Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England 2017/18

Date of Final Protocol: 30 June 2017
GSK study number (e-track): 207781
GSK study abbreviated title: EPI FLU-055 VS UK

Collaborating Study Sponsor: University of Surrey, Guildford UK
Collaborating Study Sponsor: GlaxoSmithKline Biologicals, Rue de l'Institut, 89, 1330 Rixensart, Belgium

University of Surrey investigators and primary protocol authors:

Prof PPD **(Principal Investigator)*** Professor of Primary Care and Clinical Informatics Chair in Health Care Management, University of Surrey PPD	* Department of Clinical and Experimental Medicine University of Surrey Guildford PPD W: PPD
PPD Programme Manager Department of Clinical and Experimental Medicine, University of Surrey PPD	
PPD Practice Liaison Officer Department of Clinical and Experimental Medicine, University of Surrey PPD	
PPD Senior Database Developer Department of Clinical and Experimental Medicine, University of Surrey PPD	
PPD Primary Care Scientist Department of Clinical and Experimental Medicine, University of Surrey PPD	
PPD Senior Research Fellow Department of Clinical and Experimental Medicine, University of Surrey PPD	

Contributing authors from GlaxoSmithKline:

PPD Epidemiology, Clinical R&D US/BE* PPD	*GSK Vaccines Rue de l'Institut 89 1330 Rixensart Belgium
PPD Clinical Epidemiology Project Lead, Clinical R&D US PPD	
PPD Statistician PPD	
PPD Epi Lead Statistician PPD	
PPD SERM Head PPD	
PPD Safety Scientist PPD	

Funding: GlaxoSmithKline Biologicals SA

Table of contents

1. SYNOPSIS 4
2. LIST OF ABBREVIATIONS AND GLOSSARY 6
3. RESPONSIBLE SPONSORS 8
4. INTRODUCTION 9
a. Rationale for the pilot study and background 9
b. Objectives and endpoints 12
5. RESEARCH METHODS 14
a. Study Design 14
6. PROJECT MANAGEMENT 33
7. ETHICAL CONSIDERATIONS 35
8. INFORMATION GOVERNANCE CONSIDERATIONS 36
9. DISSEMINATION AND PUBLIC REGISTER DISCLOSURE 37
10. APPENDIX 39
11. REFERENCES 54

1. SYNOPSIS

Background:
The European Medicines Agency (EMA) set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The EMA guideline came into effect in February 2017 and included its last Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on passive enhanced safety surveillance for seasonal influenza vaccines in the EU. In 2014/2015 and 2015/2016, GlaxoSmithKline Biologicals (GSK) collaboratively with the University of Surrey carried out pilot studies (EPI-FLU-045 - EPI-FLU-046). These surveillance studies were conducted in England since nearly all primary care consultations and vaccinations are recorded in computerised medical record (electronic health record, EHR) systems.

Aim:
The EPI-FLU-055 pilot study aims to fulfil the EMA guideline. The requirement is to rapidly detect an increase in the frequency or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, with increased exposure to the vaccine.

Objectives:
The eligible study period for both primary and secondary objectives is expected to be from 01 September until 30 November 2017.

- *Primary objective:* To estimate the weekly and cumulative incidence rates of adverse events of interest (AEIs) within 7 days following vaccination with any seasonal influenza vaccine using card-based adverse drug reaction (ADR) reporting system. Data will be presented overall, by brand (*Fluarix Tetra* vs. others), by age strata, and UK Chief Medical Officer (CMO)-specified risk groups status (at risk/not at risk).
- *Secondary objective:* To estimate the weekly and cumulative incidence rates of AEIs within 7 days following vaccination with any seasonal influenza vaccines using the card-based ADR reporting system as well as routinely collected AEIs. Data will be presented overall, by brand (*Fluarix Tetra* vs. others), by age strata, and UK CMO-specified risk groups status (at risk/not at risk).

Method:
The EPI-FLU-055 pilot study will build on the key learnings from the EPI-FLU-045 and EPI-FLU-046 pilot studies carried out in the 2 previous influenza seasons (2015/2016 and 2016/2017) in order to adapt the approach to collect and report adverse events. The EPI-FLU-055 pilot study is intended to collect data about vaccination status and adverse events following immunisation (AEFI) on a weekly basis, from 01 September 2017 onwards, using a standardised approach.

Study design: The third pilot study will be a prospective passive enhanced safety surveillance study with weekly and cumulative analysis of incidence rate of reported AEIs. A combination of card-based ADR reported data and routinely collected medical data will be used to provide relevant information about influenza vaccine safety, and analyse these data in a near to real time manner, ideally within a week or so of data collection.

Setting: 10 volunteer general practices in England, primarily using the GSK influenza vaccine will be enrolled. After the end of each influenza seasons, these general practices select which brand of influenza vaccine they will use in the subsequent season. The observation period will coincide with the start of influenza vaccination period in the respective GP practices and is intended to end on 30th November 2017.

Participants: Influenza vaccine recipients who are registered with participating GP practices, and/or their guardian or carer.
Registered patients who have explicitly opted out of data sharing will be excluded from the analysis.

Data sources: All data pertaining to the study will be extracted from practice electronic health record (EHR) systems. Anonymised data, (strictly defined as "pseudonymised"), will be transferred to the secure network at University of Surrey where analysis will occur on its secure network. No individual patient level data will leave this network. Data from the ADR forms completed by the patients will be entered into the GP practice EHR system.

Variables: The extract will include: demographic data, information about vaccine exposure, data about co-morbidities supporting eligibility for influenza vaccination as defined by the UK CMO's high risk groups will be collected, as well as EMA specified AEIs occurring within 7 days of vaccination, combining data routinely collected during GP-consultation and data reported using a customised card-based ADR reporting system listing EMA defined AEIs.

Bias: Any disparities in the data generated compared with the national population and the immunisation recommendations in the UK will be discussed.

Study size: As per EMA requirement and Vaccine Working Party (VWP) recommendations, a target of at least 1000 vaccinees across all age groups (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years). The sample size proposed in this study accounts for the probability of observing at least one event in the 10 enrolled GP practices together with the level of precision associated with the finding.

Statistical methods: Weekly and cumulative incidence rates of AEIs within 7 days following vaccination with a seasonal influenza vaccine (GSK's *Fluarix Tetra* or another influenza vaccine) will be estimated, with 95% confidence intervals (CIs).

Outputs:
Weekly analysis: A weekly analysis of influenza vaccination and uptake by vaccine brand, different age and at-risk (as per UK CMO recommendations) groups and reports of AEIs in vaccinees will be produced. Those reported at consultations in the practice (medically attended) as well as those reported through ADR cards will be listed.

Final analysis: Interim weekly safety reports and a final comprehensive study report at the end of observation period will be produced. The findings will be discussed in light of the rates of adverse reactions observed in the RCGP network, in clinical trials performed with GSK's seasonal influenza vaccines and, as appropriate, with rates observed in EPI-FLU-045 and EPI-FLU-046 studies.

2. LIST OF ABBREVIATIONS AND GLOSSARY

ADR	Adverse drug reaction
AEFI	Adverse events following immunization
AEI	Adverse events of interest – as defined by EMA for this report
BMI	Body Mass Index
CAG	Confidential Advisory Group
CI	Confidence interval
CMO	Chief Medical Officer at Department of Health, London
CRN	Clinical Research Network
DCEM	Department of Clinical and Experimental Medicine, at University of Surrey
DES	Directed enhanced services
EDPPS	European Data Protection Supervisor
EHR	Electronic Health Record (used in EMA publications)
EMA	European Medicines Agency
EPI-FLU-045	The first pilot study in 2015/2016: Enhanced safety surveillance of seasonal influenza vaccines: feasibility study in England
EPI-FLU-046	The second pilot study in 2016/17: Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England
EU	European Union
GIS	Geographical Information System
GMS	General Medical services – the standard NHS primary care provision
GP	General Practitioner – A family physician providing NHS care to a registered list of patients
GPSoC	GP System of Choice, range of NHS approved computerised medical record systems that provide the required level of functionality to support primary care delivery
GSK	GlaxoSmithKline Biologicals
IGT	Information Governance Toolkit
JCVI	Joint Committee on Vaccination and Immunisation
LAIV	Live attenuated influenza vaccine
MAH	Marketing Authorisation Holders
NIHR	National Institute of Health Research
NHS	National Health Service
NHS Digital	NHS DIGITAL (source of National data against which denominators and other population data can be checked & security policy, including its IGT)
NRES	National Research Ethics Service
ODS – NHS Digital	Organisation Data Service NHS Digital – system that provides codes for all NHS bodies, including general practices and population data about these bodies
PASS	Post Authorisation Safety study
PHE	Public Health England
PRAC	Pharmacovigilance Risk Assessment Committee of EMA
QIV	Quadrivalent Influenza Vaccine
QOF	Quality and Outcomes Framework

RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
RSC	Research and Surveillance Centre (part of RCGP)
REC	Research Ethics Committee
RES	Research and Enterprise Support
RSE	Relative Standard Error
SAE	Serious Adverse Event – An SAE (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
SLA	Service level agreement
SOAP	Simple Object Access Protocol
UK	United Kingdom
VWP	Vaccine Working Party

3. RESPONSIBLE SPONSORS

University of Surrey
Guildford, Surrey
GU2 7XH
United Kingdom

GSK Vaccines
Rue de l'Institut 89
1330 Rixensart
Belgium

4. INTRODUCTION

a. Rationale for the pilot study and background

The European Medicines Agency (EMA) is a decentralised body of the European Union (EU responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. Part of this responsibility is to coordinate the EU's safety-monitoring or pharmacovigilance system for medicines, monitor the safety of medicines through the EU network, and take action, if information indicates that the benefit-risk balance of a medicine has changed since it was authorised.

In response to a recent expansion of national vaccination programmes in EU member states, the European Medicines Agency has released interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU[i]. This set out new standards for surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The key objective of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, as exposure to the vaccine increases. Of note, since 2015, European regulatory requirements to evaluate the safety and immunogenicity of seasonal influenza vaccines in small scale clinical trials were withdrawn[ii]. Such trials had insufficient power to adequately evaluate safety concerns arising from annual formulation changes (e.g. adverse events occurring at a rate of 1–2%). These clinical trials are replaced by enhanced, preferably active, safety monitoring and vaccine effectiveness assessments.

In the initial EMA Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU suggested that there would be three options envisioned for enhanced surveillance:

- *Enhanced Active surveillance (post authorisation safety studies [PASS]):* Active follow-up of a cohort of children and adults for 7 days after immunisation for reactogenicity endpoints/adverse events.
- Enhanced Passive Surveillance: Rapidly estimate vaccine usage and facilitate adverse drug reaction (ADR) reporting, in order to determine reporting rate as a surrogate of incidence of the adverse events of interest (AEIs).
- Data mining or other use of electronic health record/ computerized medical record.

The present collaborative pilot study between MAH GlaxoSmithKline Biologicals (GSK) and the Clinical Informatics and Health Outcomes Research Group at the University of Surrey builds on the lessons learned from the pilot studies (EPI-FLU-045 VS UK and EPI-FLU-046 VS UK). The study addresses the EMA commitment for enhanced safety surveillance of seasonal vaccines in Europe. The EPI-FLU-045 VS UK pilot study showed that the proposed surveillance setting in the UK was suitable for rapid detection and evaluation of AEIs during an influenza season. Nevertheless, the outcomes were not available in a near real time manner. This was successfully addressed in the EPI-FLU-046 VS UK pilot study.

Both pilot studies confirmed that a card-based ADR reporting system in addition to report of AEI from routinely collected was a valid methodology. In the EPI-FLU-046 VS UK pilot study, the ADR cards were customized (including pre-specified EMA AEIs) and a specific field was created to allow

reporting that no AEI was experienced during the period of interest. Thanks to those modifications, the return rate drastically increased up to approximately 50%. In addition, the encoding of AEIs was facilitated for GPs which led to a more standardised and more accurate way to ultimately collect the AEIs.

The EHR data provided a reliable estimate of the denominator of vaccines administered throughout the participating GP practices. The use of routinely collected data provided additionally demographic characteristics and account for underlying conditions, or comorbidities, discharged letter from hospital or prescriptions from pharmacist for patients registered in the participating GP practices.

The primary purpose of the 2016/17 pilot study was to improve the combination of a card-based ADR reporting system and the use of routine data to collect adverse events following vaccination with seasonal influenza vaccines, as per EMA guidance and PRAC requirements. The ADR cards had been further customized since the first pilot study to account for the EU requirements. The 2017/18 pilot study will build on the lessons learned from the first 2 pilot studies and aim to continue standardizing the approach to collect and report AEIs.

The results of the current study will further inform decisions regarding future influenza vaccine safety surveillance and contribute to the cumulative awareness and knowledge associated with reporting of adverse event following immunisation (AEFI) in Europe.

The Clinical Informatics Research Group, in the Department of Clinical and Experimental Medicine (DCEM) at the University of Surrey is home of the data and analysis hub for the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC). The RCGP RSC provides a national primary care surveillance system and is supported by Public Health England (PHE). The RCGP RSC network of GP practices has a membership designed to give national coverage of 1.5%-2% of the English population.[iii] The data processing, analysis capability, and leadership of the RCGP RSC developed by and are performed at the University of Surrey will be used for this investigation.

The most important work of the RCGP RSC network is its influenza surveillance; many GP practices have been involved in this work for decades[iv]. Data are uploaded from the network on a weekly basis to a secure sever with the possibility to switch the frequency of the release to a twice weekly upload during epidemics. The methods developed by the University of Surrey will be used in this passive enhanced safety surveillance study, with a focus on adverse events reporting after vaccination.

