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

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1. ABSTRACT

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. In 2014/2015, GSK collaboratively with University of Surrey carried out a first pilot study (EPI-FLU-045). We carried out this surveillance in England as nearly all primary care consultations and vaccinations are recorded in computerised medical record (CMR) systems.

Aim:
The EPI-FLU-046 pilot study aims to meet the EMA interim guidance including its last Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on passive enhanced safety surveillance for seasonal influenza vaccines in the EU. The requirement is to rapidly detect a significant increase in the frequency 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

Method:
The EPI-FLU-046 pilot study will build on the key learnings from the EPI-FLU-045 pilot study carried out at the start of the 2015/2016 flu season in order to fine tune the approach to collect and report adverse events. The EPI-FLU-046 pilot study collected data about vaccination status and adverse events following immunisation (AEI) on a weekly basis, from 01 September 2016 onwards, using a standardised approach.

Study design: The second pilot study will be implemented as a prospective passive enhanced safety surveillance study with weekly crude and cumulative incidence rate of AEIs reported and analysed. We will use a combination of adverse drug reaction (ADR) cards and routinely collected data to provide relevant information about influenza vaccine safety, and analyse these data in a near to real time manner, ideally within a week of data collection.

Setting: 10 volunteer English general practices, primarily using the GSK influenza vaccines. English general practices are generally professional partnerships who individually select which vaccine to use. The observation period will start when influenza vaccination starts in the respective practices and an end at a date set by EMA (in the 2015/16 season, when we conducted EPI-FLU-045 the end date was set as 30th November 2015).

Participants: People who receive an influenza flu vaccine registered with participating practices, or their guardian or carer.

Variables: We will collect demographic data, information about vaccine exposure, including data about co-morbidities that explain eligibility for influenza vaccination as defined by the Chief Medical Officer's (CMOs) high risk groups. We will also collect data about EMA specified AEIs; collecting data reported direct to GPs in-consultation, as well as those reported back to their practice using a

customised ADR card scheme that asks specifically about EMA defined AEIs. As many of these are commonly reported symptoms, using the EHR system, we will simultaneously report rates of AEIs in the unvaccinated population registered in the enrolled practices (although in the non-immunized we consider them "illness-disease episodes (IDE).

Data sources: All data required from the study will be extracted from practice electronic health record (EHR) systems. Anonymised data, (strictly defined as "pseudonymised"), will be extracted 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. The extract will include those data listed in the section above. ADR cards completed by patients will have their data entered into the practice EHR system.

Bias: We will report any disparities in the data provided compared with the national population and the immunisation recommendations in the UK.

Study size: A target of at least 100 vaccinees in each defined age groups (6 months to 5 years; 6 to 12 years; 13 to 18 years; ≥18-65 years; >65), as defined in the EMA interim guidance.
Our study size took into account the probability of observing at least of event in our population together with the level of precision associated with the finding.

Statistical methods: We will estimate the weekly crude and cumulative incidence rate of AEIs within 7 days following vaccination with a seasonal influenza vaccine. At the end of the pilot study data will be analysed using parametric or non-parametric descriptive statistics; and regression to adjust for demographic factors and comorbidities.

Outputs:
Weekly analysis: We will produce a weekly analysis of influenza vaccination and uptake by different age and at-risk (CMOs) groups and the EMA listed AEIs reported by the immunised patients. We will list those reported at consultations in the practice and by ADR card.

We will produce an interim analysis report within eight working weeks of the starts of the vaccination period, and an end of observation period report. The findings will be compared with the rates of adverse reactions observed in clinical trials performed with GSK's seasonal influenza vaccines as well as the background rates fund in the EPI-FLU-045 and EPI-FLU-046 pilot studies from the population of non-vaccinees in the participant GP practices.

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
CMO	Chief Medical Officer at Department of Health, London
CMR	Computerised Medical Record (system) synonym of EHR
CRN	Clinical Research Network
DCEM	Department of Clinical and Experimental Medicine, at University of Surrey
EDPPS	European Data Protection Supervisor
EHR	Electronic Health Record (used in EMA publications) synonym of CMR
EMA	European Medicines Agency
EPI-FLU-045	The first pilot to monitor EMA defined AEIs, conducted winter 2015/2016
EPI-FLU-046	This investigation: 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
HSCIC	Health and Social Care information Centre (source of National data against which denominators and other population data can be checked & security policy, including its IGT)
HSCIC ODS	HSCIC Organisation Data Service – system that provides codes for all NHS bodies, including general practices and population data about these bodies
IDE	illness-disease episodes
MAH	Marketing Authorisation Holders
NIHR	National Institute of Health Research

NRES	National Research Ethics Service
NHS	National Health Service
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
RCT	Randomized Controlled Trial
RSC	Research and Surveillance Centre (part of RCGP)
REC	Research Ethics Committee
RES	Research and Enterprise Support
SAE	Serious Adverse Event – A serious adverse event (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
UK	United Kingdom

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4. INTRODUCTION

a. Rationale for the pilot study and background

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London. The Agency is 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 to be replaced by enhanced, preferably active, safety monitoring and vaccine effectiveness assessments.

The interim EMA guidance issued in April 2014 provides suggested surveillance methods, but back and forth communications between Marketing Authorisation Holders (MAHs) and the EMA indicate that there is flexibility around the specifications due to heterogeneity in vaccine coverage, brand distribution, and data collection options across member states. Additional on-going discussions will be summarised in the updated EMA guidance.

