 3	Once or twice 4	Not at all 5	Score:
Q4	During the **past 4 weeks,** how often have you used your reliever inhaler (usually blue)?	3 or more times a day 1	1-2 times a day 2	2-3 times a week 3	Once a week or less 4	Not at all 5	Score:
Q5	How would you rate your **asthma control** during the **past 4 weeks?**	Not controlled 1	Poorly controlled 2	Somewhat controlled 3	Well controlled 4	Completely controlled 5	Score:

Total Score

What does your score mean?

Score: 25 – WELL DONE

- Your asthma appears to have been UNDER CONTROL over the last 4 weeks.
- However, if you are experiencing any problems with your asthma, you should see your doctor or nurse.

Score: 20 to 24 – ON TARGET

- Your asthma appears to have been REASONABLY WELL CONTROLLED during the past 4 weeks.
- However, if you are experiencing symptoms your doctor or nurse may be able to help you.

Score: less than 20 – OFF TARGET

- Your asthma may NOT HAVE BEEN CONTROLLED during the past 4 weeks.
- Your doctor or nurse can recommend an asthma action plan to help improve your asthma control.

APPENDIX 3: ASTHMA CONTROL QUESTIONNAIRE

Please answer questions 1–6.

Circle the number of the response that best describes how you have been during the past week

1. On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
	1	Hardly ever
	2	A few minutes
	3	Several times
	4	Many times
	5	A great many times
	6	Unable to sleep because of asthma
2. On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0	No symptoms
	1	Very mild symptoms
	2	Mild symptoms
	3	Moderate symptoms
	4	Quite severe symptoms
	5	Severe symptoms
	6	Very severe symptoms
3. In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
	1	Very slightly limited
	2	Slightly limited
	3	Moderately limited
	4	Very limited
	5	Extremely limited
	6	Totally limited
4. In general, during the past week, how much **shortness of breath** did you experience because of you asthma?	0	None
	1	A very little
	2	A little
	3	A moderate amount
	4	Quite a lot
	5	A great deal
	6	A very great deal
5. In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?	0	None
	1	1–2 puffs most days
	2	3–4 puffs most days
	3	5–8 puffs most days
	4	9–12 puffs most days
	5	13–16 puffs most days
	6	More than 16 puffs most days

To be completed by a member of the clinic staff

7. FEV_1 pre-bronchodilator:	0	>95% predicted
	1	95–90%
FEV_1 predicted	2	89–80%
	3	79–70%
FEV_1 % predicted	4	69–60%
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	5	59–50%
	6	<50% predicted

APPENDIX 4: BRIGHTON COLLABORATION CASE DEFINITION OF ANAPHYLAXIS

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 5: 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-4 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?*

5. *"Since the vaccine,*

   i. *Have you needed to give your child more reliever medicine (e.g. ventolin) than normal?*

   ii. *Have you had to take <participant's name> to see a Doctor because of his/her breathing?*
   iii. *(If YES) – did you have to take them to hospital?*
   iv. *(If YES) – did <participant's name> have to stay in hospital overnight?*

   v. *Did <participant's name> have to start any medicines, like an oral steroid? If so, for how long?*

FINALLY: Remind family to take nasal swab at 72 hours and 6 days after LAIV.

APPENDIX 6: 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 4 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-4 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 TRACK / C-ACT / ACT Questionnaire over the telephone

   (see separate questionnaires)

4. Finally, ask the following questions:

   Since the vaccine,

   i) 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?
   iv) Did <participant's name> have to start any medicines, like an oral steroid? If so, for how long?