Title	Post-licensure observational safety study of specific outcomes after Optaflu vaccination among adults in The Health Improvement Network (THIN) database of routine UK primary care records
Protocol version identifier	Version 2
Date of last version protocol	8th May 2012
EU PAS registry number	TBA
Active substance	cTIV
Medicinal product	Optaflu
Product reference	V58_30OB
Procedure number	EMEA/H/C/758
Marketing authorisation holder(s)	Novartis Vaccines and Diagnostics GmbH
Joint PASS study	No
Research question and objectives	To investigate the safety of cTIV vaccination in adults in routine clinical care in the UK with regard to pre-specified outcomes : ▫ To plot the number of study outcomes pre-and post-vaccination in outcome specific pre-defined time windows (risk windows) in relation to the date of vaccination. When events are identified in a high risk post-exposure window, to provide a ratio of observed to expected rates. ▫ To report the incidence of study outcomes in the six months after vaccination.

Country(ies) of study	UK
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2.0 LIST OF ABBREVIATIONS

ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
CSD	Cegedim Strategic Data
cTIV	Cell culture trivalent influenza vaccine
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
GBS	Guillain Barré Syndrome
GP	General Practitioner
IBD	Inflammatory bowel disease
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NVD	Novartis Vaccines and Diagnostics
REB	Research Ethics Board
PASS	Post authorization safety study
PPV	Pneumococcal polysaccharide vaccine
SCCS	Self-controlled case series
THIN	The Health Improvement Network
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event and Reporting System
VAESCO	Vaccine and Adverse Event Surveillance and Communication

3.0 RESPONSIBLE PARTIES

3.1 Main Author(s) of the Protocol

Gillian Hall

3.2 Principal Investigator

Gillian Hall

3.3 Coordinating Investigator(s)

The study will be performed at one center.

3.4 CRO or Other Service Provider

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3.5 Advisory Committee

An adjudication committee will be appointed.

4.0 ABSTRACT

Name of Sponsor Novartis Vaccines and Diagnostics	**Protocol number:** V58_30OB	**Health authority study registration number(s):**	**Date of Protocol Abstract:** 12 February 2013
Title of Study: Post-licensure observational safety study of specific outcomes after Optaflu vaccination among adults in The Health Improvement Network database of routine UK primary care records			
Study Period*:* The total study period (data collection) is estimated to be June 2012 to April 2015. Individual patients will be included from three months before the date of the vaccination to six months afterwards.	**Study Type:** EMA required observational post-licensure study (PASS).		
Rationale and Background: This post-licensure study was committed to the EMA at the time of marketing authorization for Optaflu® in 2007. Optaflu® is a new subunit influenza vaccine that is no longer produced in embryonated hen eggs, but in a suspension of a specific cell line cloned from Madin Darby Canine Kidney tissue. The Cell culture trivalent influenza vaccine (cTIV) is a sterile preparation of purified influenza antigens in an isotonic buffer solution for intramuscular administration. The final product contains the membrane proteins hemagglutinin and neuramidase as active ingredients. As recommended by the World Health Organisation, these proteins are derived from three influenza virus strains (A/H1N1, A/H3N2 and B). The study investigates the safety of cTIV in a large population of adults. These new safety data will be added to the existing ones and are to confirm the results of the clinical database. The outcomes to be studied are those with a documented increased risk after exposure to other influenza vaccines or are rare events stated to have been caused by influenza vaccination in case reports in the literature. All but thrombocytopenia, paraesthesia and inflammatory bowel disease were included in a specific guidance regarding pandemic influenza vaccines: anaphylactic reactions and angioedema, Bell's palsy and neuritis (optic and brachial), convulsions, demyelination including Guillain-Barre syndrome (GBS), non-infectious encephalitis and vasculitis (European Medicines Agency Committee for Medicinal Products for Human Use, 2009). No additional outcomes have been suggested by existing clinical data.			
Research Question and Objectives: To investigate the safety of cTIV vaccination in			

Name of Sponsor Novartis Vaccines and Diagnostics	**Protocol number:** V58_30OB	**Health authority study registration number(s):**	**Date of Protocol Abstract:** 12 February 2013

adults in routine clinical care in the UK with regard to pre-specified outcomes:

- To plot the number of study outcomes pre-and post-vaccination in outcome specific pre-defined time windows (risk windows) in relation to the date of vaccination. When events are identified in a high risk post-exposure window, to provide a ratio of observed to expected rates.

- To report the incidence of study outcomes in the six months after vaccination.

Study Design: The study is an observational, retrospective, post-marketing safety study of cTIV use in routine UK care.

The study population, exposure and outcomes will be identified from the THIN database over two consecutive influenza vaccination seasons 2012/13 and 2013/14. A third season will be added if sales forecasts, and so numbers exposed (target n=9000), are not achieved. THIN is an observational database of UK electronic primary care patient records.

Population: All adults (18 years and older) with a record of an influenza vaccination with cTIV in the study influenza vaccination seasons.

Variables:

Exposure(s) of interest

The exposure of interest is the vaccination with cTIV (Optaflu produced by Novartis Vaccines & Diagnostics). To identify exposure subjects with a record of an influenza vaccination in their THIN database record will have the vaccination brand or batch number identified. Batch numbers will be compared to those for cTIV supplied to the UK.

Outcome(s)

The following safety outcomes will be identified from the THIN database:

- Anaphylactic reactions (including angioedema)
- Bell's palsy

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- Convulsions
- Demyelination in total and Guillain-Barre syndrome (GBS) alone
- Paraesthesia
- Non-infectious encephalitis
- Neuritis (optic and brachial)
- Vasculitis
- Inflammatory bowel disease
- Thrombocytopenia

Possible outcomes will be identified from THIN primarily using Read codes (NHS Centre for Coding and Classification, 1996) and free text entries. Those documented as confirmed in secondary care will be included, except for Bell's palsy and convulsions, which can be diagnosed in primary care alone. In addition, the outcomes will be compared to stricter definitions and the analyses repeated. A flow chart of case ascertainment is given at the end of Section 9.4.2 and the role of the Adjudication Committee is described there and in Section 9.4.4.

Other Variables

Details of age, sex, and chronic diseases will be obtained from the THIN database. Administration of concomitant pneumococcal polysaccharide vaccine (PPV) will also be identified.

Data Sources: The study population, exposure and outcomes will be identified from the THIN database over 2 consecutive influenza seasons 2012/13 to 2013/14. THIN is an observational database of UK electronic primary care patient records. Within the electronic patient record the practice staff routinely record details of medical events, treatments and any preventive medicine. This includes recording of the date, type and batch number of vaccinations as they are administered. A pre-study feasibility assessment has shown that batch numbers or brand name can be identified for more than 90% of seasonal influenza vaccinations in the THIN database.

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Study Size: As this study will be completed on the THIN database, the number of subjects available for inclusion will be fixed and only the time period for the study can vary.

A total sample size of 9,000 subjects will rule out outcomes occurring with a frequency of 1 in 3,000 if no outcome is observed. This basis is used because all of the study outcomes are rare so no cases may be identified in the post-exposure risk windows.

Data Analysis: The THIN database will be searched for patients who have been exposed to cTIV. Electronic clinical records for these patients will be searched from three months before to 6 months after the vaccination date to identify possible cases of the study outcomes. Records for these patients will be reviewed and judged as a case or not against by an Adjudication Committee using pre-defined case definitions.

This is a hypothesis generating study; the descriptive analyses are not driven by a statistical hypothesis. The study analysis will be performed in two stages:

In stage 1 study outcomes will be identified from three months before vaccination until six months afterwards. Temporal plots will be prepared which show the distribution of each study outcome in relation to the vaccination date in time-windows. Outcome specific time-windows will be defined. These will be based on the biologically plausible time frame when an outcome caused by the vaccine might be expected to occur (the risk-window). If an outcome occurs in the risk window, the ratio of observed to expected cases will be calculated to investigate whether the temporal plots have generated a signal of an association between cTIV exposure and a study outcome. The observed rates will be those in the risk window and the expected will be from outside this period.

Stage 2 will be a descriptive analysis reporting the incidence of each study outcome in the six months after vaccination, in age and sex categories. The six month incidence rate calculations will be repeated for those chronic disease groups who are recommended to have influenza vaccinations namely those with a history of chronic respiratory, heart, liver, or neurological disease or diabetes or immunosuppression. The chronic disease groups will be defined on the basis of the clinical records on the THIN database.

A sensitivity analysis for both stages will include a sub-group of outcomes fitting a more detailed secondary definition developed by an Adjudication Committee.

Name of Sponsor Novartis Vaccines and Diagnostics	**Protocol number:** V58_30OB	**Health authority study registration number(s):**	**Date of Protocol Abstract:** 12 February 2013

Informed Consent and Ethical Approval: Informed consent is not required in this non-interventional study. A protocol will be submitted to the THIN Scientific Review Committee for approval. Practice and patient confidentiality will be maintained throughout the study using an established system.

Milestones:

Start of data collection: The first exposed patients will be identified from the database approximately eight weeks after approval of the study by NVD and is subject to THIN Scientific Review Committee approval.

Interim report(s): The annual study update (each year until 9,000 exposed) will report interim analysis after the each influenza season – April 2014. The number of vaccinated subjects, incidence of study outcomes in the six months after vaccination by age and sex categories (when sufficient numbers) and the temporal relationship of outcomes to vaccination will be included.