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 study (EPI-FLU-045 VS UK) implemented during the 2014/2015 influenza seasons and which aims to address 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 to rapidly detect and evaluate potential new safety concerns each influenza season. Nevertheless, the possibility to report the finding in a near real time manner could be improved. In addition, this first pilot study confirmed that a card-based ADR system added to AEFI collected from Practice EHR systems. The electronic health record (EHR) data provided a preliminary estimate the denominator of vaccines administered in the recruited GP practices. The use of routinely collected data in addition provided demographic characteristics and account for underlying conditions, or comorbidities in the registered practice population.

The primary purpose of the 2016/17 pilot study is to improve the combination of a card-based ADR system and the use of routine data to collect adverse events following vaccination with seasonal influenza vaccines, as per EMA guidance and PRAC requirements, and to identify additional data which may need to be collected in order to appropriately address the requirement. Of note, the ADR cards have been further developed since the first study to account for the EU requirements (appendix 3). The results will inform decisions regarding future influenza vaccine safety surveillance activities in England and contribute to the cumulative awareness and knowledge associated with spontaneous reporting of 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 practices has a membership designed to give national coverage of 1.5%-2% of the English population.[iii] The RCGP RSC has been described as the gold standard sentinel network. 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 Surrey team are constantly updating and modernising their information processing, security and governance processes. The data are automatically extracted from the network of 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. Seatle, WA, www.tablleau.com), to produce a weekly surveillance report in a timely manner.

The most important work of the RCGP RSC network is its influenza surveillance; many 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 reporting on adverse events.

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 early as possible.

The 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.

Our customised ADR card is the enhancement provided over simple AEI surveillance of general practice EHR systems.

The national flu immunisation programme 2015/16 – recommendations

In the UK, 2015/2016 influenza plan recommended the following groups to be vaccinated[v]:

- People aged 65 years or over (based on age on 31 March 2016)
- People aged from 6 months to less than 65 years of age with a serious medical condition such as:
    - chronic (long-term) respiratory disease, such as severe asthma,
    - chronic obstructive pulmonary disease (COPD) or bronchitis
    - chronic heart disease, such as heart failure
    - chronic kidney disease at stage three, four or five
    - chronic liver disease
    - chronic neurological disease, such as Parkinson's disease or motor neurone
    - disease, or learning disability
    - diabetes
    - splenic dysfunction
    - a weakened immune system due to disease (such as HIV/AIDS) or
    - treatment (such as cancer treatment)
- All pregnant women (including those women who become pregnant during the flu season)
- All those aged two, three, and four years (but not five years or older) on 31 August 2015 (i.e., date All children of school years 1 and 2 age through locally commissioned arrangements
- Primary school-aged children in areas that participated in primary school pilots in 2014/15
- People living in long-stay residential care homes or other long-stay care facilities where rapid spread is likely to follow introduction of infection and cause high morbidity and mortality. This does not include, for instance, prisons, young offender institutions, or university halls of residence
- People who are in receipt of a carer's allowance, or those who are the main carer of an older or disabled person whose welfare may be at risk if the carer falls ill
- Consideration should also be given to the vaccination of household contacts of immunocompromised individuals, specifically individuals who expect to share living

accommodation on most days over the winter and therefore for whom continuing close contact is unavoidable

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

Expansion of national vaccination has created a greater 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. The continuation of the pilot study in the 2016/17 season will help to build a framework for passive enhanced safety surveillance in England, but will also contribute to an EU-wider programme of enhanced safety surveillance for seasonal influenza vaccines.

b. Objectives and endpoints

Per EMA interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU, the EPI-FLU-046 pilot study aims at rapidly detect a clinically significant change (compared to what was known or expected with the previous vaccine composition) in the frequency and/or severity of expected reactogenicity (local, systemic or allergic reactions) that may indicate a potential for more serious risks as exposure to the vaccine increases

With the proposed approach combining a ADR-card based system and a computerised medical record (CMR) system, we intend to provide an estimation of the vaccine coverage (using vaccination status of registered patients using the EHR system from the enrolled practices) and rate of AEIs following the receipt of seasonal influenza vaccine. Using the CMR system, routine data will be extracted using methods that Surrey developed and deploys to extract RCGP RSC surveillance data. Coded clinical data routinely collected as part of clinical consultations in primary care will be extracted from up to 10 general practices in order to estimate medically attended or non-medically attended AEIs (derived from the ADR cards distributed to patients). Sensitive coded data and free-text data, will not be extracted.

As per EU requirement, we will also evaluate assess data quality, in particular focussing on data completeness and timeliness.

Primary objectives:

- To estimate on a weekly basis the crude and cumulative incidence rate of AEIs within 7 days following vaccination with a seasonal influenza vaccine using passive surveillance of GP EHR record systems enhanced by a card-based ADR reporting system. Extracted data will be presented overall, by brand (Fluarix tetra vs. others), by EMA defined age strata, and CMO-specified risk groups.

Secondary objectives:

- To estimate on a weekly basis the crude and cumulative incidence rate of AEIs within 7 days following vaccination with all seasonal influenza vaccines extracting data recorded in the CMR and information reported through the ADR card based system, presented overall, by brand (Fluarix tetra vs. others), by age strata, and CMO-specified risk groups.