Seasonal influenza vaccines present several specific challenges for pharmacovigilance. These include immunisation in large population cohorts in a relatively short and fixed time period each year, and multiplicity of vaccine products on the market with the need to conduct product-specific safety surveillance.

Routine pharmacovigilance systems for influenza vaccines would need capability to rapidly detect and evaluate potential new safety concerns each influenza season. The main objective of enhanced safety surveillance is to detect and evaluate a potential increase in product and batch-specific reactogenicity and allergic events in a near real-time manner in the earliest vaccinated cohorts in order to react accordingly as promptly as possible.

Similarly to the first two pilot studies, the Enhanced Passive Surveillance approach is the one chosen for this third pilot study. The use of customised ADR cards is the enhancement provided over simple AEI surveillance through routine data collection.

The UK national flu immunisation programme 2017/18 – recommendations

Groups eligible for flu vaccination are based on the recommendation of the Joint Committee on Vaccination and Immunisation (JCVI). The national flu immunisation programme aims to provide direct protection to those who are at higher risk of flu associated morbidity and mortality. This includes older people, pregnant women, and those with certain underlying medical conditions. In 2012 JCVI recommended extending vaccination to children to provide both individual protection to the children themselves and reduce transmission across all age groups by recommending an intranasal live attenuated influenza vaccine (LAIV).

In the UK, 2017/2018 influenza plan recommended the following groups to be vaccinated[v]:

- all children aged two to eight (but not nine years or older) on 31 August 2017 (with LAIV)
- All primary school-aged children in former primary school pilot areas (with LAIV)
- Those aged six months to under 65 years in clinical risk groups
- Pregnant women
- Those aged 65 years and over
- Those in long-stay residential care homes
- Carers

In 2017/18 changes to the programme are as follows:

- **Morbidly obese:** Vaccination of the morbidly obese (defined as body mass index [BMI] of 40 and above) will attract a payment under the directed enhanced services (DES) in 2017/18.
- **Age segments in children to receive the seasonal vaccination (children aged 4-5 years):** These children will now be offered flu vaccination (LAIV) in reception class, rather than through general practice. No payment will be made under the DES if they are vaccinated in general practice (unless the child is in an at risk group);
- **School Year 4 (children aged 8-9 years):** As part of the phased roll-out of the children's programme, this year children in school year 4 will also be offered the vaccination.

Eligible adults aged 18 years and over will have the choice of getting their flu vaccine at a pharmacy the Community Pharmacy Seasonal Influenza Vaccination Advanced Service. Of note, the intent will be to issue cards to all vaccinated patients belonging the recruited practices, however, considering the UK influenza vaccination plan, some vaccinations are expected to occur outside of the GP settings describe as opportunistic vaccination, perform by third parties including pharmacist and thus it cannot be excluded that for some patients, ADR cards are not distributed. The AEIs will however be captured through the routine data collection process.

The list above is not exhaustive, and the healthcare practitioner should apply clinical judgement to take into account the risk of influenza exacerbating any underlying disease

Expansion of national vaccination has increased the need for timely information and reassurance on the balance of risks and benefits for those receiving the vaccines. The collaborative pilot study is conceived in response to the EU requirements triggered by the EMA's call for enhanced safety surveillance in Europe. This third pilot study in the 2017/18 season will help to build a framework for passive enhanced safety surveillance in the UK, but will also contribute to an EU-wider programme of enhanced safety surveillance for seasonal influenza vaccines.

b. Objectives and endpoints

Per EMA guideline on enhanced safety surveillance for seasonal influenza vaccines in the EU, the EPI-FLU-055 pilot study intends to rapidly detect a clinically meaningful change to the known safety profile of influenza vaccines, in terms of the frequency and/or severity of expected reactogenicity (local, systemic or allergic reactions) that may indicate a potential safety signal.

Vaccine coverage will be estimated through the EHR system from the participating GP practices and rates of AEIs following the receipt of seasonal influenza vaccine will be calculated by combining a card-based ADR reporting system and routinely collected.

As per EU requirement, data quality will be evaluated, with special focus on data completeness and timeliness.

The eligible study period is expected to be from 01 September until 30 November 2017.

Primary objective:

- To estimate the weekly and cumulative incidence rates of adverse events of interest (AEIs) within 7 days following vaccination with any seasonal influenza vaccine using card-based adverse drug reaction (ADR) reporting system. Data will be presented overall, by brand (*Fluarix Tetra* vs. others), by age strata, and UK Chief Medical Officer (CMO)-specified risk groups status (at risk/not at risk).

Secondary objective:

- To estimate the weekly and cumulative incidence rates of AEIs within 7 days following vaccination with any seasonal influenza vaccines using the card-based ADR reporting system as well as medically attended AEIs. Data will be presented overall, by brand (*Fluarix Tetra* vs. others), by age strata, and UK CMO-specified risk groups status (at risk/not at risk).

Tertiary objective:

- To estimate on a weekly basis the vaccine uptake among the subjects registered in the enrolled GP practices, by age strata (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years) and CMO-specified risk groups.
- To assess the completeness of vaccination data in the EHR
- To assess the timeliness of availability of vaccination data in the EHR
- To evaluate the return rate of ADR cards
- To assess the timeliness of AEI reports in the EHR from medically attended AEIs and from the card-based ADR reporting system

- To assess the timeliness of generating weekly reports

Primary endpoint:

- Occurrence of AEIs (Appendix 2) within 7 days post vaccination reported using a card-based ADR reporting system overall, by age strata (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years) and UK CMO-specified risk groups status (at risk/not at risk), each week and cumulatively, overall and by vaccine brand (*Fluarix Tetra* vs. others). AEIs will be presented by system organ categories.

Secondary endpoint:

- Occurrence of AEIs within 7 days post vaccination reported using data entered in EHR (i.e., AEIs derived from a card-based ADR reporting system and medically attended AEIs) overall, by age strata (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years) and UK CMO-specified risk groups status (at risk/not at risk), each week and cumulatively, overall and by vaccine brand (*Fluarix Tetra* vs. others). AEIs will be presented by system organ categories.

Tertiary endpoints:

- Seasonal influenza vaccination status among the subjects registered in the enrolled GP practices, overall, by vaccine brand, by age strata (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years) and UK CMO-specified risk groups and date of vaccine administration collected in the EHR system
- Level of missing data related to vaccination information (date of event, vaccine brand, vaccine batch).
- Lag time between date of vaccine administration and date at which vaccination record is encoded in the EHR system
- Return of ADR cards
- Time interval between AEI onset date and recording in the EHR by source (medically attended vs via ADR cards).
- Time interval between the date data extraction and date at which the weekly report is generated.

5. RESEARCH METHODS

a. Study Design

Study setting and population

Routinely collected primary care data from up to ten GP practices will be extracted, to support passive surveillance. Additionally, this passive surveillance will be enhanced by the use of a card-based ADR reporting system. ADR card will distributed to patients and upon return entered into the EHR system.

EPI-FLU-055 VS UK study targets to follow vaccinated patients between 01/09/2017 and 30/11/2017.

A customized ADR card will be used, which lists pre-defined categories of AEIs to be reported, similarly to study EPI-FLU-046 (2016/2017 season). A field will also be included to report AEIs not listed as well as a field to indicate that no AEI occurred within the 7 days-time window. Patients will be provided with the ADR cards and asked to complete the ADR cards with any AEIs occurring within 7 days post vaccination and to return the cards to the GP practices not later than 14 days post-vaccination[vi].

GP practices ordering mainly GSK's *Fluarix Tetra* vaccine for the 2017/18 season will be contacted to inquire about their interest in participating in this study. This may also include existing research contacts and networks of the University of Surrey. GP practices selection will ensure distributed location across England (in London, a Northern city, and rural settings in the North and South) and that the participating population spans different age strata, different levels of deprivation, different ethnic mix, different brand of computerised medical record systems, and different practice sizes. However, this will be tempered by our need to recruit before the start of the influenza immunisation season.

GP practices will also be included based on their ability to comply with the protocol requirements (e.g., number of subjects registered, IT system used). GP practices will be reimbursed for their involvement in this study, according to the National Institute of Health Research (NIHR) guidelines for industry sponsored studies[vii].

Of note, regulatory compliance studies can be registered with the National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio[viii]. Advice will be sought as to whether this study qualifies.

Inclusion criteria

1. Surveillance is planned to apply to vaccination between 1st September and 30th November 2017

As this is a GP sentinel safety surveillance study, all individuals who receive influenza vaccination in the 10 participating GP practices between 1 September and 30 November 2017 are planned to be eligible for inclusion in the analysis. A date of 30 November allows for safety evaluation and potential signal detection early in the annual vaccination period and was selected for the 2016/2017 season.

2. GP Practices primary vaccine supplier will be preferentially GSK

To fulfil its commitment, the Company will recruit from GP practices ordering preferentially GSK's *Fluarix Tetra*. Therefore, an inclusion criterion is that GP practices use GSK as their principal vaccine supplier.

Exclusion criteria

Data will not be extracted from patients having "opted out" in respect of use of their medical data

Registered patients who have explicitly opted out of data sharing will be excluded from the analysis. These patients will be identified by the opt-out codes within GP information systems. Patients will be informed of their option to opt-out via posters in the GP practices and information sheets accompanying the ADR cards.

Data extraction and data management

There are a number of GP EHR systems in use; the systems eligible for use in English primary care must be part of GP System of Choice (GPSoC)[ix]. GP practices have a single EHR system, which contains comprehensive data about patients, their medical history including treatment and all the aspects of providing General Medical Services (GMS – the standard NHS primary care provision) or other primary care schema. There are predominantly 3 brands; the market leader is Egton Medical Information Systems (EMIS), followed by The Phoenix Partnership (TPP) SystmOne, and In Practice Systems (INPS) Vision.

Two data sources are considered for this study, i.e., the general practice EHR data (routine data collection) which provides the standard passive surveillance component and the ADR cards system completed by patients corresponding to the enhanced component. The ADR cards are being returned to the patient's own practice to ensure confidentiality. Using a specific code, the data from these cards will be also coded into the EHR and uploaded weekly.

1. General Practice EHR data recorded by the practice team. Weekly data about vaccine exposure, and any subsequent AEIs will be uploaded (anonymised) to University of Surrey. The EHR data contains both AEIs recorded by the practice team, as well as data reported to the GP practice on an ADR card by a vaccinated patient.
2. ADR cards completed by patients. Among the 10 participating GP practices, patients who are vaccinated against influenza will be provided ADR cards. These ADR cards customised following practice feedback to match EMA requirements will be used to collect AEIs reported after the receipt of influenza vaccination.

The method and governance procedure has been developed by the University of Surrey, using an approved provider, Apollo. If not applicable, alternatively, another approved data extraction supplier will be chosen, or the relevant study data will be directly extracted by the University of Surrey team using standard data extraction tools such as Morbidity Information Query Export Syntax (MIQUEST), tool sponsored by the Department of Health.

Data extractions will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer.

Pseudonymisation is a process that involves the removal of all personal identifiers – such as name, date of birth, etc. Furthermore, encrypted data will be kept during transfer and on a secure network that meets NHS Information Governance standards to minimise the risk of re-identification. Pseudonymisation is the standard approach for this type of surveillance. A legally binding definition of pseudonymisation has been introduced into European law[x] on the recommendation of the European Data Protection Supervisor (EDPS)[xi].

Data are anonymised (strictly defined as "pseudonymised") as near to source as possible. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES[1] and RSA 1024[2] before transmission, and utilises public and private key pairs unique to each project. Pseudonymisation is applied at this stage to allow for backwards identification should there be a need to do so as part of an ethically approved study.

For this study, it is required to link an adverse event to the vaccine (specific brand and batch number) administered. Pseudonymisation allows this without knowing any of the strong personal identifiers of that individual.

All data processing and analysis in the study will be conducted within the secure IT environment of the Clinical Informatics Research Group, at the University of Surrey. The information security policies and procedures of the Research Group have been approved by the NHS Digital as meeting Information Governance Toolkit (IGT) standards[xii].

The system is continuously being updated and modernized in respect of information processing, security and governance processes. The data are automatically extracted from the network of GP practices using a Simple Object Access Protocol (SOAP) web service, on a weekly basis. Data are uploaded to a secure Microsoft SQL server, and processed into aggregated tables; these are then linked to a pre-defined report structure using business intelligence software (Tableau Software, Inc. Seattle, WA, www.tablleau.com), to produce a weekly surveillance report in a timely manner.

Using the EHR system, routine data as well as the content of encoded ADR cards will be extracted using methods that Surrey developed and deploys to extract RCGP RSC surveillance data. Sensitive coded data and free-text data will not be extracted. Only relevant EHR data for this study (e.g. disease or symptom, vaccination status and brand) coded by the GPs or other health professional will

[1] This is also referred to as "3DES", which is the commonly used name for the triple data encryption algorithm (TDEA, also written Triple DEA) symmetric-key block cipher.
[2] RSA stands for Rivest, Shamir and Aldeman who founded RSA Laboratories. They created large numbers with only two prime factors, a core component of the encryption process

be extracted[xiii]. Large volume of research that has come out of UK primary care is based on coded data[xiv]. The quality of primary care data are such that the expectation will be able to detect frequent AEIs.[xv]

GP practices will be required to use the relevant Read code for ADR notifications, when recording data from a returned card (Read Code: PPD - Adverse drug reaction notification).

Relevant coded data will be extracted, however these are limited to the administration regime, AEIs and batch number fields of prescribing data.