End of data collection: April 2015, based on expected use of the vaccine at the time of protocol preparation, two vaccination seasons will be required to identify at least 9,000 exposed patients.

Report of study results: May 2015.

5.0 AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
1	4-4-2013	All	Updated format. Study design was not changed.	New NVD study protocol template approved on Nov 27th, 2012
		4.0 Abstract and 9.3.1 Exposure sections	Addition of feasibility study results	Exposure feasibility study completed
		9.5 Study size	Update to study numbers and so timelines	New sales estimates from NVD
		Appendix 1	Addition of ENCePP checklist	New requirement based on PV guidance EMA/813938/2011 (Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-authorization safety studies, 2012)

6.0 MILESTONES

Milestone	**Planned date**
Agreement signed and final protocol agreed	Estimated March 2013
Start of data extraction and registration in the EU PAS register	March 2013 + 10 weeks[1]
Progress report of number exposed in first season (2012/13)	June 2013 or eight weeks after start date, whichever is later
Interim (year 1) report.	April 2014 (end of 2012/2013 vaccination season + 6 months observation + 3-6 months for extraction of data, review and adjudication + analysis and reporting)
Progress report of number exposed over two vaccination seasons (2012/13 and 2013/14)	June 2014
End of data collection (creation of analytical dataset)	April 2015 (end of 2013/2014 vaccination season + 6 months observation + 3-6 months for extraction of data, review and adjudication of outcomes)[2]
Final report	May 2015
Manuscript	July 2015

[1]Dependant on SRC approval (which is usually within 6 weeks of submission) and provision of batch numbers from NVD. [2]A third influenza season will be required if sufficient patient numbers are not achieved in two seasons. In this case a second progress and interim report will be completed.

7.0 RATIONALE AND BACKGROUND

Influenza is a highly contagious acute viral infection that affects people of all ages. Most people recover in a week or two, but influenza can cause serious morbidity and mortality, particularly among vulnerable individuals including the elderly and those with pre-existing chronic disease (Neuzil 1999; McBean 2004). Influenza epidemics occur mainly in the winter in the Northern hemisphere and can result in widespread disruption to healthcare and other services. A vaccine is produced every year based on the strains of virus expected to be circulating. Vaccination against seasonal influenza is recommended between September and November for at risk groups including the elderly, those at-risk because of chronic disease and people living in long-stay residential care homes. Influenza vaccination has been shown to reduce the number of hospitalizations and deaths due to respiratory disease (Mangtani 2004).

The cell culture trivalent influenza vaccine (cTIV), Optaflu® is new vaccine that was filed for registration with European Medicines Agency in 2007 for use in adults over the age of 18 years. cTIV is no longer produced in embryonated hen eggs, but in a suspension of a specific cell line cloned from Madin Darby Canine Kidney tissue. The influenza cell culture subunit vaccine (cTIV) is a sterile preparation of purified influenza antigens in an isotonic buffer solution for intramuscular administration. The final product contains the membrane proteins hemagglutinin and neuramidase as active ingredients. As recommended by the World Health Organization, these proteins are derived from three influenza virus strains (A/H1N1, A/H3N2 and B).

The safety of cTIV has been evaluated in twelve completed clinical studies all randomized controlled clinical trials with 7.972 adult and 2.264 pediatric subjects who received at least one dose of cTIV. No potential safety concerns were raised by the European Medicines Agency (EMA) based on these data. In the past studies of other seasonal influenza vaccinations have shown an increased risk of Bell's palsy, Guillain-Barre syndrome (GBS), paraesthesia and inflammatory bowel disease (Mutsch 2004; Juurlink 2006; Bardage 2011). Case reports and case series have suggested rare causal associations between influenza vaccinations and neuritis, allergic reactions, non-infectious encephalitis, thrombocytopenia and vasculitis (Hull 1997; Peng 2004; Hjalmarsson 2009; Zafrir 2009; Mantadakis 2010). Recommendations for pharmacovigilance plans for pandemic influenza vaccines by the EMA's Committee for Medicinal Products for Human Use (CHMP) list biologically plausible adverse events of special interest (AESI) and recommends a post-authorization safety study that follows exposed subjects for at least six months after the last dose of vaccine (European Medicines Agency Committee for Medicinal Products for Human Use, 2009). These AESI are anaphylactic reactions and angioedema, Bell's palsy, convulsions, demyelination including Guillain-Barre syndrome (GBS), neuritis, non-infectious encephalitis and vasculitis. Influenza vaccination has also been reported to increase the risk of narcolepsy (Bardage, 2011) however, as the increased risk was in those children and adolescents it will not be included as an outcome in the study. The possibility of

including syncope was reviewed but it was concluded that a general practice database is not an appropriate data source to investigate this as an outcome. If a patient faints it will not always be reported to the GP. If syncope is more likely to be reported to the GP after a vaccination this could introduce bias.

The purpose of this study is to investigate the safety of cTIV in routine post-marketing use in the UK with regard to serious biologically plausible outcomes. Anaphylactic reactions and angioedema, Bell's palsy, convulsions, demyelination including GBS, neuritis (optic and brachial), non-infectious encephalitis, thrombocytopenia, vasculitis, paraesthesia and inflammatory bowel disease will be studied.

8.0 RESEARCH QUESTION AND OBJECTIVES

To investigate the safety of cTIV vaccination in adults in routine clinical care in the UK with regard to pre-specified outcomes:

- To report and plot the number of study outcomes pre-and post-vaccination in outcome specific pre-defined time windows in relation to the date of vaccination. When events are identified in a high risk post-exposure window, to provide a ratio of observed to expected rates.
- To report the incidence of study outcomes in the six months after vaccination.

9.0 RESEARCH METHODS

9.1 Study Design

The study is an observational, retrospective, post-marketing safety study of cTIV use in routine UK care.

9.2 Setting

9.2.1 Study Period

- The study period, from June 2012 to April 2015, will commence three months before the start of the cTIV vaccination campaign in the UK in 2012-2013 and end twelve months after the end of the 2013-2014 vaccination season.

- Individual patients will be included from three months before the date of their cTIV vaccination to six months afterwards.

9.2.2 Study Subjects

The source population will be the THIN database. Study populations, vaccine exposure, study outcomes and patient characteristics will be identified from THIN. In summary, THIN is an observational database of electronic medical records from primary care practices throughout the UK. The database therefore provides information on safety during usual care in the general population. Details of demographics and administrative data, primary care diagnoses and prescription treatment are routinely recorded against date in separate files within individual patient records. Secondary care diagnoses and deaths are also captured because of the structure of the UK health service where primary care physicians act as "gatekeepers" to secondary care. Major events from before computerization are added retrospectively. Data on preventive medicine can be recorded including details of any vaccinations. The practice staff can record vaccinations given and batch number. Medical events are automatically coded at entry using the Read clinical coding system (NHS Centre for Coding and Classification, 1996). Additional information is often available as free text linked to the coded fields or in electronic or scanned discharge summaries. Details of preventive medicine and laboratory results are included in the Additional Health Data (AHD) file. It should be noted that for many practices the electronic record is the primary record and there is no paper version for comparison.

Consequently, THIN provides the advantages of being an observational general population database covering approximately 6% of the UK population (11% in Scotland where cTIV sales are expected to be stronger). The THIN records reflect routine practice and use of vaccines.

UK electronic primary care records have previously been used for the study of the safety of vaccines (Kaye 2001; Tata 2003) including influenza vaccines (Smeeth 2004; Hubbard 2005; Stowe 2009). In the UK the majority of influenza vaccinations are given by primary care practitioners.

9.2.3 Study Population Selection

The study population will be all permanently registered patients 18 years of age and over with a record on THIN that they have received at least one dose of cTIV vaccine as a seasonal influenza vaccination between September 2012 and March 2014 inclusive.

9.3 Variables

The sections below described the theoretical aspects of relevant variables. Data sources and operational definitions are discussed in 9.4.

9.3.1 Exposure of Interest

The exposure of interest is cTIV (Optaflu NVD) vaccination used as a seasonal vaccination in routine clinical care by primary care professionals. In the UK, vaccination against seasonal influenza is recommended between September and April for at risk groups. In the 2011-2012 season the following 'at-risk' groups were recommended for vaccination in Scotland (http://www.sehd.scot.nhs.uk/cmo/):

- anyone aged 65 or over.
- anyone aged six months or over with chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression or diabetes.
- people living in long-stay residential care homes
- unpaid and young carers who provide significant help to someone who could not manage on their own.

In the UK most seasonal influenza vaccinations are given to 'at-risk' groups by their primary care physician. By week 13 of 2011 the Scottish uptake of seasonal influenza vaccination was 75% in people aged 65 years or more, 56% for the under 65 at-risk group and 65% for pregnant women http://www.sehd.scot.nhs.uk/cmo/CMO(2011)08.pdf. Vaccination is also offered to health and social care workers as a part of occupational health.

A pre-study feasibility assessment has investigated the recording of seasonal influenza immunization on the THIN database and the identification of brand used. In the 2010-2011 and 2011-2012 seasons the percentage of patients over 65 years of age with a record of an influenza immunization on THIN was slightly higher than those published regional statistics (Table 1). Either a brand name or batch number could be identified for 94.3% of a sample of 1,000 immunizations.