Tertiary objectives:

- 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 18 years; ≥18-65 years; >65) and CMO-specified risk groups.
- To assess the completeness of vaccination data in the EHR
- To assess the timeliness of vaccination data in the EHR
- To evaluate the return rate of ADR cards
- To assess the timeliness of AEI reporting in the EHR (medically attended AEs) and from card based ADR reporting system
- To assess the timeliness of AEI reporting and from card based ADR reporting system in a meaningful format to GSK

Primary endpoints:

- Occurrence and onset dates of AEIs (appendix 2) within 7 days post vaccination reported using a card based ADR reporting system in vaccinated patients overall, by brand (also indicating those for whom brand data are unavailable), by age strata (6 months to 5 years; 6 to 12 years; 13 to 18 years; ≥18-65 years; >65) and CMO-specified risk groups. AEIs will be presented by categories depending of the nature of the event.
    - Fever or other febrile illness
    - Local reactions
    - General reaction (e.g., fatigue, myalgia, etc.)

Secondary endpoints:

- Occurrence and onset dates of AEIs within 7 days post vaccination reported using the EHR in vaccinated patients by age strata (6 months to 5 years; 6 to 12 years; 13 to 18 years; ≥18-65 years; >65) and CMO-specified risk groups, each week and cumulatively by brand (also indicating those for whom brand data are unavailable). AEIs will be presented by categories depending of the nature of the event.
    - Fever or other febrile illness
    - Local reaction
    - General reaction (fatigue, myalgia, etc.)
    - All other presentations that have been reported following vaccination (e.g., example Bell's palsy, Guillain-Barré syndrome), For

Tertiary endpoints:

- Seasonal influenza vaccination status among the subjects registered in the enrolled GP practices, vaccine brand, by age strata (6 months to 5 years; 6 to 12 years; 13 to 18 years; ≥18-65 years; >65) and CMO-specified risk groups and date of vaccine administration collected in the CMR system
- Level of missing data related to vaccination information (date of event, vaccine brand, vaccine batch). We will report where we have some but not all vaccination data.
- Time interval between AEI onset date and recording in the EHR by source (ADR card-based or not). Noting that not all events are recorded on the date they occurred.
- Lag time between date of vaccine administration and daft at which vaccination record is encoded in the CMR system
- Return rate of ADR cards comparing the number of cards distributed and the number of cards returned
- Time interval between AEI onset date and recording in the CMR by source (ADR card-based or not) and time at which data become available for review to GSK

5. RESEARCH METHODS

a. Study Design

Study setting and population

For this pilot project, routinely collected primary care data from up to ten GP practices will be extracted, to provide passive surveillance. However, this passive surveillance is enhanced by all practices additionally using a card-based ADR reporting system. To protect confidentiality this ADR card will be returned to the practice and data from it will be recorded in that patient's EHR. The data will be used to estimate proportions of AEIs among influenza-vaccinated individuals.

The proposed pilot study (EPI-FLU-046 VS UK) is to follow a cohort of patients who would be exposed to seasonal influenza vaccination in the months between 01/09/2016 and 30/11/2016.

We have developed a more specific ADR card. In last year's study the card-based ADR reporting system, use the yellow card developed by the UK Medicines and Healthcare products Regulation Agency (MHRA). However, feedback from practices was this was difficult to interpret and code into the practice EHR system. We have therefore developed a specific card to meet the requirements of the EMA. Patients will be provided with the appropriate ADR reporting card and invited to return the card to the GP practices within 7 days, but not later than 14 days, post-vaccination[vi].

Invitation letters will be sent to GP practices ordering mainly GSK's Fluarix tetra vaccine for the 2016/17 season. After receiving a positive feedback from the GP practices indicating their willingness to participate, we will look for practices ideally distributed across England (in London, a Northern city, and rural settings in the North and South) and aim to sample purposefully across these locations investigating the different age strata or risk/ target populations. It is particularly important, in the

first stages, to recruit large practices, thus we will send an invitation to GPs targeting ideally the practice who ordered preferentially Fluarix Tetra. We will include practices based on our assessment of their ability to comply with the protocol requirements; and fit with our sampling frame. 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].

Additionally, regulatory compliance studies can be registered with the National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio[viii]. We will seek advice as to whether this study would qualify.

The average practice size in England and Wales is 7,034[ix], we estimate that data will be collected on a population of approximately 70,340 patients (across ten practices). In the period from September to December 2015, 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%. We have estimated influenza vaccine uptake using the coverage estimates published by Public Health England (PHE)[x].

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)[xi]. Practices have a single CMR system, which comprehensively contains data about their registered patients, their illnesses, therapy, 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.

These different systems have different data models, and our goal would be to be able to process data from all. These information systems broadly adopt 2 coding schemes (Read 2 and CTV3), but slightly different interfaces and preferred terms in the look-up tables.

<u>Inclusion criteria</u>

1. **Surveillance will apply to vaccination between 1st September and 30th November 2016 (or other date set by EMA):**

As this is a population-based safety surveillance study, all individuals who receive influenza vaccination in the 10 volunteer practices between 1 September and a date to be specified by EMA are eligible for inclusion in the analysis. Last year 30 November was set as the cut-off by EMA because it is primarily interested in signal detection and safety reporting early in the annual vaccination period. We anticipate a cut-off on or around 30 November.

2. **Practices primary vaccine supplier will be GSK**

The intent for GSK, as per EMA requirements, would be to focus on GSK vaccines (Fluarix Tetra) specifically. i.e. An inclusion criteria is that practices state their principal vaccine supplier will be GSK.

3. All influenza vaccinated subjects in these practices will be offered an ADR card

In all enrolled GP practices ADR cards will be distributed to all subjects vaccinated willing to complete the cards or, as appropriate, a parent or carer. We will request practices to let us know their flu vaccine clinic dates and prompt around ADR card issue.

Exclusion criteria

We will not extract data where patients have any "opt out" code for use of their data

In the database analysis, only registered patients who have explicitly opted out of data sharing will be excluded from the analysis. We will identify these patients using the opt-out codes within GP information systems where the patients have made an explicit choice to opt out; patients will be informed of their option to opt-out via posters in the practices and information sheets accompanying the ADR cards.