The following routinely collected patient data will be extracted for the study:

- Demographic information: age, gender, ethnicity, date of registration.
- Seasonal influenza vaccine information: date of administration, brand and batch number when available
- To understand any inequities in access according to level of social deprivation using Geographical Information System (GIS) methods, full postcodes will be immediately transformed into deprivation scores, using the Index of Multiple Deprivation, within GP computer systems upon date extraction.
- Primary care consultations following vaccination, any other markers of health care utilisation, and referral to further care.
- AEIs (Appendix 2) or any other reported AE recorded in the EHR.
- Data from at least one year prior to the start of the study to determine the category of UK CMO-specified risk group for influenza vaccination the subjects belong to:
  - Life-style/risk factors, CMO risk status – e.g. BMI, smoking status.
  - Records of other diseases and long term conditions – e.g. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, immunosuppression, pneumonia, etc.
  - Pregnancy status during the course of the study period.

Sample size consideration

The average practice size in England is 7,034 patients[xvi], an estimate of approximately 70,340 patients are expected to be registered (across the ten participating GP practices). Of note, in the period from September to December 2016, the seasonal influenza vaccine uptake for over 65 year olds was 71.0%; for those in a clinical risk group aged 6 months to 65 years old, the uptake was 45.1%; and for pregnant women, it was 42.3%. The estimate of influenza vaccine uptake had been made estimated using the coverage estimates published by Public Health England (PHE)[xvii].

The eligible target population to be medically followed by the GPs would be estimated at 50,000 subjects (approximately 5,000 per practice using a conservative approach). As per EMA Pharmacovigilance Risk Assessment Committee (PRAC)/Vaccine Working Party (VWP) request, at least 1,000 vaccinated subjects with 7 days of follow-up after vaccination are targeted to be enrolled. In this study, up to 5,000 vaccinated subjects with 7 days of follow-up after vaccination are expected to be enrolled. This sample size estimation sets out to estimate the probability to observe at least

one AEI in the study population and evaluate the level of "certainty" around this finding; over a 14 week-surveillance period (01 September – 30 November 2017).

The recruitment will be performed by GP practice and this might create a clustering effect. Based on the previous year study (EPI-FLU-046 study) the clustering effect is expected to be negligible. Similarly to last year, in the present study, the clustering effect was not accounted for in the power calculation but will be considered during the analysis.

Cluster effect

Cluster effect requires special statistical considerations when designing the study, and later when analysing the data. Groups tend to form because of certain selection factors, so individuals within the group tend to be more similar to each other with respect to important potential confounders than those selected truly at random.

For instance, patients medically followed by the same GP are usually more prone to receive similar treatment for a given condition than those being treated for the same condition by different physicians. Furthermore, patients attending a single GP practice are likely to share similarities including geography, socioeconomic status, ethnic background, or age by virtue of the area they have all chosen to live In the same way, GPs who have chosen to work together are likely to share similarities

Similarities, or homogeneity, between subjects in clusters reduces the variability of their responses, compared with that expected from a random sample. As a consequence, a compensatory increase in sample size is required to maintain power in studies characterised by a cluster effect and the degree of similarity of within clusters should also be assessed. The intra-cluster correlation coefficient (ICC) is a measure of the relatedness or similarity of clustered data. There are different methods of calculating the ICC, usually requiring a pilot study, but all compare the variance within clusters with the variance between clusters.

Sample size calculation

Table 1 shows the exact 95% CI, the probability of observing at least one AEI during the study period in the study cohort and the relative standard error (RSE) for a range of scenarios in term of cohort size, vaccine coverage and expected probability of AEI[xviii]. With an overall cohort size of about 50,000 subjects medically followed by the participating GP practices, an estimated study period of 14 weeks, a vaccine coverage of 2%, 5%, 10% or 20% and an expected probability of AEI varying from 0,01% to 20%, the corresponding probability to observe at least one event in our study population varies from 9 to >99%, and the associated relative standard error varies from 2.0% to 316% depending on the scenario.

Table 2 shows the evolution by week of the exact 95% CI, the cumulative probability of observing at least one AEI in the study cohort and the relative standard error (RSE) in the course of the study for a range of scenarios in term of cohort size, vaccine coverage and probability of AEI of 1%. With an overall sample size of a minimum of about 50,000 subjects medically followed by the enrolled GP practices, a follow-up period of 14 weeks, a vaccine coverage of 2%, 5%, 10% or 20%, the

corresponding cumulative probability to observe at least one event in our study population varies from 51% to 100% after week 1, and the associated relative standard error varies from 9% to 118% depending on the scenario.

Table 1 Exact 95% Confidence Intervals, Relative Standard Error and probability to observe at least one AEI according to expected probabilities of occurrence of AEI[xix]

Expected Population medically followed by the enrolled practices	Vaccine coverage	Vaccinated subjects	Subjects with events	Expected Proportion of subjects with ≥1 AEI reported	Lower 95%CL	Upper 95%CL	Probability to observe ≥1 AEI in the study population	Associated Relative standard error (RSE)
50000	20%	10000	2000	20.00%	19.2%	20.8%	>99.99%	2.0%
50000	20%	10000	1500	15.00%	14.3%	15.7%	>99.99%	2.4%
50000	20%	10000	1000	10.00%	9.4%	10.6%	>99.99%	3.0%
50000	20%	10000	500	5.00%	4.6%	5.4%	>99.99%	4.4%
50000	20%	10000	400	4.00%	3.6%	4.4%	>99.99%	4.9%
50000	20%	10000	200	2.00%	1.7%	2.3%	>99.99%	7.0%
50000	20%	10000	100	1.00%	0.8%	1.2%	>99.99%	9.9%
50000	20%	10000	10	0.10%	0.0%	0.2%	>99.99%	31.6%
50000	20%	10000	9	0.09%	0.0%	0.2%	99.99%	33.3%
50000	20%	10000	8	0.08%	0.0%	0.2%	99.97%	35.3%
50000	20%	10000	7	0.07%	0.0%	0.1%	99.91%	37.8%
50000	20%	10000	6	0.06%	0.0%	0.1%	99.75%	40.8%
50000	20%	10000	5	0.05%	0.0%	0.1%	99.33%	44.7%
50000	20%	10000	4	0.04%	0.0%	0.1%	98.17%	50.0%
50000	20%	10000	3	0.03%	0.0%	0.1%	95.02%	57.7%
50000	20%	10000	2	0.02%	0.0%	0.1%	86.47%	70.7%
50000	20%	10000	1	0.01%	0.0%	0.1%	63.21%	100.0%
50000	10%	5000	250	5.00%	4.4%	5.6%	>99.99%	6.2%
50000	10%	5000	200	4.00%	3.5%	4.6%	>99.99%	6.9%
50000	10%	5000	100	2.00%	1.6%	2.4%	>99.99%	9.9%
50000	10%	5000	50	1.00%	0.7%	1.3%	>99.99%	14.1%
50000	10%	5000	5	0.10%	0.0%	0.2%	99.33%	44.7%
50000	10%	5000	4.5	0.09%	0.0%	0.2%	98.89%	47.1%
50000	10%	5000	4	0.08%	0.0%	0.2%	98.17%	50.0%
50000	10%	5000	3.5	0.07%	0.0%	0.2%	96.98%	53.4%
50000	10%	5000	3	0.06%	0.0%	0.2%	95.03%	57.7%
50000	10%	5000	2.5	0.05%	0.0%	0.2%	91.80%	63.2%
50000	10%	5000	2	0.04%	0.0%	0.1%	86.47%	70.7%
50000	10%	5000	1.5	0.03%	0.0%	0.1%	77.69%	81.6%
50000	10%	5000	1	0.02%	0.0%	0.1%	63.22%	100.0%
50000	10%	5000	0.5	0.01%	0.0%	0.1%	39.35%	141.4%
50000	5%	2500	125	5.00%	4.2%	5.9%	>99.99%	8.7%
50000	5%	2500	100	4.00%	3.3%	4.8%	>99.99%	9.8%
50000	5%	2500	50	2.00%	1.5%	2.6%	>99.99%	14.0%
50000	5%	2500	25	1.00%	0.6%	1.5%	>99.99%	19.9%
50000	5%	2500	12.5	0.50%	0.3%	0.9%	>99.99%	28.2%
50000	5%	2500	2.5	0.10%	0.0%	0.3%	91.80%	63.2%
50000	5%	2500	2.25	0.09%	0.0%	0.3%	89.47%	66.6%
50000	5%	2500	2	0.08%	0.0%	0.3%	86.48%	70.7%
50000	5%	2500	1.75	0.07%	0.0%	0.3%	82.63%	75.6%
50000	5%	2500	1.5	0.06%	0.0%	0.3%	77.70%	81.6%
50000	5%	2500	1.25	0.05%	0.0%	0.3%	71.36%	89.4%
50000	5%	2500	1	0.04%	0.0%	0.2%	63.22%	100.0%
50000	5%	2500	0.75	0.03%	0.0%	0.2%	52.77%	115.5%
50000	5%	2500	0.5	0.02%	0.0%	0.2%	39.35%	141.4%
50000	5%	2500	0.25	0.01%	0.0%	0.2%	22.12%	200.0%
50000	2%	1000	50	5.00%	3.7%	6.5%	>99.99%	13.8%
50000	2%	1000	40	4.00%	2.9%	5.4%	>99.99%	15.5%
50000	2%	1000	20	2.00%	1.2%	3.1%	>99.99%	22.1%
50000	2%	1000	10	1.00%	0.5%	1.8%	>99.99%	31.5%
50000	2%	1000	1	0.10%	0.0%	0.6%	63.23%	99.9%
50000	2%	1000	0.9	0.09%	0.0%	0.6%	59.36%	105.4%

Expected Population medically followed by the enrolled practices	Vaccine coverage	Vaccinated subjects	Subjects with events	Expected Proportion of subjects with ≥1 AEI reported	Lower 95%CL	Upper 95%CL	Probability to observe ≥1 AEI in the study population	Associated Relative standard error (RSE)
50000	2%	1000	0.8	0.08%	0.0%	0.6%	55.08%	111.8%
50000	2%	1000	0.7	0.07%	0.0%	0.5%	50.35%	119.5%
50000	2%	1000	0.6	0.06%	0.0%	0.5%	43.13%	129.1%
50000	2%	1000	0.5	0.05%	0.0%	0.5%	39.35%	141.4%
50000	2%	1000	0.4	0.04%	0.0%	0.5%	32.97%	158.1%
50000	2%	1000	0.3	0.03%	0.0%	0.5%	25.92%	182.5%
50000	2%	1000	0.2	0.02%	0.0%	0.4%	18.13%	223.6%
50000	2%	1000	0.1	0.01%	0.0%	0.4%	9.52%	316.2%

Table 2 Exact 95% Confidence Intervals, Relative Standard Error and cumulative probability to observe at least one AEI by week associated with a probability of occurrence of event of 1%

Week	Expected Population medically followed by the enrolled practices	Cumulative Vaccine coverage after 14 weeks	Cumulative number of Vaccinated subjects	Cumulative number of Subjects reported ≥1 AEI	Average Proportion of AEI reported	Lower 95%CL	Upper 95%CL	Cumulative Probability to observe at least one event	Associated Relative standard error (RSE)
1	50000	20%	714	7	1.00%	0.4%	2.0%	99.92%	37.2%
2	50000	20%	1428	14	1.00%	0.5%	1.6%	>99.99%	26.3%
3	50000	20%	2142	21	1.00%	0.6%	1.5%	>99.99%	21.5%
4	50000	20%	2857	28	1.00%	0.7%	1.4%	>99.99%	18.6%
5	50000	20%	3571	35	1.00%	0.7%	1.4%	>99.99%	16.7%
6	50000	20%	4285	42	1.00%	0.7%	1.3%	>99.99%	15.2%
7	50000	20%	5000	50	1.00%	0.7%	1.3%	>99.99%	14.1%
8	50000	20%	5714	57	1.00%	0.8%	1.3%	>99.99%	13.2%
9	50000	20%	6428	64	1.00%	0.8%	1.3%	>99.99%	12.4%
10	50000	20%	7142	71	1.00%	0.8%	1.3%	>99.99%	11.8%
11	50000	20%	7857	78	1.00%	0.8%	1.2%	>99.99%	11.2%
12	50000	20%	8571	85	1.00%	0.8%	1.2%	>99.99%	10.7%
13	50000	20%	9285	92	1.00%	0.8%	1.2%	>99.99%	10.3%
14	50000	20%	10000	100	1.00%	0.8%	1.2%	>99.99%	9.9%
1	50000	10%	357	3	1.00%	0.2%	2.4%	97.23%	52.7%
2	50000	10%	714	7	1.00%	0.4%	2.0%	99.92%	37.2%
3	50000	10%	1071	10	1.00%	0.4%	1.7%	>99.99%	30.4%
4	50000	10%	1428	14	1.00%	0.5%	1.6%	>99.99%	26.3%
5	50000	10%	1785	17	1.00%	0.6%	1.5%	>99.99%	23.6%
6	50000	10%	2142	21	1.00%	0.6%	1.5%	>99.99%	21.5%
7	50000	10%	2500	25	1.00%	0.6%	1.5%	>99.99%	19.9%
8	50000	10%	2857	28	1.00%	0.7%	1.4%	>99.99%	18.6%
9	50000	10%	3214	32	1.00%	0.7%	1.4%	>99.99%	17.6%
10	50000	10%	3571	35	1.00%	0.7%	1.4%	>99.99%	16.7%
11	50000	10%	3928	39	1.00%	0.7%	1.4%	>99.99%	15.9%
12	50000	10%	4285	42	1.00%	0.7%	1.3%	>99.99%	15.2%
13	50000	10%	4642	46	1.00%	0.7%	1.3%	>99.99%	14.6%
14	50000	10%	5000	50	1.00%	0.7%	1.3%	>99.99%	14.1%
1	50000	5%	178	1	1.00%	0.0%	3.1%	83.29%	74.6%
2	50000	5%	357	3	1.00%	0.2%	2.4%	97.23%	52.7%
3	50000	5%	535	5	1.00%	0.3%	2.2%	99.54%	43.0%
4	50000	5%	714	7	1.00%	0.4%	2.0%	99.92%	37.2%
5	50000	5%	892	8	1.00%	0.4%	1.8%	99.99%	33.3%
6	50000	5%	1071	10	1.00%	0.4%	1.7%	>99.99%	30.4%
7	50000	5%	1250	12	1.00%	0.5%	1.7%	>99.99%	28.1%
8	50000	5%	1428	14	1.00%	0.5%	1.6%	>99.99%	26.3%
9	50000	5%	1607	16	1.00%	0.6%	1.6%	>99.99%	24.8%
10	50000	5%	1785	17	1.00%	0.6%	1.5%	>99.99%	23.6%
11	50000	5%	1964	19	1.00%	0.6%	1.5%	>99.99%	22.5%
12	50000	5%	2142	21	1.00%	0.6%	1.5%	>99.99%	21.5%
13	50000	5%	2321	23	1.00%	0.6%	1.5%	>99.99%	20.7%
14	50000	5%	2500	25	1.00%	0.6%	1.5%	>99.99%	19.9%
1	50000	2%	71	0	1.00%	0.0%	5.1%	51.01%	118.1%
2	50000	2%	142	1	1.00%	0.0%	3.9%	76.00%	83.5%
3	50000	2%	214	2	1.00%	0.1%	3.3%	88.36%	68.0%
4	50000	2%	285	2	1.00%	0.1%	2.5%	94.30%	58.9%
5	50000	2%	357	3	1.00%	0.2%	2.4%	97.23%	52.7%
6	50000	2%	428	4	1.00%	0.3%	2.4%	98.65%	48.1%
7	50000	2%	500	5	1.00%	0.3%	2.3%	99.34%	44.5%
8	50000	2%	571	5	1.00%	0.3%	2.0%	99.68%	41.6%
9	50000	2%	642	6	1.00%	0.3%	2.0%	99.84%	39.3%