Table 1 The percentage of people aged ≥65 years who received a seasonal influenza vaccination on THIN and in regional authority statistics

	England	N. Ireland	Scotland	Wales
2010-2011				
THIN	74.5	79.1	75.1	70.8
Regional statistics[1]	72.8	74.9	75.3	65.8
2011-2012				
THIN	75.6	80.9	78.4	71.9
Regional statistics[1]	74.0	77.0	76.2	67.7

[1](Department of Health)

Information on how the commercial product should be stored and administered is in accordance with applicable national or EU guidelines and is described in the package insert.

9.3.2 Outcome(s)

The study will encompass the following safety outcomes:

Allergic reactions

- Anaphylactic reaction and angioedema,

Neurological

- Bell's palsy,
- Convulsions,
- First central nervous system demyelinating event (including Guillain-Barré syndrome (GBS), non-infectious acute disseminated encephalomyelitis (ADEM), multiple sclerosis, Schilder's disease, transverse myelitis and other demyelinating disease of CNS).
- GBS alone
- Paraesthesia
- Neuritis, (optic and brachial)
- Non-infectious encephalitis

Autoimmune

- Vasculitis
- Inflammatory bowel disease (IBD)

Hematological

- Thrombocytopenia

These have been identified as biologically plausible outcomes by the CHMP and in other safety studies. Details of the epidemiology and outcome definitions are summarized by outcome in the Operational Definition Section 9.4.2.

9.3.3 Other Variables

Details of age, sex, and chronic diseases will be obtained from the THIN database. Chronic diseases will be those conditions with which an influenza vaccination is recommended for those under the age of 65 years namely chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression or diabetes. Co-administration of other vaccines may occur as is consistent with clinical practice. In particular pneumococcal polysaccharide vaccine (PPV) may be given concurrently. Administration of PPV will be identified.

9.4 Data Sources

The source population will be the THIN database (see Sections 9.2.2, 9.4.1, 9.4.2 and 9.4.3). UK electronic primary care record databases have previously been used for the study of seizures (Gasse 2000; Gao 2008), GBS (Tam 2007; Stowe, 2009), Bell's palsy (Rowlands 2002; Stowe 2006) demyelinating disease and optic neuritis (Gupta 2005), anaphylaxis (Andrews 2010), vasculitis (Watts 2009), thrombocytopenia (Schoonen 2009) and IBD (Lewis 2002; Gupta, 2005).

9.4.1 Operational Exposure Definition

Exposed patients will be identified from THIN. Exposure will be defined as a record of influenza vaccination, dated in the study vaccination seasons, which has a cTIV batch number or specifically names cTIV as the vaccination given. The unique batch numbers for cTIV available commercially in areas covered by THIN (the whole of the UK) will be provided by NVD. THIN obtains a copy of the primary record of vaccination. Records which include 'refused' or 'advise given' will be excluded. Patients who receive cTIV in both study vaccination seasons will be included twice provided that there is no overlap in the study period. When there is overlap (due to a late vaccination one season and a very early one the next) the second vaccination will be excluded.

9.4.2 Operational Outcome Definition and Identification Process

This section discusses an outcome definition, identification procedure and pre- and post-exposure risk window for each study outcome. It should be noted that some conditions could potentially fit within more than one outcome. For example, ADEM could be included within demyelination or non-infectious encephalitis categories. In practice cases will only be counted within one outcome except for GBS which will be studied alone and in the general demyelinating disease group. Figure 1 shows the identification process.

Multiple sclerosis is the most common form of demyelinating disease and is a chronic condition with relapsing episodes. This study is not designed to study the rate of relapses and, in-line with previous studies of vaccines and demyelinating events, only first episodes will be included. Any new episode of GBS will be included when this outcome

is studied alone. IBD is also a chronic relapsing condition. As with demyelinating disease, only first episodes will be included.

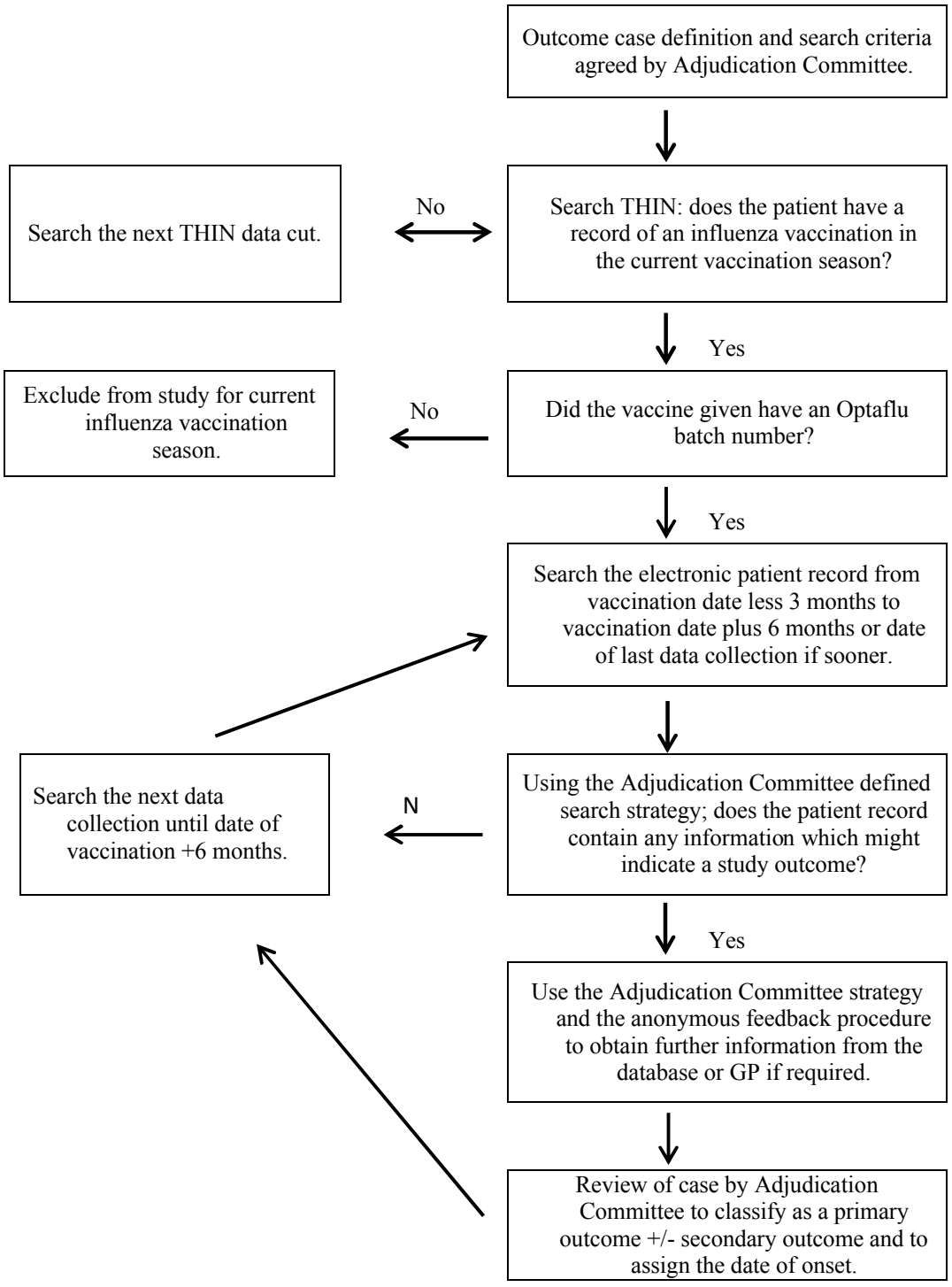
For each outcome, possible cases will be identified by searching exposed patient's records for appropriate Read codes. When no specific Read code is available non-specific Read codes together with free text entries will be searched. The coded medical record, free text associated with the Read codes and any relevant correspondence with secondary care will be reviewed for information on secondary care diagnosis, date of onset and disease episodes. When necessary, further details will be requested from the primary care practice.

Primary case definitions will include all outcomes diagnosed in secondary care, except for seizures and Bell's palsy which are diagnosed by the primary care physician in some cases (Andrews, 2010). For these two outcomes confirmation will be based on all data in the GP system not just the Read code.

In addition a more detailed secondary definition will be developed and a sensitivity analysis will include only a sub-group of outcomes within this definition. The secondary case definition will be developed by an Adjudication Committee based on published case definitions (Section 11). While published case definitions (including the Brighton Collaboration definitions) will be used when possible, these have often been developed for clinical trials and adverse event reports. It is likely that there will be less information in the GP record so lower diagnostic certainty may be necessary. Brighton Collaboration definitions are published for anaphylaxis (Ruggeberg 2007), encephalitis (Sejvar 2007), GBS (Sejvar 2011), seizure (Bonhoeffer 2004) and thrombocytopenia (Wise 2007). A definition for Bell's palsy is under review but not yet published (https://brightoncollaboration.org). A similar design was used in the Vaccine Adverse Events Surveillance and Communication study of the association of GBS with adjuvanted pandemic influenza vaccine, which included UK primary care records (Dieleman 2011). Each case identified will be compared to the study case definition by reviewers blinded as to the date of exposure and categorized as a case or not a case. The primary analysis will be included as there may not be sufficient information to classify all outcomes against a detailed specification.