Data extraction and data management

The method and governance procedure has been developed by the University of Surrey, using an approved provider, Apollo. Alternatively, we will use another approved data extraction supplier, or securely extract the relevant study data ourselves using standard data extraction tools such as Morbidity Information Query Export Syntax (MIQUEST), a Department of Health sponsored data extract tool.

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 from data – such as name, date of birth, etc. However, there is a risk that if data are linked to other data a person might be identified[xii]. Therefore although all identifiers are removed we keep data encrypted 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[xiii] on the recommendation of the European Data Protection Supervisor (EDPS)[xiv].

We only "pseudonymise" (rather than fully anonymise) so that we can link further data to the same individual's record. For this study we need, for example, we need to be able to link a possible adverse event to with whether that individual had been vaccinated (and with the specific brand and batch number). Pseudonymisation allows us to do this without knowing any of the strong personal identifiers of that individual.

All data processing and analysis in the present proposed 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 Health and Social Care Information Centre (HSCIC) as meeting Information Governance Toolkit (IGT) standards[xv].

We will only extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the EHR system.[xvi] The overwhelming majority of the large volume of research that has come out of UK primary care is based on coded data[xvii]. The richness of primary care data are such that we anticipate being able to detect important AEIs.[xviii] We will request practices to use the relevant Read code for ADR notifications, when recording data from a returned card (Read Code: 9G4 - Adverse drug reaction notification).
We extract some data associated with coded data, however these are limited to the administration regime and batch number fields of prescribing data. The latter may be important in identification of brand.

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

- Demographic information: age, gender, ethnicity, registered date.
- Postcode: 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 extraction.
- Primary care consultations following vaccination, any other markers of health care utilisation, and referral to further care.
- Reactogenicity outcomes of seasonal influenza vaccination as listed in the research literature and any contemporary EU guidance.
- Life-style/risk factors – 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.

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.

A formal service level agreement (SLA) will be established with the enrolled GP practices, consenting to the use of their routinely collected data (including demographics and AEIs collected using the ARD cards) for the purposes of vaccine enhanced safety surveillance. This data will be extracted, stored, and processed by the team at the University of Surrey, and only aggregated tables will be made available in publications or to third parties.

[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

Data collection using an ADR card

In order to facilitate the coding of data using a standardised approach, ADR card matching with the EMA requirement have been developed, in utilising feedback from participant practices involved in the pilot study in 2014/15 (Appendix 3).

Sample size calculation

The eligible target population to medically followed by the GPs is estimated at 50,000 subjects (approximately 5,000 per practice). We expect to enrol up to 5,000 vaccinated subjects with a 7 days of follow-up after vaccination (as per EMA interim guidance request). 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; this is over the 14 week period of enhanced surveillance (01 September – 30 November 2016)

We have not taken into account any effect of clustering in our surveillance study design or power calculation. Cluster Randomized Controlled Trials (RCTs) require special statistical considerations when designing the trial, and later when analysing the data. Such trials may not be as much statistically powered as standard RCTs. 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 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. This results in a loss of statistical power to detect a difference between the intervention and control groups. A compensatory increase in sample size is required to maintain power in a cluster RCT, and the degree of similarity of within clusters should also be assessed.

Those limitations are expected to be also applicable to observational studies.
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.

Of note the cluster effect has not taken into consideration in the calculation of the sample size. It may increase the relative standard error and thus decrease the precision around the proportions presented below. Nevertheless, this will be however accounted for during the analysis.

Table 1 shows the 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[xix]. 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 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 2% to 100%, and the associated relative standard error varies from 2.0% to 200% depending on the scenario.

Table 2 shows the evolution by week of the 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 5%, 10% or 20%, the corresponding probability to observe at least one event in our study population varies from 53% to 99% after week 1, and the associated relative standard error varies from 53% to 37% depending on the scenario.

The recruitment will be performed by GP practice and this creates a clustering effect. This effect will decrease the precision of the proportion estimates but it is difficult to predict to which extend because it depends on the unknown intra cluster correlation.

Table 1 Confidence intervals, Relative Standard Error and probability to observe at least one AEI according to expected probabilities of occurrence of AEI[xx]