Week	Expected Population medically followed by the enrolled practices	Cumulative Vaccine coverage after 14 weeks	Cumulative number of Vaccinated subjects	Cumulative number of Subjects reported ≥1 AEI	Average Proportion of AEI reported	Lower 95%CL	Upper 95%CL	Cumulative Probability to observe at least one event	Associated Relative standard error (RSE)
10	50000	2%	714	7	1.00%	0.4%	2.0%	99.92%	37.2%
11	50000	2%	785	7	1.00%	0.4%	1.8%	99.96%	35.5%
12	50000	2%	857	8	1.00%	0.4%	1.8%	99.98%	34.0%
13	50000	2%	928	9	1.00%	0.4%	1.8%	99.99%	32.7%
14	50000	2%	1000	10	1.00%	0.5%	1.8%	>99.99%	31.5%

Statistical analyses

All data processing and statistical analysis will be performed within the secure IT environment of the Clinical Informatics Research Group, at the University of Surrey. R and SAS Software will be used for the statistical analyses. Statistical analyses will be described in details in a statistical analysis plan, including the methodology to account for the clustering effect.

Coded data will be interpreted by the creation of ontologies allowing to map to case-definitions, where available. However, no in depth descriptions required for case definition will be used such as in clinical trials. Meaning will be inferred from brief clinical coded information.

Sequence of analysis

Interim analysis

Weekly safety report

Weekly safety reports will be generated in order to be able to detect and potentially report any safety concerns in near real time manner. Analyses will be performed overall and by vaccine brand (*Fluarix Tetra* vs. others).

The weekly incidence rates of AEIs within 7 days will be estimated as follows:

- The denominator will consist of the number of subjects vaccinated two weeks before the week of interest
- The numerator will encompass all subjects from the denominator reporting the AEI within 7 days following vaccination with a seasonal influenza vaccine

Final analysis after end of the surveillance period

Analyses of demographics/baseline characteristics

Characteristics of the participating GP practices (Clinical Commissioning Group (i.e. the administrative health division used in England), North/South, Urban/Rural, IMD, number of registered subjects (rounded to the nearest 1000 to avoid the identification of the GP practices) will be tabulated.

Demographic characteristics will be summarized using descriptive statistics:

- Frequency tables will be generated for categorical variables such as gender
- Mean, median, standard deviation, maximum and minimum will be provided for continuous data such as age.

Analyses of the primary objective

All analyses will be carried out overall and by vaccine brand (*Fluarix Tetra* vs. others), by age strata (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years) and UK CMO-specified risk groups status (at risk/not at risk).

The weekly incidence rates (per 100 subjects) of AEIs within 7 days will be estimated as follows:

- The denominator will consist of the number subjects vaccinated the week before the week of interest (so reaching up to 7 days of follow-up post vaccination during the week of interest) and having received an ADR card.
- The numerator will encompass all subjects from the denominator reporting the AEI within 7 days following vaccination with a seasonal influenza vaccine derived from the ADR card

The cumulative incidence rates (per 100 subjects) of AEIs within 7 days will be estimated as follows:

- The denominator will be the number of subjects vaccinated at any point from study start up to the week before the week of interest (i.e. cumulatively since the beginning of the study) and having received an ADR card.
- The numerator will encompass all subjects from the denominator reporting the AEI within 7 days following vaccination with a seasonal influenza vaccine derived from the ADR card

95% confidence interval (CI) will be computed on the estimated incidence rates.

Analyses of the secondary objective

All analyses will be carried out overall and by vaccine brand (*Fluarix Tetra* vs. others), by age strata (6 months to 5 years; 6 to 12 years; 13 to 17 years; ≥18-65 years; >65 years) and UK CMO-specified risk groups status (at risk/not at risk).

The weekly incidence rates (per 100 subjects) of AEIs within 7 days will be estimated as follows:

- The denominator will be the number of all subjects vaccinated the week before the week of interest (so reaching up to 7 days of follow-up post vaccination during the week of interest)
- The numerator will encompass all vaccinated subjects reporting the AEI within 7 days following vaccination with a seasonal influenza vaccine using data entered in the EHR (i.e., AEIs derived from ADR card and medically attended AEIs)

The cumulative incidence rates (per 100 subjects) of AEIs within 7 days will be estimated as follows:

- The denominator will be the number of all subjects vaccinated at any point from study start up to the week before the week of interest (i.e. cumulatively since the beginning of the study)
- The numerator will encompass all subjects from the denominator reporting the AEI within 7 days following vaccination with a seasonal influenza vaccine using data entered in the EHR (i.e., AEIs derived from ADR card and medically attended AEIs)

95% CI will be computed on the estimated incidence rates.

Analyses of the tertiary objectives

The percentage of subjects vaccinated with a seasonal influenza vaccine during the study vaccination period in the 10 participating GP practices will be tabulated by vaccine brand, age categories and CMO-specified risk groups.

Completeness of seasonal influenza vaccination data in the EHR will be assessed by computing the percentage of subjects with data on influenza vaccines recorded in EHR (date of vaccination, vaccine brand, vaccine batch number).

Timeliness of vaccination data in the EHR will be assessed as follows:

- Time interval in days between the seasonal influenza vaccination dates and the dates at which the records were entered in EHR will be summarized using descriptive statistics (mean, standard deviation, median, range, first and third quartile).

Timeliness of AEI reporting in EHR (medically attended AEs and from the card-based ADR reporting system) will be assessed as follows:

- Time interval in days between the first onset date of AEIs within the 7 days post-vaccination period and the dates at which the records were entered in EHR will be summarized using descriptive statistics (mean, standard deviation, median, range, first and third quartile).

The percentage of subjects who received and who returned the ADR card will be tabulated by vaccine brand.

Sensitive analyses

The cumulative incidence rates (per 100 subjects) of AEIs within the 7 days post-vaccination period derived from the ADR card, with 95%CI, will also be tabulated for subjects who returned the ADR card.

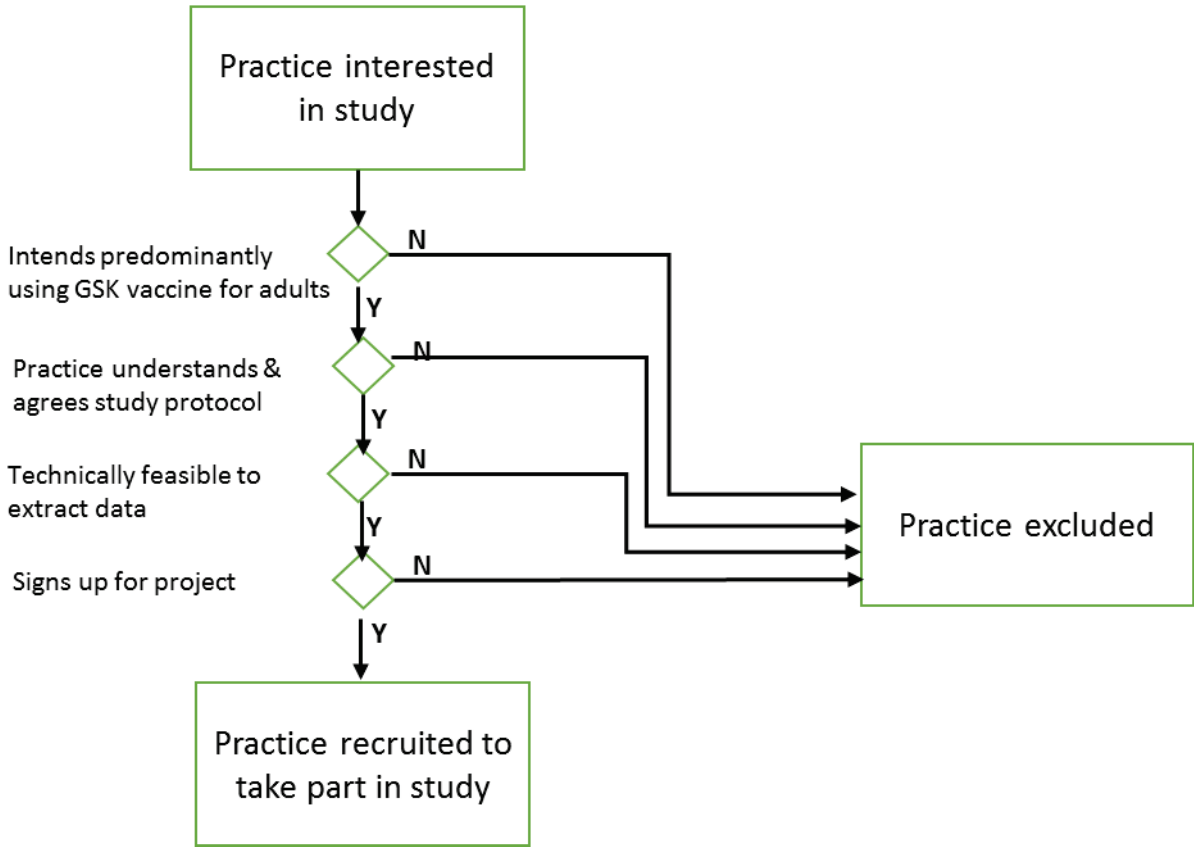
The cumulative incidence rates (per 100 subjects) of AEIs within the 7 days post-vaccination period, with 95%CI, will also be tabulated for subjects from the RCGP RSC network of GP practices.

Schematic description of process from site selection to data extraction

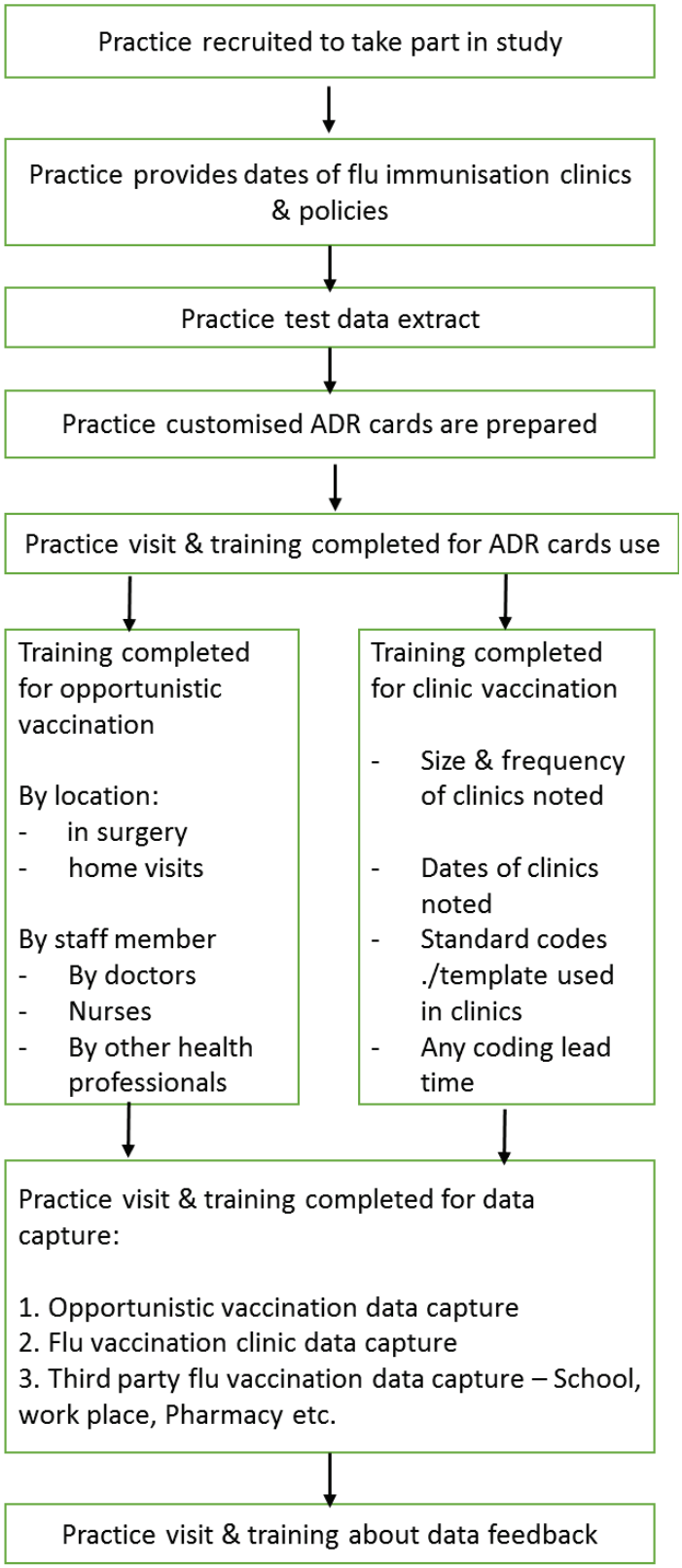
A series of flow charts have been developed to facilitate understanding of recruitment flow, the training and other process that have to be developed as participating GP practices, and to explain the data flow in the practice.