Pre and post-exposure risk windows are given for each outcome based on data from previous studies and case reports. For most outcomes, little data were available to help define pre-exposure risk windows - the periods of low risk immediately pre-vaccination which will be excluded from the 'expected' estimation (see (Sun 2012) for an example with DTaP-IPV-Hib3 vaccination). Biologically plausible windows were defined based on the duration and treatment of that disease when vaccination might be avoided. Consequently these vary between outcomes. Both sets of risk windows will therefore be reviewed by the Adjudication Committee for the Analysis Plan when Read code lists and database search strategies will also be confirmed.

Figure 1 Identification of study outcomes



Anaphylaxis and angioedema

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, as well as immunizations (Ruggeberg, 2007). Clinical manifestations of anaphylaxis are typically described as starting within seconds to minutes of exposure to a given substance. The case fatality rate is reported to be 1% (Peng, 2004). Distinction between anaphylaxis and anaphylactoid reaction is impossible on the basis of clinical signs and symptoms alone. The Brighton collaboration definition of anaphylaxis includes both conditions (Ruggeberg, 2007).

Angioedema is the rapid spontaneous swelling of the dermis, subcutaneous tissue, mucosa and submucosal tissues. It is caused by a build-up of fluid leaking from thin walled blood vessels and is caused by an allergy like reaction. Cases where angioedema progresses rapidly are a medical emergency as airway obstruction and suffocation can occur.

Background rates

- The incidence of anaphylaxis following immunization is in the range of 1–10 per 1 million doses distributed depending on the vaccine studied (Ruggeberg, 2007).
- A UK primary care study reported a background incidence per 100,000 person-years for anaphylaxis as 8.4 (Peng, 2004). The 2010 Vaccine and Adverse Event Surveillance and Communication (VAESCO) study in eight European countries reported a background rate per 100,000 person-years of 0.6–11.2 for unspecified and 0.9-24.0 for specified anaphylaxis in those 10 years of age and older (VAESCO, 2011). The UK primary care database rates were 6.9 and 0.9 per 100,000 person-years respectively.
- In a UK primary care database, 73% of 120 coded entries for anaphylaxis signified acute episodes. Most of the remaining entries were indications for the prescription of prophylactic agent (Peng, 2004). There is no Read code for anaphylaxis or anaphylactic reaction (only anaphylactic shock).

Risk Window

- Most cases start within 1 hour of exposure but in a minority of cases, symptoms may present up to 12 hours after exposure (Ruggeberg, 2007).

The case definition of a serious allergic reaction will be a record of anaphylaxis, anaphylactoid reaction or angioedema diagnosis with documentation that the diagnosis was made or confirmed in secondary care. These cases will be identified by searching for Read codes and free text terms for allergic reaction, anaphylaxis, anaphylactoid reaction

or angioedema. First prescriptions of prophylactic protection for anaphylaxis will also be identified and, if no record of a prevalent or incident diagnosis is found, information on the indication for therapy will be obtained and reviewed. A post-exposure risk window of 0-1 days and pre-exposure window of 14 days will be reviewed.

Non-infectious Encephalitis

Encephalitis is defined as inflammation of the parenchyma of the brain. A clinical diagnosis of encephalitis depends on the demonstration of brain dysfunction in the presence of evidence of an inflammatory process; this dysfunction may be cortical, subcortical (e.g., deep gray nuclei, brainstem), or both. Myelitis is defined as inflammation of the parenchyma of the spinal cord. An inflammatory process involving both the brain and the spinal cord may be referred to as "encephalomyelitis". A UK study of 2003 patients with encephalitis found that 42% were due to infection, 21% were immune-mediated (including 11% ADEM), while the remainder had no known cause (Granerod 2010). Post-influenza encephalitis, which occurs a shortly after recovery from influenza is thought to be an autoimmune process associated with demyelination and vasculopathy (Hayase 1997).

Background Rates

The VAESCO study in eight European countries reported a background rate per 100,000 person-years of between 0.4–22.7 for non-viral encephalitis in people 10 years of age and over. The UK rate was 4.3 per 100,000 person-years (VAESCO, 2011).

Risk Windows

- In two cases of post-influenza encephalitis in children in England onset was within three days of respiratory symptoms (Protheroe 1991). Three Finnish adults had onset approximately seven days after the start of influenza (Sulkava 1981).
- An analysis of the US Vaccine Adverse Event and Reporting System (VAERS) after H1N1 vaccination reported mean days to ADEM and transverse myelitis of 20 and 30 days respectively (Williams 2011).
- The Vaccine Safety Datalink Project used a risk period of 1-21 days for the study of meningoencephalitis after an influenza vaccination (Greene 2010).

Cases of non-infectious encephalitis diagnosed in secondary care will be included as confirmed cases. The definition will include ADEM, progressive multifocal leukoencephalopathy, transverse myelitis and encephalomyelitis. Possible cases will be identified by searching for Read codes indicating encephalitis including the terms encephalopathy, encephalitis, encephalomyelitis, Rasmussen (for Rasmussen syndrome) and meningoencephalitis. Additional information will be requested from the GP for both non-infectious and non-specific codes and terms.

A post-exposure risk window of 1-60 days with a 14 day pre-exposure window will be reviewed.

First central nervous system demyelinating event

Demyelination is a degenerative process that erodes away the myelin sheath that normally protects nerve fibers. Demyelination exposes these fibers so impairs nerve impulse conduction and this may affect physical systems. Demyelination is seen in a number of diseases, particularly multiple sclerosis. While optic neuritis (including Devic's disease), progressive multifocal leukoencephalopathy and transverse myelitis can be demyelinating diseases, they are included in other study definitions not under this outcome. In the UK multiple sclerosis patients are encouraged to have seasonal influenza vaccination.

Guillain-Barré syndrome (GBS) is an acute polyneuropathy consisting of different subtypes. Acute inflammatory demyelinating polyradiculoneuropathy, the classic demyelinating form of GBS, accounts for 90% of all GBS cases in the Western world. Acute motor axonal neuropathy and acute motor and sensory axonal neuropathy are axonal forms of GBS that are more prevalent in Asia, South and Central America, often preceded by infection by Campylobacter jejuni (VAESCO, 2011). Miller Fisher is a variant of GBS so will be included.

Background rates

- The VAESCO study in eight European countries reported a background rate per 100,000 person-years of 7.0–51.7 for demyelination for people of 10 years of age or older. The UK rate was 15.9 per 100,000 person-years (VAESCO, 2011). Optic neuritis and transverse myelitis were not included in the VAESCO definition. The UK incidence of multiple sclerosis is reported as 5.5 cases per 100,000 person-years (Alonso 2007).
- The VAESCO background rate per 100,000 person-years for GBS was between 1.4 and 7.8 in those 10 years of age or older; 1.5 per 100,000 in the UK (VAESCO, 2011).

Risk Windows

- Chronic inflammatory demyelinating polyneuropathy was reported 2 days after an influenza vaccination (Brostoff 2008).
- The US national spontaneous reporting system for adverse events reported a median onset interval of 13 days between influenza vaccine and GBS, 1990-2003 (Haber 2004).
- French case reports after hepatitis B vaccination reported that, in 57% of reports, the delay between vaccine injection and onset of neurological symptoms was 60

days or less (Hocine 2007). The risk windows in this study were 0-60 and 61-365 days. No increased risk was identified. The Vaccine Safety Datalink Project of seasonal trivalent inactivated influenza vaccine used a window of 1-42 days for demyelinating disease (Greene, 2010).

- A self-controlled case series (SCCS) of GBS and vaccination have used risk periods of 0–30 days, 31–60 days, and 61–90 days (Stowe, 2009) and 6 weeks post-exposure (Andrews 2011). Influenza-like illness was associated with GBS 0-30 and 31-60 days after diagnosis (relative incidences 16.6 and 4.7 respectively) (Stowe, 2009). A nested case-control study used a risk window of 60 days based on plots between date of infection and recording of GBS (Campylobacter, Epstein-Barr virus, influenza-like illness, acute respiratory infections and infectious intestinal diseases) (Tam, 2007).
- A SCCS study of GBS and influenza vaccine excluded the initial 7 days post-vaccine because GBS during this period were considered almost certainly not the result of vaccination but could be associated with disease onset that occurred before vaccination. The relative incidence was 1.45 (1.05-1.99) using the next six weeks as a risk interval and 1.35 (1.01-1.81) when the next eight weeks were included. (Juurlink, 2006)

Confirmed outcomes will have a diagnosis of a first episode of demyelinating disease made in secondary care (including GBS). Possible cases will be identified by searching for Read codes and free text entries indicating demyelinating disease. A post-exposure risk window of 0 to 60 days and a pre-exposure window of 90 days will be reviewed.

GBS cases will have a Read code for GBS, Miller Fisher syndrome or infective polyneuritis and documentation that a diagnosis of GBS or Miller Fisher syndrome was made in secondary care. Risk windows of 7-60 days post-exposure and 90 day pre-exposure will be reviewed.