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%	100,00%	2,0%
50000	20%	10000	1500	15,00%	14,3%	15,7%	100,00%	2,4%
50000	20%	10000	1000	10,00%	9,4%	10,6%	100,00%	3,0%
50000	20%	10000	500	5,00%	4,6%	5,4%	100,00%	4,4%
50000	20%	10000	400	4,00%	3,6%	4,4%	100,00%	4,9%
50000	20%	10000	200	2,00%	1,7%	2,3%	100,00%	7,0%
50000	20%	10000	100	1,00%	0,8%	1,2%	100,00%	9,9%
50000	20%	10000	10	0,10%	0,0%	0,2%	99,95%	31,6%
50000	20%	10000	9	0,09%	0,0%	0,2%	99,88%	33,3%
50000	20%	10000	8	0,08%	0,0%	0,2%	99,70%	35,3%
50000	20%	10000	7	0,07%	0,0%	0,1%	99,27%	37,8%
50000	20%	10000	6	0,06%	0,0%	0,1%	98,27%	40,8%
50000	20%	10000	5	0,05%	0,0%	0,1%	95,96%	44,7%
50000	20%	10000	4	0,04%	0,0%	0,1%	90,85%	50,0%
50000	20%	10000	3	0,03%	0,0%	0,1%	80,09%	57,7%
50000	20%	10000	2	0,02%	0,0%	0,1%	59,40%	70,7%
50000	20%	10000	1	0,01%	0,0%	0,1%	26,42%	100,0%
50000	10%	5000	250	5,00%	4,4%	5,6%	100,00%	6,2%
50000	10%	5000	200	4,00%	3,5%	4,6%	100,00%	6,9%
50000	10%	5000	100	2,00%	1,6%	2,4%	100,00%	9,9%
50000	10%	5000	50	1,00%	0,7%	1,3%	100,00%	14,1%
50000	10%	5000	5	0,10%	0,0%	0,2%	95,96%	44,7%
50000	10%	5000	4,5	0,09%	0,0%	0,2%	93,90%	47,1%
50000	10%	5000	4	0,08%	0,0%	0,2%	90,85%	50,0%
50000	10%	5000	3,5	0,07%	0,0%	0,2%	86,42%	53,4%
50000	10%	5000	3	0,06%	0,0%	0,2%	80,09%	57,7%
50000	10%	5000	2,5	0,05%	0,0%	0,2%	71,28%	63,2%
50000	10%	5000	2	0,04%	0,0%	0,1%	59,40%	70,7%
50000	10%	5000	1,5	0,03%	0,0%	0,1%	44,22%	81,6%
50000	10%	5000	1	0,02%	0,0%	0,1%	26,42%	100,0%
50000	10%	5000	0,5	0,01%	0,0%	0,1%	9,02%	141,4%
50000	5%	2500	125	5,00%	4,2%	5,9%	100,00%	8,7%
50000	5%	2500	100	4,00%	3,3%	4,8%	100,00%	9,8%
50000	5%	2500	50	2,00%	1,5%	2,6%	100,00%	14,0%
50000	5%	2500	25	1,00%	0,6%	1,5%	100,00%	19,9%
50000	5%	2500	12,5	0,50%	0,3%	0,9%	100,00%	28,2%
50000	5%	2500	2,5	0,10%	0,0%	0,3%	71,29%	63,2%
50000	5%	2500	2,25	0,09%	0,0%	0,3%	65,76%	66,6%
50000	5%	2500	2	0,08%	0,0%	0,3%	59,41%	70,7%
50000	5%	2500	1,75	0,07%	0,0%	0,3%	52,22%	75,6%
50000	5%	2500	1,5	0,06%	0,0%	0,3%	44,22%	81,6%
50000	5%	2500	1,25	0,05%	0,0%	0,3%	35,54%	89,4%

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	5%	2500	1	0,04%	0,0%	0,2%	26,42%	100,0%
50000	5%	2500	0,75	0,03%	0,0%	0,2%	17,33%	115,5%
50000	5%	2500	0,5	0,02%	0,0%	0,2%	9,02%	141,4%
50000	5%	2500	0,25	0,01%	0,0%	0,2%	2,65%	200,0%

Table 2 Confidence intervals, Relative Standard Error 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%	99,37%	37,2%
2	50000	20%	1428	14	1,00%	0,5%	1,6%	100,00%	26,3%
3	50000	20%	2142	21	1,00%	0,6%	1,5%	100,00%	21,5%
4	50000	20%	2857	28	1,00%	0,7%	1,4%	100,00%	18,6%
5	50000	20%	3571	35	1,00%	0,7%	1,4%	100,00%	16,7%
6	50000	20%	4285	42	1,00%	0,7%	1,3%	100,00%	15,2%
7	50000	20%	5000	50	1,00%	0,7%	1,3%	100,00%	14,1%
8	50000	20%	5714	57	1,00%	0,8%	1,3%	100,00%	13,2%
9	50000	20%	6428	64	1,00%	0,8%	1,3%	100,00%	12,4%
10	50000	20%	7142	71	1,00%	0,8%	1,3%	100,00%	11,8%
11	50000	20%	7857	78	1,00%	0,8%	1,2%	100,00%	11,2%
12	50000	20%	8571	85	1,00%	0,8%	1,2%	100,00%	10,7%
13	50000	20%	9285	92	1,00%	0,8%	1,2%	100,00%	10,3%
14	50000	20%	10000	100	1,00%	0,8%	1,2%	100,00%	9,9%
1	50000	10%	357	3	1,00%	0,2%	2,4%	87,26%	52,7%
2	50000	10%	714	7	1,00%	0,4%	2,0%	99,37%	37,2%
3	50000	10%	1071	10	1,00%	0,4%	1,7%	99,98%	30,4%
4	50000	10%	1428	14	1,00%	0,5%	1,6%	100,00%	26,3%
5	50000	10%	1785	17	1,00%	0,6%	1,5%	100,00%	23,6%
6	50000	10%	2142	21	1,00%	0,6%	1,5%	100,00%	21,5%
7	50000	10%	2500	25	1,00%	0,6%	1,5%	100,00%	19,9%
8	50000	10%	2857	28	1,00%	0,7%	1,4%	100,00%	18,6%
9	50000	10%	3214	32	1,00%	0,7%	1,4%	100,00%	17,6%
10	50000	10%	3571	35	1,00%	0,7%	1,4%	100,00%	16,7%
11	50000	10%	3928	39	1,00%	0,7%	1,4%	100,00%	15,9%
12	50000	10%	4285	42	1,00%	0,7%	1,3%	100,00%	15,2%
13	50000	10%	4642	46	1,00%	0,7%	1,3%	100,00%	14,6%
14	50000	10%	5000	50	1,00%	0,7%	1,3%	100,00%	14,1%
1	50000	5%	178	1	1,00%	0,0%	3,1%	53,24%	74,6%
2	50000	5%	357	3	1,00%	0,2%	2,4%	87,26%	52,7%
3	50000	5%	535	5	1,00%	0,3%	2,2%	97,04%	43,0%
4	50000	5%	714	7	1,00%	0,4%	2,0%	99,37%	37,2%
5	50000	5%	892	8	1,00%	0,4%	1,8%	99,87%	33,3%
6	50000	5%	1071	10	1,00%	0,4%	1,7%	99,98%	30,4%
7	50000	5%	1250	12	1,00%	0,5%	1,7%	100,00%	28,1%
8	50000	5%	1428	14	1,00%	0,5%	1,6%	100,00%	26,3%
9	50000	5%	1607	16	1,00%	0,6%	1,6%	100,00%	24,8%
10	50000	5%	1785	17	1,00%	0,6%	1,5%	100,00%	23,6%
11	50000	5%	1964	19	1,00%	0,6%	1,5%	100,00%	22,5%
12	50000	5%	2142	21	1,00%	0,6%	1,5%	100,00%	21,5%
13	50000	5%	2321	23	1,00%	0,6%	1,5%	100,00%	20,7%