The flow charts are presented below

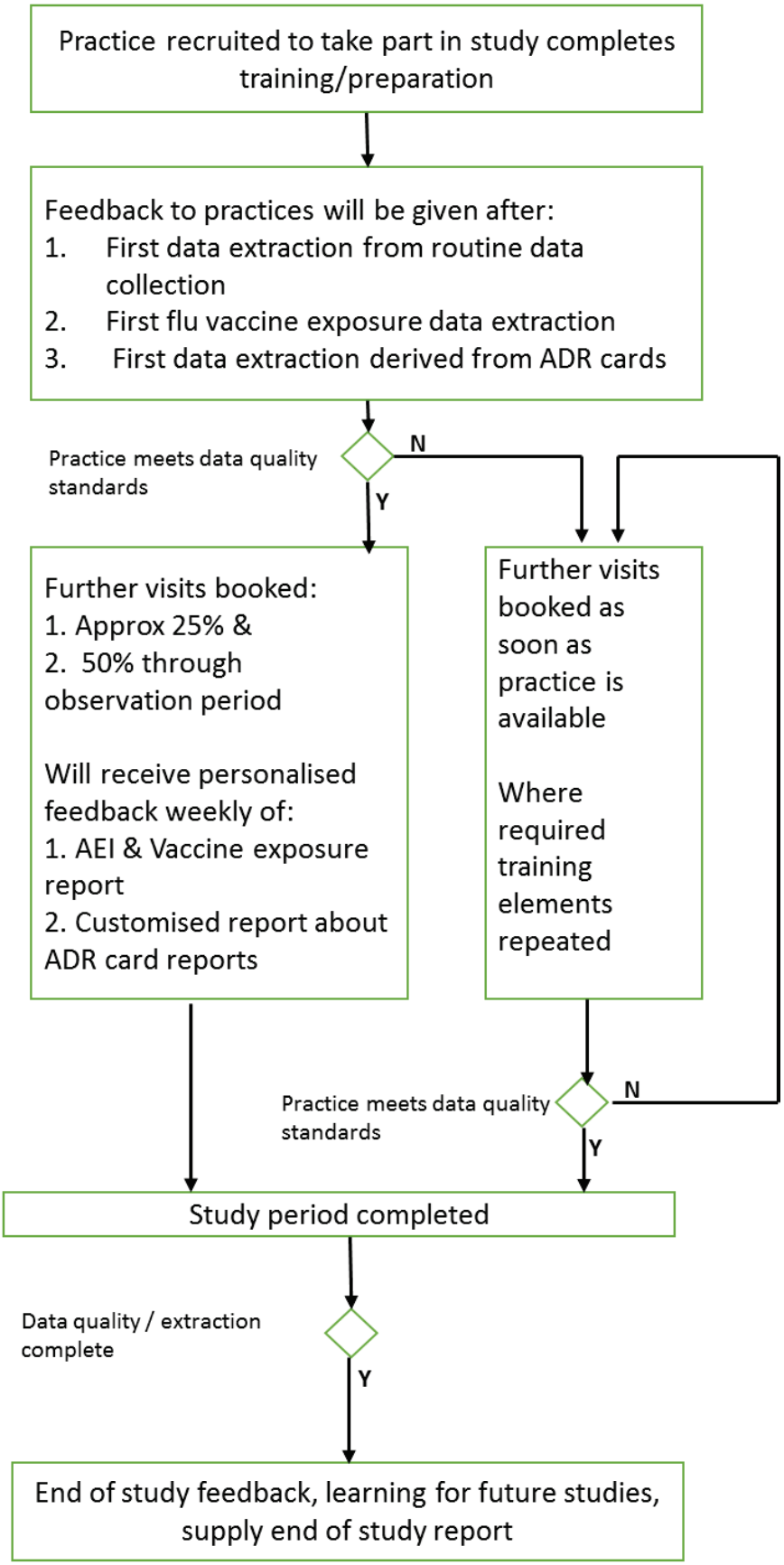
Flow chart 1: Practice selection process



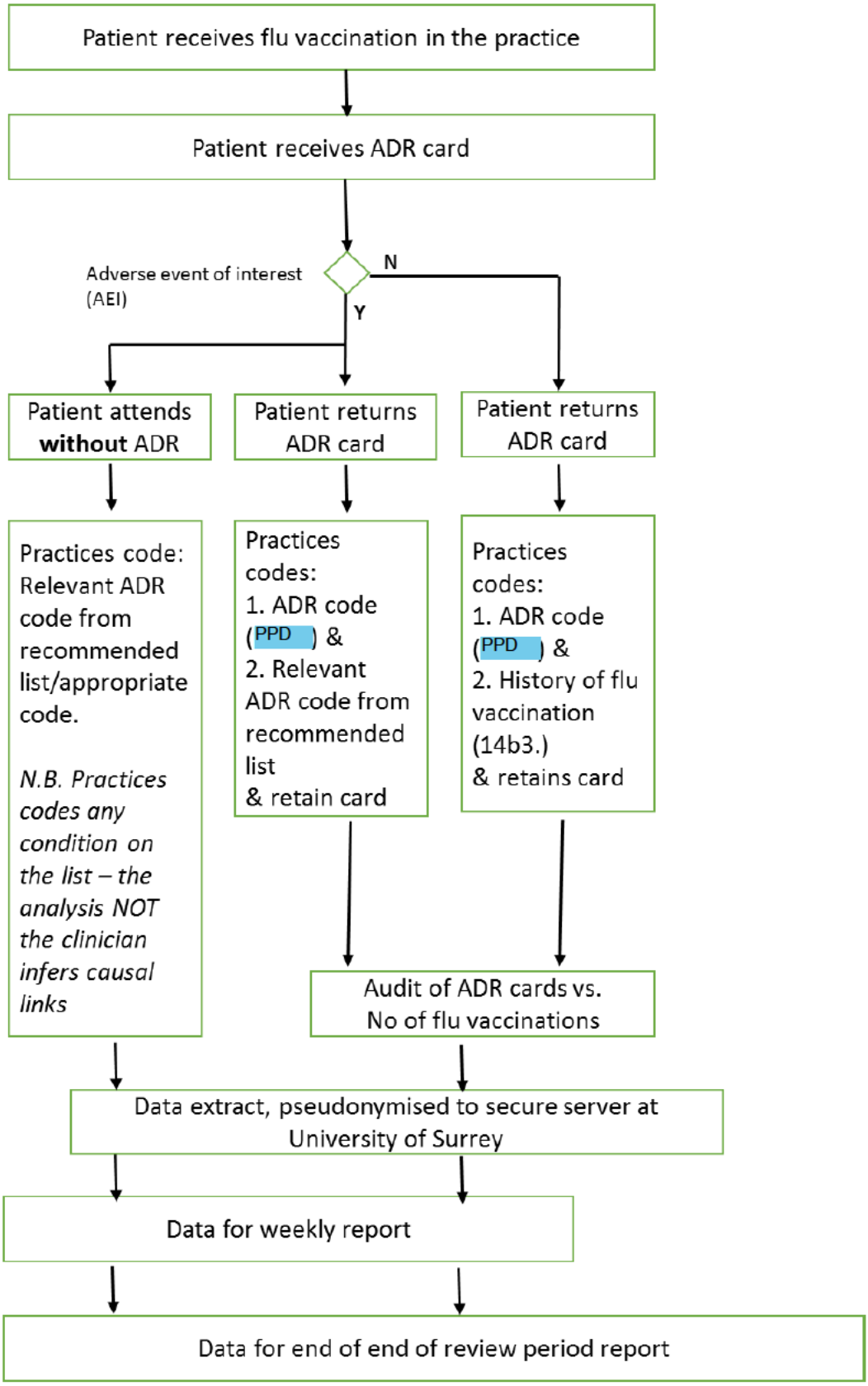
Flow chart 2: Preparation pre-study & site initiation process



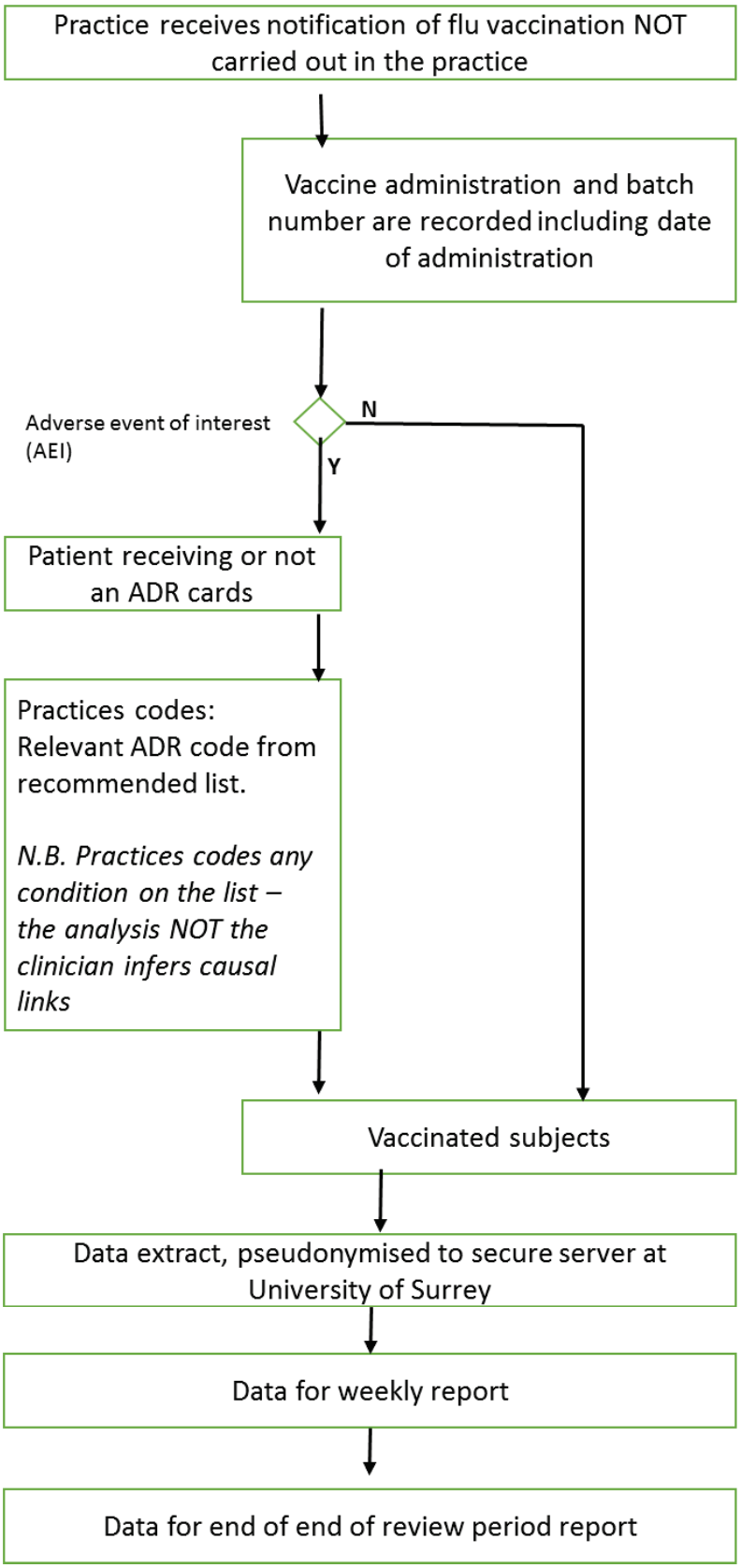
Flow chart 3: Visits during study linked to data quality



Flow chart 4: Data capture flow chart – patient flu vaccinated in the surgery

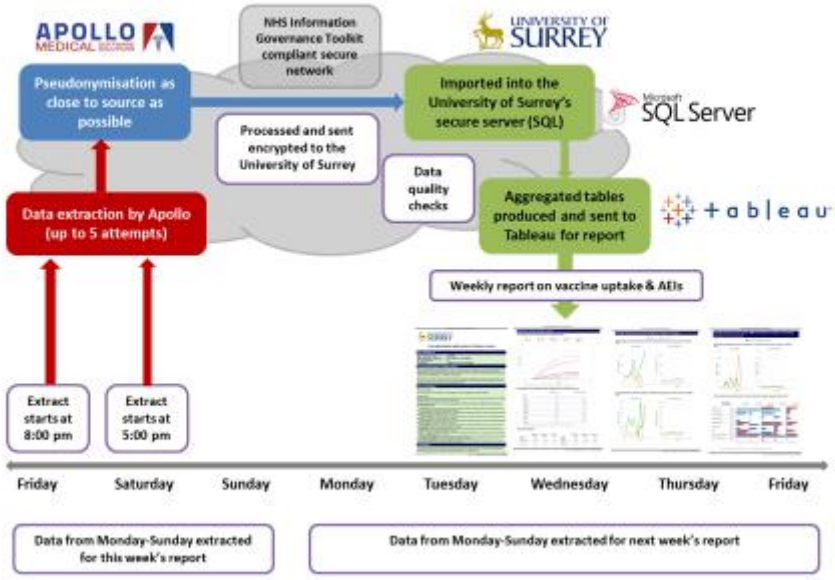


Flow chart 5: Data capture flow chart – patient NOT vaccinated in the surgery



The added value of combining those two systems is to be able to enhance the collection of AEIs (using the customized cards) and ensure further that the data is comprehensively collected (using the routine EHR system).