Paraesthesia

Paraesthesia refers to a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body. The sensation, which happens without warning, is usually painless and described as tingling or numbness, skin crawling, or itching. Chronic paraesthesia is often a symptom of an underlying neurological disease or traumatic nerve damage. Paraesthesia can be caused by disorders affecting the central nervous system, such as stroke and transient ischemic attacks, GBS, multiple sclerosis, transverse myelitis, and encephalitis. Other causes include a tumor or vascular lesion pressed up against the brain or spinal cord or nerve entrapment syndromes.

An increased risk of paraesthesia was found after vaccination against H1N1 influenza (compared to unvaccinated people) in those immunized early in the campaign who were considered to be high risk (Bardage, 2011). While the risk was higher in the first six

weeks after vaccination when it might be due to local effects, it remained increased after six weeks. In a study of VAERS passive surveillance reports for trivalent inactivated influenza vaccines in adults, paraesthesia was one of the most common terms among serious events (Vellozzi 2009).

Background rates

- No general population background rates were identified.

Risk windows

- The incidence of paraesthesia is expected to be high immediately after vaccination due to localised short-term effects (Mayet 2011).
- The risk of paraesthesia remained high more than six weeks after vaccination (Bardage, 2011).

The primary study case definition will be a diagnosis of idiopathic (not related to other outcomes) paraesthesia. Secondary care confirmation is required. Possible cases will be identified by searching for Read codes.

The post-exposure risk windows of 7-42 days and 43-77days and pre-exposure window of 14 days will be reviewed.

Bell's palsy

Bell's palsy is a paralysis of cranial nerve VII (the facial nerve) resulting in inability to control facial muscles on the affected side. It is defined as an idiopathic unilateral facial nerve paralysis and is characterised by rapid onset of partial or complete palsy, usually in a single day. Bell's palsy is largely a diagnosis of exclusion, but certain features in the history and physical examination help distinguish it from facial paralysis due to other conditions: for example abrupt onset with complete, unilateral facial weakness at 24 to 72 hours, and, on the affected side, numbness or pain around the ear, a reduction in taste, and hypersensitivity to sounds. The condition is usually self-limiting but the chance of recovery reduces to 50 per cent when degeneration is evident (Prescott, 1988). An increased risk of Bell's palsy was reported after intranasal influenza vaccination (Mutsch, 2004; Zhou 2004).

Most patients are treated in primary rather than secondary care 81% (Rowlands, 2002).

Background rates

- A UK Primary care database study reported an incidence per 100 000 person-years of 20.2 for Bell's palsy (Rowlands, 2002). The VAESCO study in eight European countries reported a background rate per 100,000 person-years of 5.1–48.1 for Bell's palsy in those 10 years of age or older (VAESCO, 2011). The UK rate was 31.7 per 100,000 person-years (VAESCO, 2011).

Risk Windows

- The Swiss case-control study which reported an increased risk of Bell's palsy after intranasal versus parenteral administration of influenza vaccine reported excess cases 1 to 91 days after vaccination although the period of highest risk was 31 to 60 days after vaccination (Mutsch, 2004).
- SCCS of Bell's palsy after influenza vaccination using UK primary care data, included risk window of 1- 91 days post-vaccination period (and 1–30, 31–60 and 61-91 days) (Stowe, 2006). The day of vaccination was a considered as a separate risk window as there was evidence of opportunistic recording of Bell's palsy on the day of vaccination.
- A US Vaccine Safety Datalink study of H1N1 and Seasonal Influenza Vaccine Safety used 42 day risk and comparator windows (Williams, 2011). An analysis of the US VAERs data for Bell's palsy after influenza vaccine reported that the onset of symptoms was on the day of vaccination for 7%, 1-3 days in 40% and 1-30 days in 77% of reports (Zhou, 2004).

Cases will have a Read code for Bell's palsy. When a case is recorded on the day of the vaccination free text will be reviewed to ascertain whether the diagnosis was made after vaccination. If this isn't clear, then the practice will be contacted to obtain more information. A secondary care diagnosis will not be required given the finding that most cases are diagnosed in primary care.

A post-exposure risk window of 1-90 days and a pre-exposure window of 60 days will be reviewed.

Convulsive seizure

Seizures, or convulsions, are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness (Bonhoeffer, 2004). The presence or absence of seizures is usually the key factor rather than whether or not it was febrile in origin (Bonhoeffer, 2004). Seizures occurring soon after immunization are mostly triggered by fever induced by the vaccine or are not vaccine related (Bonhoeffer, 2004).

Background Rates

- A UK database study reported a rate of 44 per 100,000 person-years for those over 60 years of age (Gao, 2008).The VAESCO study reported a background rate for convulsions in people 10 years of age or older of 42.7–377.6 per 100,000 person-years across eight European countries and 249.6 in the UK (VAESCO, 2011).

Risk Windows

- An analysis of the US VAERS after H1N1 vaccination reported mean days to seizure between 4.5days and 8 days depending on whether the seizure was febrile and if there was past history of disease and mean age between 2 and 16 years (Williams, 2011). Adult cases have been reported 5 days after an influenza vaccination (HA type, 22-7-B) (Nakamura 2003) and within 24 hours after H1N1 vaccination (Mitrakrishnan 2011).
- A VAERS analysis in children after the trivalent influenza included a total of 28 reports of seizures, 25 occurred within 2 days and one each 14 and 30 days after vaccination. The remaining child had a severe infection diagnosed on the day of vaccination (McMahon 2005).
- A study of convulsions in children after monovalent H1N1 and trivalent seasonal influenza vaccine used 7 day risk windows. An increased risk 1-3 days post-vaccination was found with the second dose of monovalent H1N1 influenza vaccine (Stowe 2011). A 'real-time' analysis of trivalent inactivated influenza vaccine used 0-7 and 7-14 day risk windows (Greene, 2010).

The primary study case definition will be a diagnosis of seizure, fit or convulsion whether or not this was febrile. Secondary care diagnosis or confirmation is not required as not all cases will be referred to hospital in the UK. Possible cases will be identified by searching for Read codes and free text entries of seizure, fit or convulsion.

The post-exposure risk windows of 0-7 days and 8-30 days and pre-exposure window of 14 days will be reviewed.

Neuritis (optic and brachial)

Optic neuritis is the general inflammation of the optical nerve. Acute demyelinating optic neuritis is a common cause of optic neuritis in parts of the world where multiple sclerosis is common. Asymmetric relapsing optic neuritis is considered to be diagnostic of multiple sclerosis whereas bilateral disease is known as Devic's disease and is considered to be a variant of demyelinating encephalomyelitis. A number of case reports of optic neuritis after influenza vaccination have been reported in the literature (Perry 1979; Ray 1996; Hull, 1997).

Idiopathic brachial neuritis is a rare disorder of unknown etiology with asymmetric involvement of the brachial plexus. It usually affects young adults and presents with acute unilateral severe shoulder pain lasting days to weeks followed by painless paresis of the upper extremity with slow but gradual recovery. Brachial neuritis has been reported after influenza (Schattner, 2005; Debeer 2008; Holland 2008) and other vaccinations (Debeer, 2008) although little information was found on the time between vaccination and onset.

Background Rate

- For those aged 10 years or more, the 2010 VAESCO study reported a background rate per 100,000 person-years for optic neuritis of 0.6–5.1 across eight European countries and 4.4 per 100,000 in the UK (VAESCO, 2011). An earlier UK study reported an incidence of optic neuritis of 1 in 100,000 person-years (MacDonald 2000).
- In the UK, the incidence of brachial neuritis is approximately 3 per 100,000 person-years (MacDonald, 2000).

Risk windows

- Optic neuritis occurred 17 days and two weeks after influenza vaccination in one patient in consecutive vaccination seasons (Hull, 1997) and 3 weeks after vaccination in another patient (Ray, 1996).
- Brachial neuritis was reported one month after vaccination with human papillomavirus (Debeer, 2008)

The study definition for both optic and brachial neuritis will be a diagnosis made or confirmed in secondary care. The database will be searched for patients with a Read code indicating optic or brachial neuritis including retrobulbar neuritis, optic papillitis, neuralgic amyotrophy, Parsonage-Aldren-Turner syndrome.

A post-exposure risk window of 1-42 days for both neuritis outcomes with a 30 day pre-exposure window will be reviewed.

Vasculitis

Systemic vasculitis refers to a heterogeneous group of disorders characterized by inflammation and necrosis of different sized blood vessels. Both arteries and veins are affected and the conditions are characterized by the vessels and organs affected (Jennette 1994). The conditions are primarily due to leukocyte migration which causes inflammation which leads to narrowing and sometimes to complete blockage of the blood vessel. There have been a number of cases reports of vasculitis after influenza vaccination including microscopic polyangiitis, Churg Strauss syndrome, Henoch-Schonlein purpura,

cutaneous leukocytoclastic vasculitis, polyarteritis nodosa (Blumberg 1980; Kelsall 1997; Perez 2000; Uji 2005).

Wegener's Granulomatosis, microscopic polyangiitis, and Churg Strauss syndrome are associated with anti-neutrophil cytoplasmic antibodies and affect small and medium blood vessels (Lane 2005). They are very rare in childhood and peak in the 65 to 70 year old age group. Giant cell arteritis is predominantly a disease of people over the age of 50. Incidence may be increasing over time and cyclical variation in disease may reflect an infectious etiology. Takayasu arteritis is a disease of the aorta and its branches, however pulmonary and cardiac arteries may be involved. Patients are usually under 40-years of age at presentation. Kawasaki disease (KD) and Henoch-Schonlein purpura are diseases of children and rarely affect adults. KD has been linked to infection, house dust mite and chemicals, and Henoch-Schonlein purpura to a pesticide and drugs (Lane, 2005).