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)
14	50000	5%	2500	25	1,00%	0,6%	1,5%	100,00%	19,9%

Statistical analyses

R Studio within the secure analysis server is the analytical tool of choice for the Research Group. We will interpret coded data by the creation of ontologies that we will map to case-definitions, where available. However, we do not have the in depth descriptions required for case definition found, for example, in clinical trials. We will be inferring meaning from brief clinical coded information; though we have long experience of this and will have the opportunity to confirm with practices and practitioners how to interpret their clinical records.

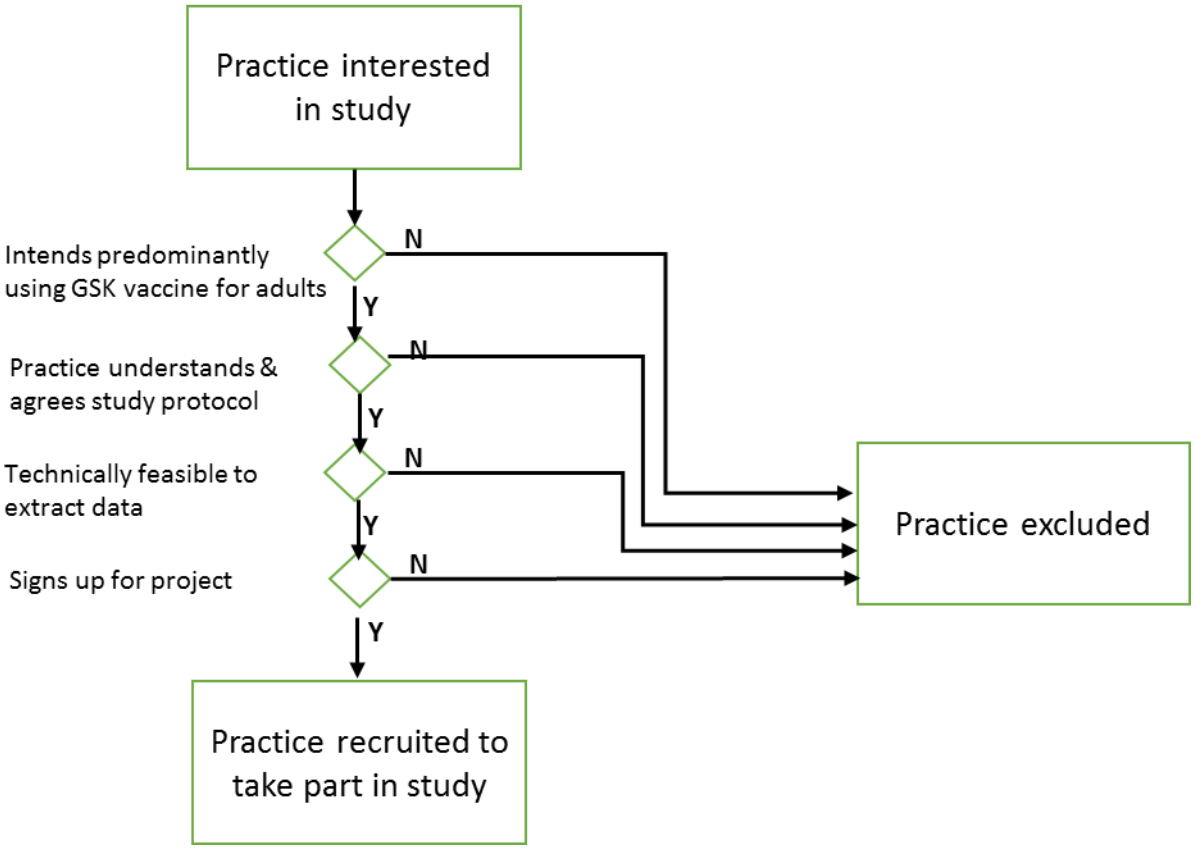
Statistical analysis will consist primarily of descriptive statistics: rates and proportions for categorical data and summary statistics for continuous variables. Confidence intervals will be calculated; however, due to the effects of clustering and practice differences in this relatively small pilot these are likely to be wide.

Statistical analyses will be planned in details in a statistical analysis plan before the start of the pilot study.