Flow chart summarizing the automated data extraction process performed using Apollo system



<u>Safety reporting, including routine pharmacovigilance</u>

<u>Safety reporting</u>

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AEI is any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The AEIs following vaccination may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. EMA recommendations regarding AEIs collected after vaccination in this study are specified in Appendix 2.

A Serious Adverse Event (SAE) is defined as any adverse event which is fatal, life threatening, disabling or incapacitating, requires in-patient treatment or prolongs existing hospitalization, is a congenital anomaly in the off-spring of the patient or which may require intervention to prevent the previously stated outcomes.

It will be clearly communicated to participating GP practices that the study does not replace reporting of AEs/SAEs that should occur as part of routine practice as specified by their local regulations. GPs should continue to report any AEs/SAEs they would typically report using the mechanisms routinely used in their GP practices. Therefore, although the data collected for this study

is primarily safety-related, reporting mechanisms of AEs to regulatory authorities should not be altered and is to continue according to each practice's standards.

In addition, if the team at the University of Surrey becomes aware of an SAE experienced by a study participant that is deemed to be related to a GSK flu vaccine, the SAE should be reported to GSK within 24 hours of awareness using the GSK reporting forms (forms are provided in the contract agreement). If GSK deems additional information necessary, request of additional information will be sent through the team at the University of Surrey.

Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance **Fax:** +PPD or PPD **Email:**PPD

6. PROJECT MANAGEMENT

This study is conducted within the University of Surrey's formal frameworks for information and research governance. In addition, all externally funded projects and collaborative projects with external partners are supported and guided by the University's Research and Enterprise Support (RES) service. RES ensures that university-supported projects are financially viable, and that legal issues of knowledge transfer and intellectual properties are addressed. The project team is supported by IT services dedicated to the Faculty and to the Department of Clinical and Experimental Medicine. At the University of Surrey, secure analysis servers are optimised for routine healthcare data processing, to provide faster deliveries for our projects.

The project is accountable to the Project Steering Board, with the day-to-day operational issues managed by the Project Operational team.

Project Steering Board

The Steering Board will meet bi-annually to receive regular and exceptional reports, including reporting of adverse events, from the Operational Team, monitor progress against set milestones, and ensure that resources and support are available to enable the successful delivery of the project within the funding agreement. In the event of a report of adverse incidents, the Project Steering Board will co-ordinate an effective management of the adverse incidents in line with local and national guidance, and if appropriate, onward reporting to the University, GSK, external partners or external research and information governance authorities.

The Project Steering Board consists of senior academics from the University of Surrey and collaborating universities, a patient representative, senior practitioners involved in the domain of influenza vaccine, and a representative of the GSK of the study.

Steering Board Member	Role and Organisation
Prof PPD	Principal Investigator, University of Surrey
Dr PPD	Research Representative, GSK
PPD	Statistician, GSK
After practice recruitment	GP/Practice representative
After practice recruitment	Patient Representative
Dr PPD	Project Manager, University of Surrey

Project operational team

The operational team is responsible for the completion of the project objectives against set milestones, and submit regular and ad-hoc reports to the Project Steering Board. The Team will meet fortnightly in person and/or via teleconference, particularly in the early stages of the project, to ensure the project meets with the milestones agreed for the project.

The Operational Team consists of research staff, the project manager and the Principal Investigator of this project:

Team Member	Lead responsibility in the project and organisation
Prof PPD	Senior Clinical Lead, University of Surrey
Dr PPD	Project Manager, University of Surrey
Dr PPD	Research Representative, GSK
PPD	Statistician, GSK
PPD	Senior Database developer, University of Surrey
Dr PPD	Senior Research Fellow, University of Surrey
PPD	Research Fellow, University of Surrey
PPD	Practice Liaison Officer

These arrangements are standard University of Surrey research and surveillance governance requirements for projects.

Peer review of the study protocol

In May 2017, the draft study protocol had been reviewed by GSK's peer review committee and in parallel by the Surrey University Peer review committee consisting of pharmacologists, general practitioners and lay advisors as well as patients' association representative.

Patient involvement

Patients were involved in the protocol review as part of the Surrey university Peer review process. Their comments were taken into consideration in the development of the protocol to help ensure its acceptability to patients. A patient representative is intended to be part of the steering committee.

7. ETHICAL CONSIDERATIONS

The primary purpose of this study is to work with practitioners, governance experts, and a commercial MAH to develop robust process for the annual enhanced safety surveillance of seasonal influenza vaccines recommended by the EMA.

The principal ethical issue is concerned with the protection and use of anonymised patient level information for the purpose of surveillance of safety of seasonal influenza vaccination as recommended by the EMA. NHS guidelines specify that a Section 251 approval is required when conducting research using anonymised patient level data, without individual level patient consent; approval is also dependent on the requesting institution meeting specific requirements of information governance, which the University of Surrey secure network exceeds. The protection and use of anonymised patient level information is addressed more fully in the next section: information governance considerations.

The University of Surrey team will seek approval from the University Ethics Review Committee. In addition, the formal opinion of the Proportional Review System of the National Ethics Review Service will be sought regarding the need for NHS Research Ethics Committee (REC) approval.

'Defining Research' (http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf), the National Research Ethics Service (NRES) guidance suggests that surveillance does not require formal review by a Research Ethics Committee. The research team will however seek an opinion from the NRES's Proportional Review system to check if formal approval from a NHS Research Ethics Committee (REC) is needed prior to the commencement of the study, as well as Section 251 approval[xx]. If the proportional review suggests that a full NHS REC review is necessary, then applications will be submitted to the REC as well as the Clinical Research Network (CRN) and, if advised, the Confidential Advisory Group (CAG) for formal approval for Section 251 of NHS Act 2006 and Health Service (Control of Patient Information) Regulations 2002 exemptions.

Section 251 of the Health and Social Care Act 2001, allowed the Secretary of State to set aside the common law duty of confidentiality for defined medical purposes. Surveillance is generally taken to be one of the defined medical purposes for which data can be used. As it has not been tested whether the Health and Social Care Act is retrospective data are generally not extracted for periods prior to that Act, without a clear need generally approved by an ethics committee.

This study is piloting enhanced passive surveillance as recommended by EMA. Such surveillance is not expected to require taking active consent. Generally, collecting surveillance data in an anonymised form is lawful, acceptable as use of data for public health purposes is recognised to be in the public interest. Based on our experience with the EPI-FLU-045 & EPI-FLU-046 pilot studies, the expectation is that this investigation meets the Health Research Authority's definition of Service Evaluation[xxi]. The expectation is that the current enhanced passive surveillance (EPI-FLU-055 pilot studies) falls under the same criteria[xxi].

8. INFORMATION GOVERNANCE CONSIDERATIONS

The Clinical Informatics Research Group at the University of Surrey has worked with routinely collected healthcare data in a number of research and evaluation projects for over 15 years. The Research Group works within the research and Information Governance frameworks for health and social care in the United Kingdom, and is compliant with the University's best practice standards. The University of Surrey is registered with the Information Commissioner's Office Data Protection Register, and is compliant with the Data Protection Act, and other legislations.

In addition, the Research Group reviewed its departmental information governance policies and procedures, against the requirements of the NHS IGT for Hosted Secondary Use Team/ Project, Version 12[xxii]. The review was approved by the Health and Social Care Information Centre, and was deemed satisfactory to support application to Confidentiality Advisory Group or the Data Access Advisory Group.

In line with the principle of the Data Protection Act 1998, data subjects will be informed of the uses of their data in this study. Participating GP practices will be asked to display project information in their website, and project information posters in reception areas, from when the practice has consented to take part in the study and until the study is completed.

The project information will specifically refer to the right of the patients to opt out if they do not wish their data to be included in this study. The codes in the data indicating that a patient does not wish to have their record available for research will be carefully considered. However, the number of patients within a practice who have chosen to opt out will be reported.

No Personally Identifiable Information (PII) such as NHS numbers, postcodes, dates of birth, etc. will be available to GSK, third parties, or disclosed in publications. Additionally, no patient level data will be sent to GSK to remove any possibility that any individual patient might be re-identified. GSK will also be blind to practice identities, and the locality at which any AEI occurs; other than where the patient gives consent, or their own chooses to report any condition in line with best practice.

9. DISSEMINATION AND PUBLIC REGISTER DISCLOSURE

The final agreed protocol of this study is intended be published in a peer review open access journal.

The outputs from the research will be disseminated primarily through peer review papers within the domains of primary care, surveillance, vaccines, and infectious diseases[xxiii] [xxiv]. Findings will be presented at relevant seminars and conferences.

The University of Surrey, in accordance with GSK policy, will post a summary of the study protocol and subsequently results within 12 months of study completion and following review and comment by GSK on GSK's Clinical Study Register, accessible at http://www.gsk-clinicalstudyregister.com and at www.clinicaltrials.gov.

10. APPENDIX

Appendix 1

Data extraction is by automated routine as detailed below:
Currently, data are extracted by weekly bulk upload. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed.
At the point of the data drop the data are filtered and processed through a pseudonymisation package encrypting the NHS number. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES and RSA 1024 before transmission, and utilises public and private key pairs unique to each project.
Pseudonymisation is applied at this stage to allow for backwards identification should there be a need to do so as part of an ethically approved study. However, the application of pseudonymisation at this stage also allows the same algorithm to be applied to additional data sources which may be linked data in future years; for example, enabling the linkage of patients' primary care and hospital data without the need to identify a person in the process of conducting this linkage.
Once the data are extracted, they are transferred using the above methodology to the custom built Data Warehouse located within University of Surrey for analysis in secure networks that meet the NHS Information Governance toolkit level 2 standard. These arrangements may change in the future in accordance with developments in technology.

Appendix 2 Code list of AEIs

Project title: Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England– Preferred code list

If a patient presents with adverse events post-vaccination (up to 7 days after), please code (ideally as a problem) as any of the following please code them into their computerised record

EMA surveillance condition	Read Code (5 Byte)	Read Code (CTV3)	Notes
Respiratory/Miscellaneous			
Conjunctivitis	F4C0.	XE16X	Sticky eyes
Rhinorrhoea	1C83.	XM00h	Runny nose
Nasal congestion	H1y1z	X77Gp	Blocked nose
Epistaxis	R047.	Xa96W	Nose bleed
Coryza	H00..	XE0XI	Common cold
Cough	171..	XM0Ch	
Oropharyngeal pain	1922. 1CB3.	1922. 1CB3.	Sore throat
Hoarseness	1CA2.	1CA2.	Hoarse voice
Wheezing	1737.	XE0qs	
Gastrointestinal			
Decreased appetite	R0300	XM07Y	
Nausea	198..	X75qw	Feeling sick
Vomiting	199..	XE0rA	Being sick
Diarrhoea	19F..	19F2.	
Fever/pyrexia			
Fever	165..	X76DI	
Mild fever (<38.5° C rectal) Moderate fever (38.6-39.5°C) High fever (>39.5°C)	2E3..	2E3..	Please include level of temperature, to help us classify the fever
Sensitivity/anaphylaxis			
Hypersensitivity reactions	SN52.	Xa5uf	Allergic reaction
Anaphylactic reactions	SN501	X70vr	Other allergic reactions
Facial oedema	16J5.	Xa0ls	Facial swelling
Rash			
Rash	M130.	X50Ge	
Generalised rash	2I14.	XM07J	
General non-specific symptoms			
Irritability	225A.	225A.	
Drowsiness	1B67.	XM06R	
Fatigue	168..	1682.	
Headache	1B1G.	XM0CV	
Neurological			
Bell's palsy	F310.	F310.	
Peripheral tremor	1B22.	XE0rn	Tremor/shaking
Guillain-Barre Syndrome (GBS)	F3700	F3700	
Seizure/ Febrile convulsions	1B64. 1B6B.	XaDbE XM03I	Seizure/ fits
Musculoskeletal			
Muscle aches/ myalgia	N2410	X75rs	
Arthropathy	N037.	X701f	Joint pain
Local Symptoms			
Local erythema	SP3y4 SP3y5 SP3y6 SP3y7	X75ty	Local reaction to vaccine

If a patient hands back an Orange Card with their symptoms – please code these and include the code 9G4.. (Drug reaction notification).

N.B.: In coding these conditions there is **no assumption about causation**; this can only come from advanced analytics.