Background rate

- The VAESCO study reported a background rate for vasculitis in people over 10 years of age (VAESCO, 2011). Kawasaki disease, Behçet's disease, polyarteritis nodosa, Wegener's granulomatosis, cryoglobulinemia, Takayasu's arteritis or pulseless disease; Churg-Strauss syndrome; giant cell arteritis or temporal arteritis; Henoch-Schönlein purpura were included. The rate per 100,000 person-years was 1.8-65.8 across eight European countries and 19.3 in the UK (VAESCO, 2011).
- The UK primary incidence of systemic vasculitides (Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, polyarteritis nodosa) has been reported elsewhere as 2.0 per 100,000 person-years in those over 15 years of age (Watts 2000).

Risk Window

- A case of microscopic polyangiitis was reported 2 weeks after trivalent influenza vaccination with 17 other cases of vasculitis listed as occurring from hours to 21 days after exposure (Kelsall, 1997). Giant cell arteritis was reported 1 week after influenza vaccination (Perez 2000).
- Vaccinations may be deferred during treatment for vasculitis as treatments can impair the immune response.

The database will be searched for patients with a Read codes or free text for a general vasculitis term or a specific code for a study vasculitides defined as Behçet's disease, polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, cryoglobulinemia, Takayasu's arteritis or pulseless disease, cutaneous leukocytoclastic vasculitis, Churg-Strauss syndrome, giant cell arteritis or temporal arteritis. Kawasaki disease and Henoch-Schönlein purpura will also be included because, although they usually occur in childhood and this study excludes people under 18 years of age, cases have been reported in adults. Free text searches will be completed at the first step of case

identification for two reasons. Firstly there is no specific Read code for giant cell arteritis so this may be recorded as free text. Secondly the vasculitis may be recorded as free text secondary to a consequential event such as Kawasaki disease and subsequent coronary artery aneurysm.

A risk window of 1-30 days post-vaccination with a 90 day pre-exposure window will be reviewed.

Inflammatory bowel disease (IBD)

IBD is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis. An increased risk of IBD has been reported after H1N1 vaccination compared to non-vaccinated people (Bardage, 2011). Patients with IBD are often treated with long-term immunosuppressive therapies so are in the 'at-risk' group encouraged to have an influenza vaccination.

Background Rate

- UK incidences per 100,000 person-years between 4.5 and 9.5 for Crohn's disease and 0.6 for ulcerative colitis have been reported (Srivastava 1992; Logan, 1998).

Risk Window

- An increased risk after H1N1 vaccination was found both within the first six weeks after immunization and from six weeks post-vaccination to the end of follow-up (maximum eleven months) (Bardage, 2011).

- Of those with a record of IBD on a primary care database, 62% had the first recorded diagnosis within 30 days of the date reported in a GP survey (interquartile range 0 to 81days) (Lewis, 2002).

Confirmed outcomes will have a diagnosis of a first episode of IBD made in secondary care. Possible cases will be identified by searching for Read codes indicating IBD. A post-exposure risk window of 0 to 60 days and a pre-exposure window of 90 days will be reviewed.

Thrombocytopenia

Thrombocytopenia is defined as a platelet count below 150×10^9/L confirmed by blood test or the presence of clinical signs and symptoms of spontaneous bleeding. This condition can be due decreased platelet production by the bone marrow; increased trapping of platelets by the spleen; or a more rapid than normal destruction of platelets. Idiopathic thrombocytopenia, or idiopathic thrombocytopenic purpura, is an immune disease and can be the result of decreased production or survival. It is normally diagnosed by excluding other causes.

A causal association between measles–mumps–rubella vaccine and idiopathic thrombocytopenic purpura has been confirmed by a number of studies (Miller 2001; Black 2003; France 2008) including one which used data from a UK primary care database (Black, 2003).

Background Rate

- An UK primary care database study (1990-2005) reported a population incidence of 3.9 per 100,000 person-years for immune thrombocytopenia (Schoonen, 2009). The 2010 VAESCO study reported a background rate for thrombocytopenia per 100,000 person years for those over 10 years of age of 6.8–57.4 across eight European countries and 19.2 in the UK (VAESCO, 2011).

Risk Windows

- Self-controlled studies of idiopathic thrombocytopenia in young children after MMR immunisation used risks window of 0–42 days (Miller, 2001; France, 2008; Stowe 2008) and 15-35 days (Farrington 1995). The latter study reported four vaccine-associated cases between 19 and 31days after immunisation.

Study definition of thrombocytopenia will be idiopathic thrombocytopenia (no known underlying cause found) diagnosed in secondary care. The database will be searched for patients with a Read code indicating any form of thrombocytopenia, thrombocytopenic purpura or a platelet count below 150×10^9/L. Read codes for splenectomy will not be included in the search as, although it is a standard treatment for adult patients with idiopathic thrombocytopenic purpura, the procedure is not generally considered in the early phases of disease.

A post-exposure risk window of 0-42 days and a pre-exposure window of 30 days will be reviewed.

9.4.3 Operational Variable(s) Definition

- Age will be defined as that on the date of immunization if the patient's birthday was 1st July of their year of birth. Year of birth rather than date of birth is recorded on THIN for confidentiality reasons.
- Sex will be that recorded in the THIN Administration File.
- Clinical information is stored on THIN as Read codes. The presence of a chronic condition of interest will be identified by searching the Medical and Additional Health Data Files for an appropriate Read code up to and including the date of the immunization.
- Concomitant PPV will be a record of this immunization as an entry in the immunization file or as a prescription given within 28 days of the cTIV vaccination. No information on type of PPV will be retrieved.

9.4.4 Advisory Committee(s)

There is no Advisory Committee for this study however an Adjudication Committee will be formed before the study commences by agreement with NVD and the principle investigator, and will have the following responsibilities:

- To agree study outcome case definitions and risk windows (pre- and post-exposure). Case definitions will be based on published versions (see Section 3.6.4) but will be relevant to primary care electronic records.
- To agree a strategy to identify outcomes including the Read code lists for the initial search.
- To review cases against the outcome definitions and to identify new episodes and assign a date of onset. Cases will be reviewed against both the primary and secondary definition and classified as a primary outcome only or both a primary and secondary outcome.
- The Adjudication Committee will also be required to agree the interim and final study results and interpretation.

The Adjudication Committee will include experience in immunology, neurology and epidemiology.

9.5 Study Size

As this study will be completed on the THIN database, the number of subjects available for inclusion will be fixed and only the time period for the study can vary.

A total sample size of 9,000 subjects will rule out outcomes occurring with a frequency of 1 in 3,000 if no outcome is observed (Eypasch 1995). Table 2 shows the number of outcomes expected in the risk window. For most outcomes this will be zero and so a risk of 1 in 3,000 can be ruled out. The exceptions are Bell's palsy and convulsions (when the longer risk window is used). Using the published background rates as the expected and 95% power, 9,000 exposed will rule out a rate ratio of 50 for Bell's palsy and 39 for convulsions (Rothman 1998). At 90% power and 9,000 exposed, the rate ratio that can be ruled out will be 30 for Bell's palsy and 24 for convulsions. It should be noted that the background rates are from the general population (mostly over 10 years of age). The elderly and sick who receive seasonal influenza vaccinations are likely to be at higher risk of outcomes. Consequently background rates of outcomes in the study may be higher than those reported here.

Table 2 The expected number of outcomes based on a sample size of 9,000[1]

	Background annual incidence (per 100,000)	*Post-exposure risk window (days)*	*Pre-exposure low risk window (days)*	*Expected number of events outside risk windows*	*Expected number of events in high risk window*
Anaphylactic reaction / angioedema	8.4	2	14	1	0
Bell's palsy	20.2	90	60	1	1
Convulsions	44	8	14	3	0
Convulsions[2]	44	23	14	3	1
First central nervous system demyelinating event	15.9	61	90	0	0
GBS alone	1.5	61	90	0	0
Paraesthesia (serious events)	Assume 9.0	35	35	0	0
Neuritis, (optic and brachial)	7.0	42	30	0	0
Optic neuritis	4.4	42	30	0	0
Brachial neuritis	3.0	42	30	0	0
Non-infectious encephalitis	4.3	60	14	0	0
Vasculitis	2.0	30	90	0	0
Inflammatory bowel disease (IBD)	7.6	61	90	0	0
Thrombocytopenia	3.9	43	30	0	0

[1]Expected based on 9,000 exposed.
[2]More than one possibility with different time windows. GBS Guillain-Barré Syndrome

The time to identify 9,000 patients has been estimated from the expected use of the vaccine. The NVD sales forecast predicts that, in the 2012 season, the majority of UK cTIV vaccinations will occur in Scotland. In subsequent seasons cTIV will be distributed throughout the UK. THIN covers 11% of the Scottish population and 6% of the total UK population. Table 3 estimates the number of exposed patients available for study using updated sales estimates provided by NVD, a lower sales figure (50% of that suggested) and the THIN coverage. It assumes that 94% will have a batch number identified based on a feasibility study. It is assumed that an additional one third of doses will not be identified because of uneven geographic distribution of use, some occupational health vaccination of key workers, errors in batch numbers and unused doses.