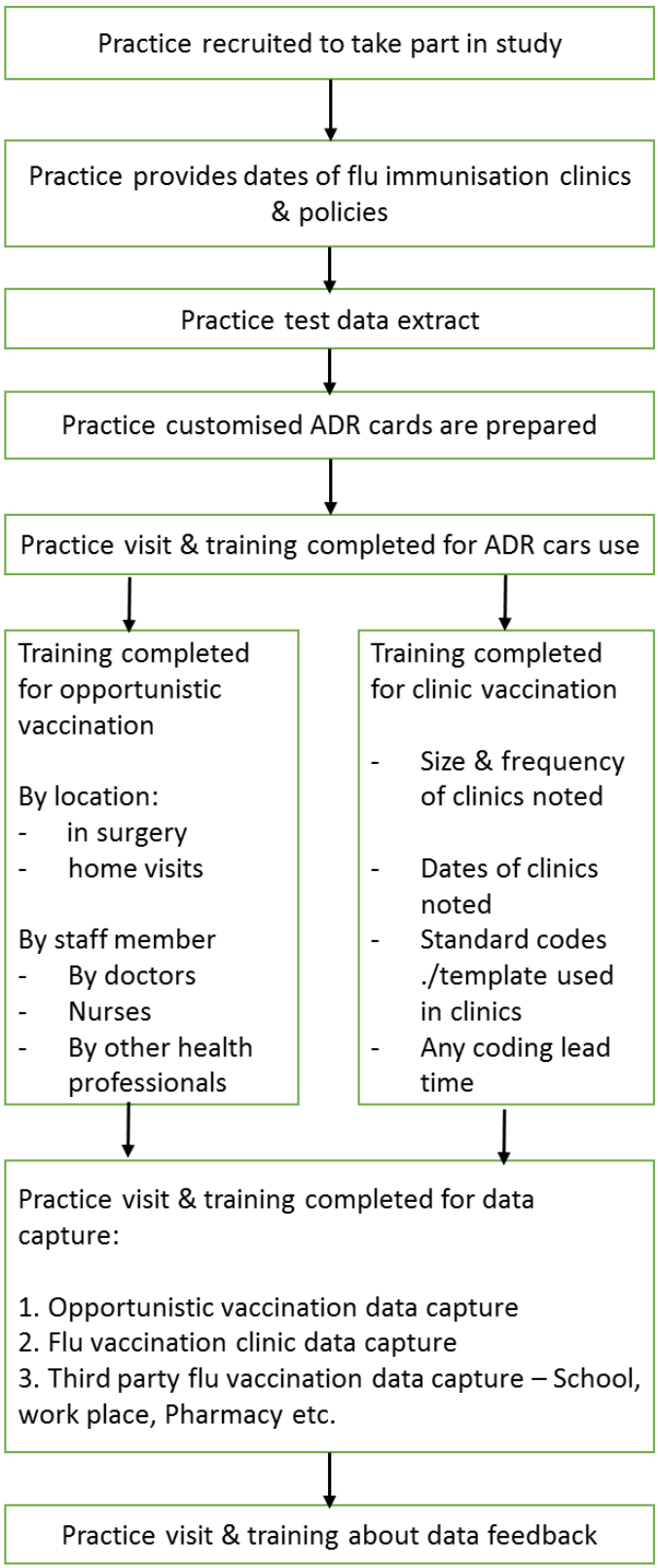
A series of flow charts have been developed to facilitate understanding of recruitment flows, the training and other process that have to be developed as sites initiate the study, and to explain the data flows in the practice.

The flow charts are presented below

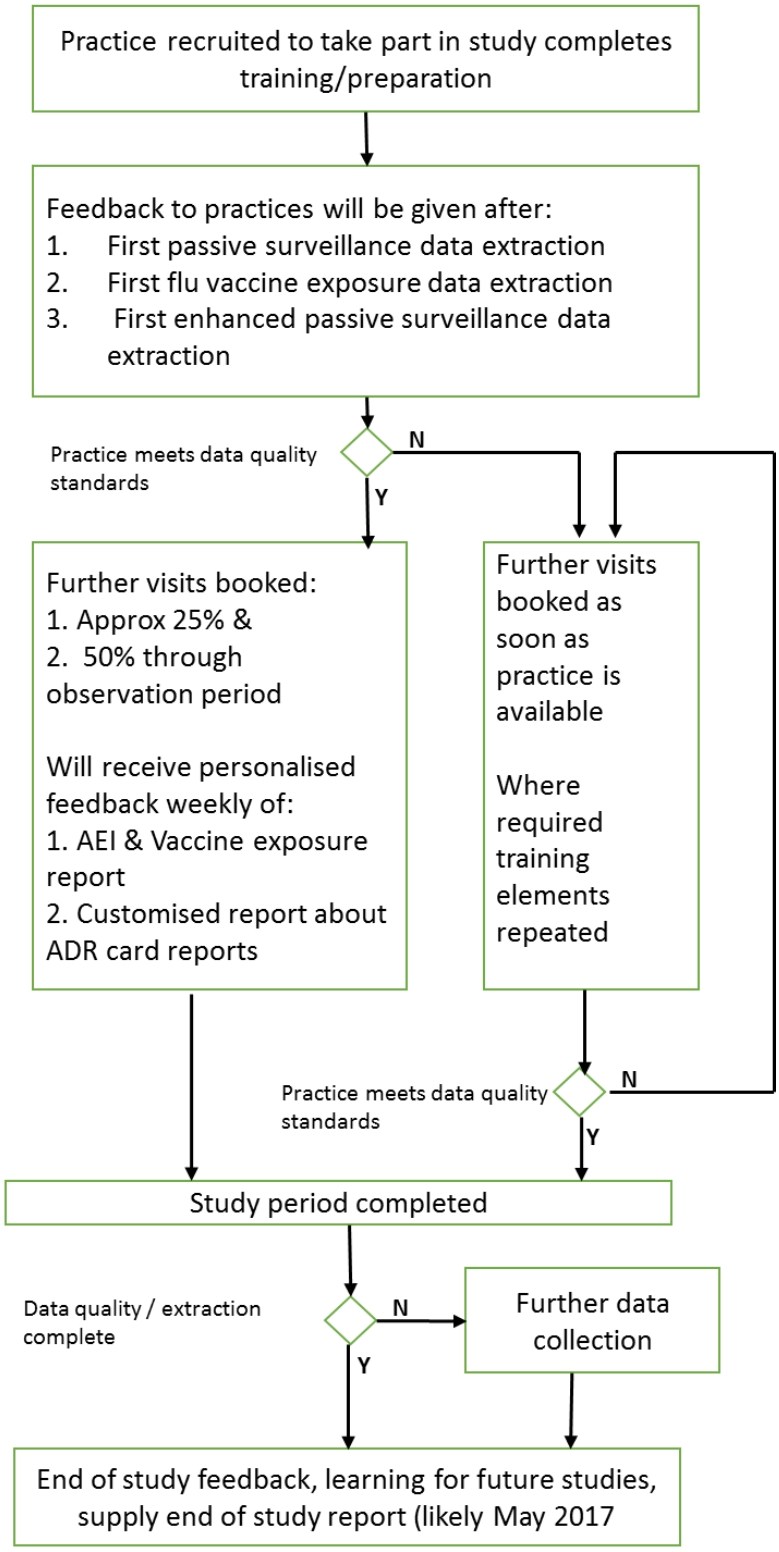
Flow chart 1: Practice selection process