UNIVERSITY OF SURREY

Principal Investigator: Professor PPD
Practice Liaison Officer: PPD

Project title: Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England– Preferred code list

If a patient presents with adverse events post-vaccination (up to 7 days after), please code (ideally as a problem) as any of the following please code them into the patients computerised record

EMA surveillance condition	Read Code (5 Byte)	Read Code (CTV3)	Notes
Respiratory/Miscellaneous			
Conjunctivitis	F4C0.	XE16X	Sticky eyes
Rhinorrhoea	1C83.	XM00h	Runny nose
Nasal congestion	H1y1z	X77Gp	Blocked nose
Epistaxis	R047.	Xa96W	Nose bleed
Coryza	H00..	XE0XI	Common cold
Cough	171..	XM0Ch	
Oropharyngeal pain	1922. 1CB3.	1922. 1CB3.	Sore throat
Hoarseness	1CA2.	1CA2.	Hoarse voice
Wheezing	1737.	XE0qs	
Gastrointestinal			
Decreased appetite	R0300	XM07Y	
Nausea	198..	X75qw	Feeling sick
Vomiting	199..	XE0rA	Being sick
Diarrhoea	19F..	19F2.	
Fever/pyrexia			
Fever	165..	X76DI	
Mild fever (<38.5° C rectal) Moderate fever (38.6-39.5°C) High fever (>39.5°C)	2E3..	2E3..	Please include level of temperature, to help us classify the fever
Sensitivity/anaphylaxis			
Hypersensitivity reactions	SN52.	Xa5uf	Allergic reaction
Anaphylactic reactions	SN501	X70vr	Other allergic reactions
Facial oedema	16J5.	Xa0ls	Facial swelling
Rash			
Rash	M130.	X50Ge	
Generalised rash	2I14.	XM07J	
General non-specific symptoms			
Irritability	225A.	225A.	
Drowsiness	1B67.	XM06R	
Fatigue	168..	1682.	
Headache	1B1G.	XM0CV	
Neurological			
Bell's palsy	F310.	F310.	
Peripheral tremor	1B22.	XE0rn	Tremor/shaking
Guillain-Barre Syndrome (GBS)	F3700	F3700	
Seizure/ Febrile convulsions	1B64. 1B6B.	XaDbE XM03I	Seizure/ fits
Musculoskeletal			
Muscle aches/ myalgia	N2410	X75rs	
Arthropathy	N037.	X701f	Joint pain
Local Symptoms			
Local erythema	SP3y4 SP3y5 SP3y6 SP3y7	X75ty	Local reaction to vaccine

If a patient hands back an Orange Card with their symptoms – please code these and include the code 9G4.. (Drug reaction notification).

N.B.: In coding these conditions there is **no assumption about causation**; this can only come from advanced analytics.

UNIVERSITY OF SURREY

Principal Investigator: Professor PPD
Practice Liaison Officer: PPD

Appendix 3 ADR form

GlaxoSmithKline Version 1 – May 15th, 2017 UNIVERSITY OF SURREY

CONFIDENTIAL Card unique number: 0000 0000 0000 0

Enhanced safety surveillance of seasonal influenza (flu) vaccine

Study of possible adverse events following immunisation – this surveillance is designed to capture all adverse events following immunisation. Please report if you get any symptoms following your "flu jab" (influenza vaccination).

1. About you – this information is kept confidential and won't leave your practice

About you* we need contact details, please supply a full address so we can link this to your medical record:

First name _____ Surname _____

Address _____

Postcode _____ Telephone: _____ Email _____@_____

Signed _____ Date ___ /___ /2017

***This personal information is only being collected to link any side effects to your record**

2. When you were vaccinated / When was the influenza vaccination given

What date were you vaccinated / was the vaccine given ___ /___ /2017

Where were you vaccinated: At your GP surgery: ☐ Yes ☐ No If no, say where: _____

3. If you were not the person vaccinated

Information about the person* ☐ Male ☐ Female Date of Birth ___ /___ /___

First name _____ Surname _____

4. Please report any side-effects/conditions in the 7 days after your flu vaccine

Please look at the list of possible vaccine side-effects on the next page – if *the person vaccinated* has experienced any adverse events – please tick the relevant box and indicate the severity

Please also mark if the symptoms/possible side effects are still persisting

Please return the card in the envelope provided to your GP – please return by post or in person.

Thank you for your help

5. If you had no side effects in the 7 days after vaccination tick and return

I /the person vaccinated has NOT had any side effects or other symptoms following vaccination: ☐

Please return the card in the envelope provided to your GP – please return by post or in person.

Thank you for your help

Formal study name:
Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England
GSK study abbreviation:
EPI-FLU 046 VS UK

Collaborating Study Sponsors:
University of Surrey, Guildford UK
GlaxoSmithKline Biologicals

Contact:

Prof PPD
Professor of Primary Care and Clinical Informatics
E-mail: PPD
Telephone: +PPD

PPD
Practice Liaison Officer
E-mail: PPD
Telephone: +PPD

Enhanced safety surveillance of seasonal influenza vaccine

Possible side effect or Condition in the 7 days after influenza vaccination	Start date of the symptom	Please tick as appropriate
Conjunctivitis – Sticky eyes	___/___/17	☐
Runny nose	___/___/17	☐
Blocked nose	___/___/17	☐
Epistaxis – Nose bleed	___/___/17	☐
Common cold	___/___/17	☐
Cough	___/___/17	☐
Sore throat	___/___/17	☐
Hoarse voice	___/___/17	☐
Wheezing	___/___/17	☐
Decreased appetite	___/___/17	☐
Nausea – feeling sick	___/___/17	☐
Vomiting – being sick	___/___/17	☐
Diarrhoea	___/___/17	☐
Fever (add temperature if measured)	___/___/17	☐
Allergic reaction (rash)	___/___/17	☐
Other allergic reactions	___/___/17	☐
Facial oedema (swelling)	___/___/17	☐
Local reaction to vaccine	___/___/17	☐
Rash	___/___/17	☐
Irritability	___/___/17	☐
Drowsiness	___/___/17	☐
Fatigue	___/___/17	☐
Tremor / shaking	___/___/17	☐
Seizure / fits	___/___/17	☐
Headache	___/___/17	☐
Muscle aches	___/___/17	☐
Joint pain	___/___/17	☐
Other 1. _____ 2. _____ 3. _____ Add below if more	 ___/___/17 ___/___/17 ___/___/17	 ☐ ☐ ☐

Appendix 4 GP surgery Poster

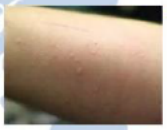
Poster - Version 2, June 21, 2017

GlaxoSmithKline

RESEARCH PROJECT IN THIS SURGERY

UNIVERSITY OF SURREY

ARE YOU HAVING A FLU VACCINE THIS YEAR?



Following a flu vaccination, have you ever experienced:

- **Headache**
- **Rash**
- **More severe allergic reactions ?**

This surgery is taking part in a research programme to explore how influenza vaccine safety could be monitored using primary care data. We will assess the reactions to vaccine (adverse event of interest (AEI)) frequencies among flu-vaccinated subjects using routinely collected data in England to provide timely and relevant information on influenza vaccine safety. AEIs are reactions to vaccines, which could include rashes, headaches, or more severe allergic reactions.

If you would like to find out more about this study or if you wish to opt out of this study, please talk to your GP or a receptionist.
Alternatively, you could contact the research team directly:

Prof PPD
Professor of Primary Care & Clinical Informatics
Phone: +PPD
E-mail: PPD

PPD
Practice Liaison Officer
Phone: +PPD
E-mail: PPD

This study is funded by GlaxoSmithKline Biologicals, and is conducted by the Department of Clinical and Experimental Medicine, University of Surrey. This study has been reviewed and approved for conduct by the National Research Ethics Committee. Ref: xx This committee reviews research studies to protect the rights and wellbeing of the patients taking part.

Appendix 5 Information Sheet – GP

Information Sheet for GP practices
Version 1 – May 15th 2017

INFORMATION SHEET FOR GP PRACTICES

Project title:

Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England

Overview

We invite you to take part in a research study. Please take time to read the following information. The proposed study represents a pilot to explore the use of routinely collected data in England to provide timely and relevant information on influenza vaccine safety. The research is carried out by the Department of Clinical and Experimental Medicine, University of Surrey, in collaboration with GlaxoSmithKline Biologicals.

Background and Rationale

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The key objective of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, as exposure to the vaccine increases.

The objective of the study is to conduct a pilot assessing adverse event of interest (AEI) frequencies among flu-vaccinated subjects using routinely collected data in ten primary care practices. Our primary surveillance is of 7-day AEI, post vaccination, but we will not exclude events recorded outside this window, which will be analysed separately.

What is the design of the study?

We have recruited ten practices representing urban and rural localities across England, and the three major computerised medical record (CMR) suppliers in the UK. The anticipated start date for data collection will be in September 2017.

The method and governance procedure has been developed by the University of Surrey as part of previous work with the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) and Public Health England (PHE), using an approved provider, Apollo Medical Software Solutions Ltd. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed. These arrangements may change from time-to-time and we will notify members if any changes occur. Patients will be given AEI reporting cards by practice staff to complete; the data from completed cards will be entered in the CMR by practice staff.

Data extractions will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer. All data are stored and managed by the University of Surrey. The information security policies and procedures of the Research Group have been approved by the

Information Sheet for GP practices
Version 1 – May 15th 2017

NHS Health and Social Care Information Centre (HSCIC). Details of the departmental information governance policies and procedures can be found in:
http://www.clininf.eu/about/information-governance.html

Why have I been invited to take part?

The study is part of a research programme which aims to explore cases of adverse events of interest following flu immunisation. You have been invited because your practice has expressed interest in becoming part of a research network within the RCGP RSC, and because you meet representativeness criteria (geographic location and computerised medical record system) for this study.

What will happen if I take part?

You will be contacted by RCGP RSC and Apollo Medical Software Solutions Ltd to sign data extraction agreements. The GP practices will be supported by the RCGP RSC and the Research Team led by Prof PPD PPD The responsibilities of the GP practices are outlined below.

What are my responsibilities?

If you agree to take part in the study, you will be required to provide such support as may be reasonably required to achieve its aims. Practices will be required to facilitate access for data extraction and staff will be required to distribute AEIs reporting cards to patients and to enter the data from these into the system.

What are the possible benefits of taking part?

The proposed study will help assess the feasibility of an influenza vaccine safety monitoring system using routine data collected in primary care, which will help patients receiving influenza vaccines.

Who can I contact for more information?

Prof PPD
Professor of Primary Care & Clinical Informatics
e-mail: PPD
Telephone: +PPD

Ms PPD
Practice Liaison Officer
e-mail: PPD
Telephone: +PPD

Appendix 6 Information Sheet - Patients

Information Sheet for patients
Version 2 – June 21st 2017

Practice logo to be added

INFORMATION SHEET FOR PATIENTS

Project title:

Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England

Overview

Please take time to read the following information. We invite you to take part in a research study, which will be exploring the use of General Practitioner (GP) data in providing up-to-date information about vaccine safety. The research is carried out by the Department of Clinical and Experimental Medicine, University of Surrey, in collaboration with GlaxoSmithKline Biologicals.

Background and Rationale

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance. The key objective of these requirements is to quickly detect a significant increase in the frequency and/or severity of reactions to vaccines (which could include rashes, headaches, or more severe allergic reactions) that may indicate a potential or more serious risk. The objective of this study is, to explore using GP data, in assessing the frequency and severity of influenza vaccine reactions (also known as adverse events of interest, or AEIs). We will assess **AEIs happening up to 7 days after vaccination**.

What is the design of the study?

In order to identify AEIs, this study will pull out routinely collected data held in the surgery for all patients who have been recently vaccinated with the influenza vaccine. No patient identifiable information (name & date of birth) will leave the surgery. These will be converted in your surgery to an anonymous and encrypted format. The method and governance procedure has been developed by the University of Surrey as part of previous work with the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) and Public Health England (PHE), using an approved provider, Apollo Medical Software Solutions Ltd.

What will happen if I take part?

After you receive your influenza vaccine, you will be asked by practice staff to complete a reporting card, which will need to be returned to the practice. This will be an adapted version of the Yellow Card, which is the standard reporting card used by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. Practice staff will then record this information into your electronic record. We will then extract this data in an anonymised format. The information provided by the surgery is treated in the strictest confidence, and it is not possible to relate any results to you personally.

What are the possible benefits of taking part?

The proposed study will help assess a possible safety monitoring system for influenza vaccine safety, which will contribute to the safety of patients receiving influenza vaccines.

Information Sheet for patients
Version 2 – June 21st 2017

If you would like to find out more about this study or if you wish to opt out of this study, please talk to your GP or a receptionist. Alternatively, you could contact the research team directly:

Prof PPD
Professor of Primary Care & Clinical Informatics
e-mail: PPD
Telephone: +PPD

PPD
Practice Liaison Officer
e-mail: PPD
Telephone: +PPD

Appendix 7 Practice feedback sample

Feedback on possible adverse events following vaccination

The European Medicines Agency (EMA), as part of the monitoring of the continuing safety of the influenza vaccination, has circulated a list of codes for possible adverse events that may be associated with vaccination.

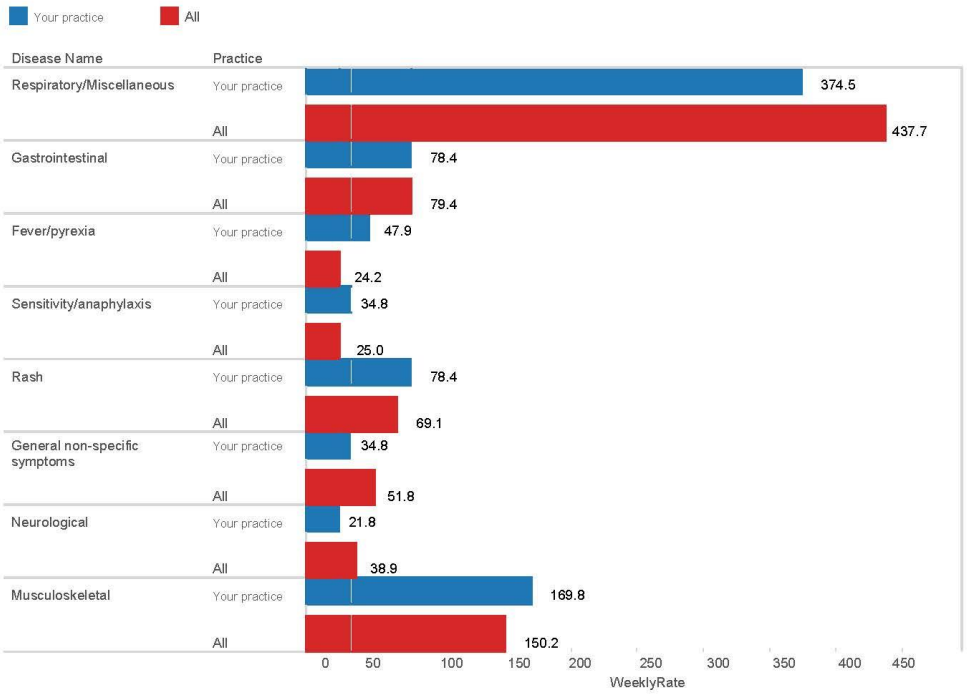
Data from will be used to monitor these possible adverse events, via twice-weekly data extract.