Table 3 Estimated number of cTIV exposed patients in THIN by influenza vaccination season

Season	*Sales estimate*[1]		*% Population covered*[2]	*Maximum exposed*		*94% with batch number*		*Assume 2/3 identified*[3]	
	Lower	*Upper*		*Lower*	*Upper*	*Lower*	*Upper*	*Lower*	*Upper*
2012/13	5,250	5,650	11%	578	622	543	541	362	360
2013/14	300,000	505,000	6%	18,000	30,300	16,920	26,361	11,280	17,574
Total								11,642	17,934

[1] For 2013/2014, the higher figure is the NVD estimate, the lower figure is 50% of this figure.
[2] For 2012/13 use will mostly be in Scotland with 11% THIN coverage, 2013/14 use throughout the UK with 6% THIN coverage.
[3] Assuming loss due to uneven distribution, occupational vaccination, incorrect batch numbers etc.

A minimum of 9,000 exposed patients should be identified in two annual vaccination seasons, 2012/2013 and 2013/2014 based on sales estimates at January 2013. If actual sales are lower, then an additional vaccination season may be required.

9.6 Data Management

9.6.1 Data Processing

The THIN database will be searched at each collection of data from GPs to identify patients exposed to cTIV. The electronic records of these patients will be searched for coded and free text entries which could indicate a diagnosis of a study outcome dated from three months before vaccination until six months afterwards. If a potential outcome is identified, then additional information will be obtained from the electronic record or, when necessary, the GP. This will result in a lag time of approximately three to six months from the date of recording by the GP to classification as a case.

The extraction of data for this study will be completed by staff at Cegedim Strategic Data Medical Research Ltd who run the database. These cuts are subject to routine quality assurance following standard operative procedures.

Further details of data management will be included in the Analysis Plan.

Blinding

Assigning of cases by an Adjudication Committee will be completed blinded to date of exposure to the vaccine.

9.6.2 Software and Hardware

The source data is THIN which is a managed research database. Normal THIN procedures for database maintenance and anti-fraud protection, archiving as well as quality standard procedures will apply to this study. The cut and analysis of data will be completed using SAS. CSD currently use SAS version 9.2.

9.7 Data Analysis

The study will primarily be a descriptive analysis of the occurrence of study outcomes. Patients who have been immunized with cTIV will be selected and study outcomes dated from three months before vaccination until six months afterwards identified. Temporal plots will be prepared which show the distribution of each study outcome in relation to the vaccination date in time-windows. The time-windows of the plot will be outcome specific. Biologically plausible risk-windows will be defined depending on the time between the exposure and outcome observed in published observational studies, passive surveillance or case reports. For example, an appropriate risk window for anaphylaxis is 1-2 days as this outcome occurs very quickly after exposure to the allergen while GBS is unlikely to occur in the first 7 days after exposure to a causal agent but can present several weeks later. The ratio of observed to expected cases will be calculated to investigate whether the temporal plots have generated a signal of an association between cTIV exposure and a study outcome. The observed number will be that from the risk window and the expected number will be from the data from the same patients but in a specified window of time outside the risk window. Data from immediately before exposure (in pre-defined pre-exposure windows) will not be included because of the risk of a 'healthy user' effect with vaccination delayed because of ill health.

A statistical analysis plan will be completed when the case definitions have been agreed by the Adjudication Committee

9.7.1 Statistical Hypotheses

The study is a descriptive and hypothesis generating analysis and, as such, is not driven primarily by a statistical hypothesis. However, the sample size of 9,000 has been selected so that under the 'rule of three' if an outcome is not identified then a frequency of 1 per 3,000 or more can be ruled out (Eypasch, 1995). This basis is used because all study outcomes are rare so no cases may be identified in the post-exposure risk windows (Table 2). Where an outcome is identified the temporal plot and observed versus expected analyses will indicate if further study is required.

9.7.2 Analysis of Demographics and Baseline Characteristics

- Age will be described as mean and standard deviation.
- Sex, history of each of the chronic conditions and PPV will be reported as a number and a percentage of the total.

9.7.3 Statistical Methods

The study will provide additional data on the safety of cTIV but will not test a specific hypothesis. Most of the outcomes are rare and there may be insufficient numbers to complete a formal comparative study.

Stage 1

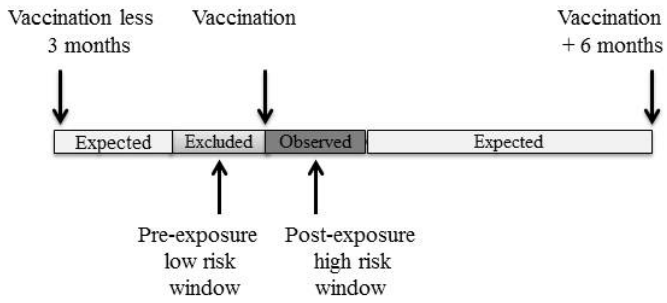
Within each study outcome, for each case identified during follow-up (3 months prior to 6 months post exposure) the time between the outcome and exposure will be calculated. A plot will be produced to show the temporal distribution of the study outcome in relation to the vaccination date in time-windows. For an example see Stowe *et al* (Stowe, 2009). The time-windows of the plot will be study outcome specific based on those defined in Section 3.6.1. In case of multiple episodes per subject, only the first outcome will be included.

Where outcomes are identified in the post-exposure risk window, the ratio of the rate of observed to expected cases will be calculated to investigate whether the temporal plots have generated a signal of an association between cTIV exposure and a study outcome. The observed rate will be the total number of occurrences of that outcome in the post-exposure risk window divided by the total number of days in the high risk window and the expected number will be the rate from the same patients but in the time outside this post-exposure the risk window and a pre-exposure window (Figure 2). Data from immediately before exposure (the pre-exposure window) will be excluded because of the risk of a 'healthy user' effect with vaccination delayed because of ill health. 95% confidence intervals will be estimated to show if the ratio is statistically significantly different to one.

Stage 2

The incidence of each study outcome in the six months after exposure to cTIV will be reported as number of study outcomes observed per 100,000 person- years follow-up. In case of multiple episodes per subject, only the first outcome will be included. This analysis will be repeated in age-sex categories, and 'at-risk' groups.

Figure 2 Expected and observed time periods in stage 1 of the analysis



Subgroup analyses

The six month incidence rates will be repeated for those chronic disease groups who are recommended to have influenza vaccinations namely those with diabetes, immunosuppression or chronic respiratory, heart, liver, or neurological disease.

If an increase in the ratio of observed to expected is identified for a study outcome then it may be difficult to distinguish whether this is related to cTIV or a pneumococcal vaccination given at the same time. If there are sufficient patients exposed only to cTIV a sensitivity analysis will repeat the analysis in this population.

9.7.4 Statistical Considerations

Handling of Lost to follow-up and missing data

All eligible exposed patients will be included regardless of whether or not they have an electronic practice record from three months pre- to six months post-vaccination (Figure 1). Other missing data is not anticipated as age and sex is recorded in >99% of THIN patients. Concomitant diseases will be included if noted in the electronic patient record but will be assumed to be absent if there is not noted.

Another issue to be addressed in an analyses based on a database is the repetition of the same Read code for one episode of disease, for example when the GP makes a record of the disease both when informed of the diagnosis and when a prescription treatment is issued. Therefore, second episodes will be reviewed for all or a sample of cases to assign either a new episode or to develop a window outside which time additional entries will be treated as new episodes.

9.8 Quality Control

9.8.1 Validation

Most study outcomes will be identified using Read codes and free text terms but will only be included as cases if there is documentation that the diagnosis was made or confirmed in secondary care. The exceptions will be convulsions and Bell's palsy with which a secondary care physician may not be consulted and only the primary care electronic record is available. The Read code and any accompanying free text or scanned documents are the primary care physicians made patient record. In these cases all available records will be reviewed to confirm diagnosis.

9.8.2 Record Retention

Investigators will retain all study records required by NVD and by the applicable regulations in a secure and safe facility. The investigator must consult a NVD representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with Good Pharmacoepidemiological Practice guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

For observational studies, study records or documents may include the analyses files, syntaxes (usually stored at the site of the database), but also questionnaires.

9.9 Limitations of the Research Methods

Both sections will be observational designs using cases identified from an observational database of electronic general practice records. The major benefit of observational studies is that they reflect the true clinical situation, taking into account the actual environment including patient profile, concomitant treatment, etc. One limitation of an observational database study is that the researcher can use only that information which is routinely available in general practice. In the present study, the only information available on the

study events is that in the general practice record including correspondence from secondary care. It is therefore likely that, for many cases, there will be insufficient clinical detail available to researchers to classify diagnoses using detailed case definitions. Consequently, any case identified through Read codes will be accepted as such if there is evidence that the diagnosis was made in secondary care. Two exceptions to this definition are seizures and Bell's palsy as febrile seizures and Bell's palsy may not always be referred to secondary care depending on severity (Rowlands 2002; Andrews 2010). For these study outcomes, all cases identified through Read codes will be included.