It is of course essential for this work that the data is accurate and that these codes are used consistently throughout the flu season. We therefore attach a table showing how many times the codes on the EMA list have been recorded in 's patient records in the 7 days from XXXX-XX-XX to XXXX-XX-XX.

Please continue to use these codes for all patients, whether or not they have been recently vaccinated. **Use of these codes does not imply a causal link between the adverse event and vaccination – any association will emerge from the data analysis.** This analysis will only be valid if the codes are used consistently for all relevant cases, regardless of the patient's vaccination status. It is therefore essential that these codes are used for all appropriate cases, whether or not the patient has been recently vaccinated.

Thank you very much for your help with this project – your input is crucial for ensuring that the influenza vaccination continues to be both safe and protective for patients

Following graph provides a visualization of compared with 7 other adverse events monitoring practices



The following table provides the total counts of possible adverse events for the 2015-09-04 to 2015-09-21 for your practice.

Disease Name	EMA surveillance condition	ReadCode Type	
Respiratory/Miscellaneous	Conjunctivitis	Preferred Read Code (F4C0.)	5
		Other Read Codes	0
	Rhinorrhoea	Preferred Read Code (1C83.)	0
		Other Read Codes	0
	Nasal congestion	Preferred Read Code (H1y1z)	0
		Other Read Codes	3
	Epistaxis	Preferred Read Code (R047.)	3
		Other Read Codes	22
	Coryza	Preferred Read Code (H00..)	1
		Other Read Codes	0
	Cough	Preferred Read Code (171..)	24
		Other Read Codes	1
	Oropharyngeal pain	Preferred Read Code (1922.)	1
		Other Read Codes	0
	Oropharyngeal pain	Preferred Read Code (1CB3.)	0
		Other Read Codes	0
	Hoarseness	Preferred Read Code (1CA2.)	1
		Other Read Codes	2
	Wheezing	Preferred Read Code (1737.)	3
		Other Read Codes	20
Gastrointestinal	Decreased appetite	Preferred Read Code (R0300)	0
		Other Read Codes	2
	Nausea	Preferred Read Code (198..)	3
		Other Read Codes	0
	Vomiting	Preferred Read Code (199..)	2
		Other Read Codes	0
	Diarrhoea	Preferred Read Code (19F..)	11
		Other Read Codes	0
Fever/pyrexia	Fever	Preferred Read Code (165..)	9
		Other Read Codes	0
	Mild fever (<38.5° C rectal) High fever (>39.5°C)	Preferred Read Code (2E3..)	2
		Other Read Codes	0
Sensitivity/anaphylaxis	Hypersensitivity reactions	Preferred Read Code (SN52.)	1
		Other Read Codes	0
	Anaphylactic reactions	Preferred Read Code (SN52.)	0
		Other Read Codes	0
	Facial oedema	Preferred Read Code (16J5.)	0
		Other Read Codes	7
	Local erythema	Preferred Read Code (SP3y5)	0
		Other Read Codes	0
Rash	Rash	Preferred Read Code (M130.)	0
		Other Read Codes	18
	Generalised rash	Preferred Read Code (2I14.)	0
		Other Read Codes	0
	Local erythema	Preferred Read Code (SP3y5)	0
		Other Read Codes	0
General non-specific symptoms	Irritability	Preferred Read Code (225A.)	0
		Other Read Codes	1
	Drowsiness	Preferred Read Code (1B67.)	0
		Other Read Codes	1
	Fatigue	Preferred Read Code (168..)	3
		Other Read Codes	0
	Malaise	Preferred Read Code (N037.)	0
		Other Read Codes	3

(Continued on next page..)

The following table provides the total counts of possible adverse events for the 2015-09-04 ***to*** 2015-09-21 ***for your practice.***
(Continues from previous page..)

Disease Name	EMA surveillance condition	ReadCode Type	
Neurological	Peripheral tremor	Preferred Read Code (1B22.)	0
		Other Read Codes	0
	Guillain-Barre Syndrome (GBS)	Preferred Read Code (F3700)	0
		Other Read Codes	0
	Seizure/ Febrile convulsions	Preferred Read Code (1B64.)	0
		Other Read Codes	0
	Seizure/ Febrile convulsions	Preferred Read Code (1B6B.)	0
		Other Read Codes	0
	Headache	Preferred Read Code (1B1G.)	5
		Other Read Codes	0
Musculoskeletal	Muscle aches/ myalgia	Preferred Read Code (N2410)	5
		Other Read Codes	34
	Arthropathy	Preferred Read Code (N037.)	0
		Other Read Codes	0

Possible adverse event code list for your reference

Disease Name	EMA surveillance Condition	Discription	Read Code
Respiratory/Miscellaneous	Conjunctivitis	Acute conjunctivitis	F4C0.
	Rhinorrhoea	Rhinorrhoea	1C83.
	Nasal congestion	Nasal airway obstruction	H1y1z
	Epistaxis	Epistaxis	R047.
	Coryza	Acute coryza	H00..
	Cough	Cough	171..
	Oropharyngeal pain	Sore mouth/Throat pain	1922.
	Oropharyngeal pain	Sore mouth/Throat pain	1CB3.
	Hoarseness	Hoarse	1CA2.
	Wheezing	Wheezing	1737.
Gastrointestinal	Decreased appetite	Loss of appetite	R0300
	Nausea	Nausea	198..
	Vomiting	Vomiting	199..
	Diarrhoea	Diarrhoea	19F..
Fever/pyrexia	Fever	Fever symptoms	165..
	Mild fever (<38.5° C rectal) High fever (>39.5°C)	O/E – Temperature level	2E3..
Sensitivity/anaphylaxis	Hypersensitivity reactions	Adverse drug reaction/Vaccine allergy	SN52.
	Anaphylactic reactions	Drug-induced anaphylaxis	SN501
	Facial oedema	Facial swelling	16J5.
	Local erythema	Erythema at injection site	SP3y5
Rash	Rash	Drug-induced rash	M130.
	Generalised rash	Rash	2I14.
	Local erythema	Erythema at injection site	SP3y5
General non-specific symptoms	Irritability	O/E - Irritable	225A.
	Drowsiness	Drowsiness	1B67.
	Fatigue	Fatigue	168..
Neurological	Peripheral tremor	Tremor	1B22.
	Guillain-Barre Syndrome (GBS)	Guillain-Barre Syndrome	F3700
	Seizure/ Febrile convulsions	Convulsion/Febrile convulsion	1B64.
	Seizure/ Febrile convulsions	Convulsion/Febrile convulsion	1B6B.
	Headache	Headache	1B1G.
Musculoskeletal	Muscle aches/ myalgia	Myalgia	N2410
	Arthropathy	Post-immunisation arthropathy	N037.

Appendix 8 Practice consent form

GP consent form
Version 1 – May 11th, 2017
IRAS Project ID:

UNIVERSITY OF SURREY

Agreement to participate in the Study

European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine Year 3

The Section of Clinical Medicine and Ageing, University of Surrey, in collaboration with GlaxoSmithKline Biologicals, is conducting a study in ten general practices across England.

This study explores the potential use of routinely collected data in England to provide timely and relevant information on influenza vaccine safety. This will be a pilot assessing adverse event of interest (AEI) frequencies among influenza vaccinated subjects using routinely collected data in primary care.

Approvals for the study from a NHS Research Ethics Committee have been obtained. Further details about the study are outlined in the accompanying information sheet.

Purpose of the Agreement:

The purpose of this agreement is to secure commitment from your practice to participate in the study. If you agree to take part, you will be required to provide such support as may be reasonably required to achieve the study's aims.

Please sign on the following page if you consent to participate in the study. Please include full contact details for the practice, the practice's lead clinician, and the contact person for matters related to the study.

Please note that in case the Section of Clinical Medicine and Ageing is audited, the study team will be obliged to share any information required.

Thanks for your help and your interest in the study. Please do not hesitate to be in contact if you need more information.

PPD

Prof PPD
Professor of Primary Care & Clinical Informatics
e-mail: PPD
Telephone: +PPD

PPD

Dr PPD
Project Manager
e-mail: PPD
Telephone: +PPD

GP consent form
Version 1 – May 11th, 2017
IRAS Project ID:

Agreement to participate in the Study

European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine Year 3

Declaration of participation in the above study

I confirm that our practice ..... (name of practice) will participate in the study.

Signature of Lead GP: .....

Lead GP Name: ..... Date: .....

Practice Contact details:

Practice Name: .....

Practice Address: .....

.....

Tel: .....

Fax: .....

Key contact at the practice for this study:

Name: .....

Role: .....

Address (if different from the Practice Address): .....

.....

Tel: .....

Fax: .....

Mobile: .....

Email: .....

11. REFERENCES

[i] European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU. London, EMA: Ref: EMA/PRAC/222346/2014; 10 April 2014. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165492.pdf. Last accessed 23 June 2017.

[ii] European Medicines Agency (EMA). Explanatory note on the withdrawal of the note for guidance on harmonization of requirements for influenza Vaccines and of the core SmPC/PL for inactivated seasonal influenza vaccines. London: EMA; 2014. Contract No.: EMA/CHMP/VWP/40560/2014. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500161022&mid=WC0b01ac058009a3dc. Last accessed 23 June 2017.

[iii] Correa A, Hinton W, McGovern A, van Vlymen J, Yonova I, Jones S, de Lusignan S. Cohort profile: Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network. BMJ Open 2016;6: e011092. doi:10.1136/ bmjopen-2016-011092. Last accessed 23 June 2017.

[iv] Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC). URL: http://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre.aspx. Last accessed 23 June 2017.

[v] Public Health England, Department of Health, NHS England. Flu plan Winter 2017/18. 2016. PHE publications gateway number: 2016697. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/600532/annual_flu_plan_2017to2018.pdf. Last accessed 23 June 2017.

[vi] Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. J Clin Epidemiol. 1997;50(10):1129–36.

[vii] National Institute for Health Research Clinical Research Network. Guide to the NIHR CRN Industry Costing Template: Costing Industry Sponsored Studies (version: March 2017). URL: https://www.nihr.ac.uk/funding-and-support/study-support-service/early-contact-and-engagement/commercial-study-costing-templates.htm. Last accessed 23 June 2017.

[viii] National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio. URL: https://www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/. Last accessed 28 June 2017.

[ix] Health and Social Care Information Centre. GP Systems of Choice (GPSoC). URL: http://systems.hscic.gov.uk/gpsoc. Last accessed 23 June 2017.

[x] European Union. Justice. Reform of EU data protection rules. URL: http://ec.europa.eu/justice/data-protection/reform/index_en.htm.

[xi] EUR-lex. EDPS recommendations on the EU's options for data protection reform. URL: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52015XX0912(01)#ntc14-C_2015301EN.01000101-E0014. Last accessed 23 June 2017.

[xii] NHS Digital. Information Governance Toolkit (IGT). URL: https://www.igt.hscic.gov.uk/. Last accessed 23 June 2017.

[xiii] de Lusignan S. Codes, classifications, terminologies and nomenclatures: definition, development and application in practice. Inform Prim Care. 2005;13(1):65-70.

[xiv] Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. Br J Gen Pract. 2015 Feb;65(631):54-5. doi: 10.3399/bjgp15X683353.

[xv] de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. Fam Pract. 2006;23(2):253-63.
[xvi] Workforce and Facilities Team, Health and Social Care Information Centre . General and Personal Medical Services: England 2003-13. 25 March 2014. URL: http://www.hscic.gov.uk/catalogue/PUB13849/nhs-staf-2003-2013-gene-prac-rep.pdf.
[xvii] Public Health England. Vaccine uptake guidance and the latest coverage data. https://www.gov.uk/government/collections/vaccine-uptake#seasonal-flu-vaccine-uptake.
[xviii] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934; 26:404-413.
[xix] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934; 26:404-413.
[xx] Health and Social Care Act 2001. Section 251. http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/. Last accessed 23 June 2017.
[xxi] NHS Health Research Authority. Defining Research. London, HRA Ref No; Ref: 0987, Revised June 2016. URL: http://www.hra.nhs.uk/documents/2016/06/defining-research.pdf Last accessed 28 June 2017.
[xxii] Department of Health. Information Governance Toolkit. https://www.igt.hscic.gov.uk/. Last accessed 23 June 2017.
[xxiii] MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies Revised January 2017. URL: https://www.mrc.ac.uk/publications/browse/mrc-policy-and-guidance-on-sharing-of-research-data-from-population-and-patient-studies/ Last accessed 28 June 2017.
[xxiv] Economic Co-operation and Development (OECD). “Promoting Access to Public Research Data for Scientific, Economic and Social Development” 2007 http://www.oecd.org/sti/sci-tech/38500813.pdf. Last accessed 23 June 2017.

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207781 (EPI-FLU-055 VS UK)
Date of protocol	Final Protocol: 30 June 2017
Detailed Title	Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England 2017/18
Collaborating study sponsor	**Anne Schuind** Clinical Epidemiology Project Lead, Clinical R&D US
Signature	PPD [redacted]
Date	6/30/2017