It is possible that differential misclassification will occur in cases diagnosed immediately after vaccination if it is known that a study outcome has been associated with vaccinations in the past, for example in GBS. The sensitivity analyses using the case definitions developed as part of the study should minimize this bias. However, these analyses may have few cases due to low incidence rates and a lack of detailed information. Other biases and confounders, such as selection bias, will be minimized as only patients exposed to cTIV will be included in this descriptive analysis.

The pneumococcal polysaccharide vaccine (PPV) can be given to some patients at the same time as exposure to cTIV. If an increase in the rate of a study outcome is identified in a risk window then it may be difficult to distinguish whether this is related to PPV or cTIV unless there are sufficient patients exposed only to cTIV to complete a sensitivity analysis. As PPV is usually offered to people who are over 65 with no previous PPV (http://www.scswis.com/index2.php?option=com_docman&task=doc_view&gid=627&Itemid=720), the overlap in vaccinations will not be complete. This dual immunization is likely to occur in any non-interventional study in the UK. However, the study will reflect the true clinical situation in UK primary care.

Given that the outcomes are rare and the exposure in the UK is now likely to be low (limited to Scotland for at least the first season) the study has been designed to exclude a rate of 1:3,000 if no cases are identified. The numbers of outcomes are unlikely to be sufficient to investigate the causal association with exposure (see Table 1). This analysis has therefore been designed to test for potential associations rather than to directly test causality. It has the advantage of no confounding due to none time-dependent variables. Similar approaches are also used in signal detection with spontaneous reports http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011295.pdf and have been used in 'near real-time surveillance' for influenza vaccine safety studies in the Vaccine Safety Datalink Project although a sequential analysis is not proposed (Greene, 2010).

Details of vaccination by employers or elsewhere outside the primary care surgery will not be captured using this method. However, as the study design does not involve comparison between exposed and non-exposed individuals this will not affect the results. It may reduce the numbers available for study but this has been accounted for by including two vaccination seasons. The study will include a minimum of 9,000 patients

who receive cTIV during the two influenza vaccination seasons from 2012/2013 to 2013/2014.

9.10 Other Aspects

Alternative methods were considered for this study. In particular a self-controlled case series comparative analysis was considered, however, there were concerns that there would be insufficient exposed patients to allow analysis of some study outcomes despite the advantage of increased power to study rare outcomes compared to a case-control study. Observation from 6 months rather than 3 months pre-vaccination was also considered but has the disadvantage of including summer months when the event rate will be different from the 'exposed' risk window (for example higher for anaphylaxis, lower for GBS). There will be residual seasonal differences during the observation period but the differences should be lower if summer is excluded.

10.0 PROTECTION OF HUMAN SUBJECTS

A protocol will be submitted to the THIN Scientific Research Committee for approval. A Multi-centre Research and Ethics Committee has approved THIN procedures. The THIN Scientific Research Committee reviews individual protocols for scientific validity and to ensure that the study is within the Ethics Committee approval.

Practice and patient confidentiality will be maintained throughout the study. Patient records on the database are anonymous. Both the practice and patient identifying details are replaced by codes which cannot be broken by the researchers. The study will require validation of information recorded on the database. Validation of outcomes is possible and will be completed using an established system that protects confidentiality. When validation of an entry or extra detail in the primary care practice is required, the researchers will contact a third party who can break the practice code. This third party will contact the practice where the patient can be identified. Any reply will be vetted by the third party to ensure that no information has been included which could reveal the identity of the patient, practice or healthcare provider, before forwarding any documents to the researchers. When access to the computerized comments field is required, the third party will vet the free text in the same manner to ensure that no identifying details are included.

NVD respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

10.1 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with Good Pharmacoepidemiological Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed Consent

No informed consent is required as the electronic records are anonymous; the identities of patients and GPs are not known. A feedback method has been developed to allow validation without breaking this anonymisation.

10.3 Responsibilities of the Investigator and IRB/IEC/REB

The collection procedures for the THIN database have been approved by a UK multi-center ethics board. The protocol will be submitted to the THIN Research Ethics Committee for approval before the study can start. This Committee does not provide waiver of informed consent as the identities of the patients and health care providers are not known.

A signed and dated statement that the protocol has been approved by the IRB/IEC/REB will be given to NVD before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform NVD immediately that this request has been made.

10.4 Protocol Adherence

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact NVD or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by NVD and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the study, potential benefit of the study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on

subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by NVD, Health Authorities where required, and the IRB/IEC/REB. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, NVD should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

11.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

A requirement for SAE/AE reporting is not anticipated as the study uses secondary data collection so data on a causal relationship of exposure to the study outcomes is not collected.

12.0 PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

12.1 Registration in Public Database(s)

The key design elements of this protocol will be posted in a publicly accessible database where applicable and in compliance with current regulations. This includes posting on the ENCePP website.

Key results of this study will be posted in a publicly accessible database within the required time-frame from completion of the data collection where applicable and in compliance with current regulations.

12.2 Publications

The results of this study will be submitted for publication as a scientific paper in a peer-reviewed journal. Manuscripts will be prepared independently by the principle investigator and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (Elm 2007). NVD will be entitled to view the results and interpretations included in the manuscript and provide comments within 45 days of receipt of the manuscript. The manuscript will not be submitted for publication until receipt of comments or the 45 days have expired.

In order to allow national competent authorities to review in advance the results and interpretations to be published, NVD will communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

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APPENDIX 1: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 18/12/2012

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number (s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	X	☐	☐	13
1.1.2 End of data collection[2]	X	☐	☐	13
1.1.3 Study progress report(s)	X	☐	☐	13
1.1.4 Interim progress report(s)	X	☐	☐	13
1.1.5 Registration in the EU PAS register	X	☐	☐	13
1.1.6 Final report of study results.	X	☐	☐	13

Comments:

-

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number (s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	14

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number (s)**
2.1.2 The objective(s) of the study?	X	☐	☐	15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	14
2.1.4 Which formal hypothesis(-es) is (are) to be tested? 2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	X	36

Comments:

The study is a descriptive and hypothesis generating analysis and, as such, is not driven primarily by a statistical hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number (s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	X	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	X	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	37-38

Comments:

-

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number (s)**
4.1 Is the source population described?	X	☐	☐	16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	X	☐	☐	15
4.2.2 Age and sex?	X	☐	☐	16
4.2.3 Country of origin?	X	☐	☐	16
4.2.4 Disease/indication?	X	☐	☐	16
4.2.5 Co-morbidity?	X	☐	☐	19
4.2.6 Seasonality?	X	☐	☐	16
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	16 & 35

Comments:

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Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number (s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	X	☐	☐	17 &19
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	X	☐	☐	16 & 17

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number (s)**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	X	☐	☐	17 & 19
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	X	☐	☐	37
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	X	

Comments:

Study of a vaccine so dose and duration not relevant.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number (s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	X	☐	☐	19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	X	☐	☐	19

Comments:

An Adjudication Committee will classify outcomes as cases or not.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number (s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	X	39
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	X	39

Comments:

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Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	X	☐	☐	16 & 19
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	X	☐	☐	16 & 19
8.1.3 Covariates?	X	☐	☐	16 & 19
8.2 Does the protocol describe the information available from the data source(s) on:	X	☐	☐	16, 19

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	19 and 36
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	32
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)				
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	X	☐	☐	16
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	X	☐	☐	16
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	X	19
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

The exposure is a vaccination which is not recorded using a coding system. Exposure will be identified by searching for name and batch number.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number (s)**
9.1 Is sample size considered?	X	☐	☐	33
9.2 Is statistical power calculated?	X	☐	☐	33

Comments:

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Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number (s)**
10.1 Does the plan include measurement of absolute effects?	☐	☐	X	
10.2 Is the choice of statistical techniques described?	X	☐	☐	37
10.3 Are descriptive analyses included?	X	☐	☐	37
10.4 Are stratified analyses included?	X	☐	☐	38
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	X	39
10.6 Does the plan describe methods addressing effect modification?	☐	☐	X	

Comments:

This is an hypothesis generating study; the descriptive analyses are not driven by a statistical hypothesis.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number (s)**
11.1 Is information provided on the treatment of missing data?	X	☐	☐	38
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	36
11.3 Are methods of quality assurance described?	X	☐	☐	36
11.4 Does the protocol describe possible quality issues related to the data source(s)?	X	☐	☐	17, 19, 33
11.5 Is there a system in place for independent review of study results?	X	☐	☐	33 & 43

Comments:

Study results will be reviewed by investigators, the Adjudication Committee and, separately, the sponsor company. Details of the quality assurance standard operative procedures are not specified.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number (s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	X	☐	☐	39
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	X	☐	☐	39
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	17 & 33
12.3 Does the protocol address other limitations?	X	☐	☐	39

Comments:

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Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number (s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X	☐	☐	41
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
13.3 Have data protection requirements been described?	X	☐	☐	41

Comments:

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Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number (s)**
14.1 Does the protocol include a section to document future amendments and deviations?	X	☐	☐	12

Comments:

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Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number (s)**
15.1 Are plans for communicating study results described?	X	☐	☐	43
15.2 Are plans described for disseminating study results externally, including publication?	X	☐	☐	43

Comments:

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Name of the main author of the protocol: Gillian Hall

Date: 04/04/2013

Signature: _____

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