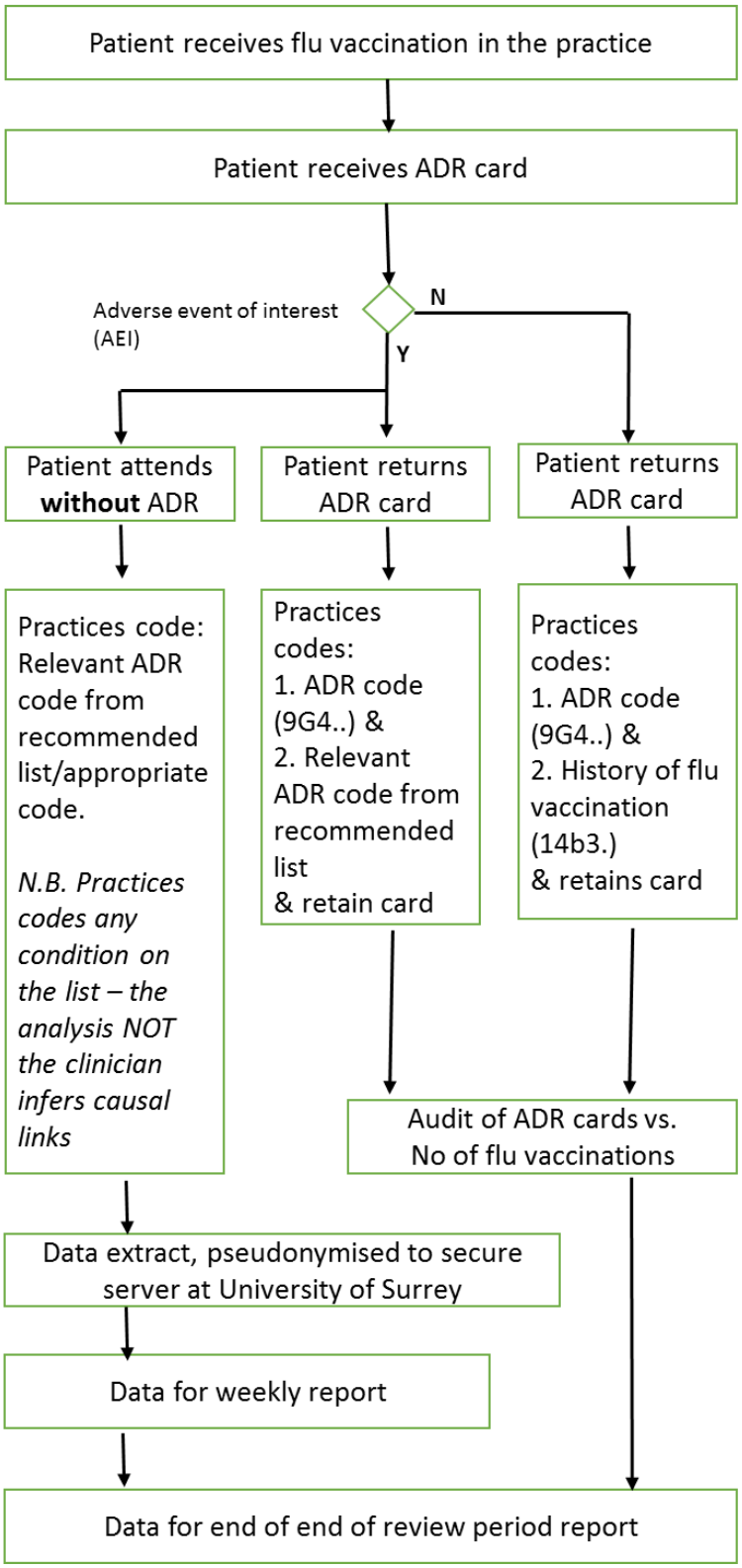
Flow chart 2: Preparation pre-study & site initiation process



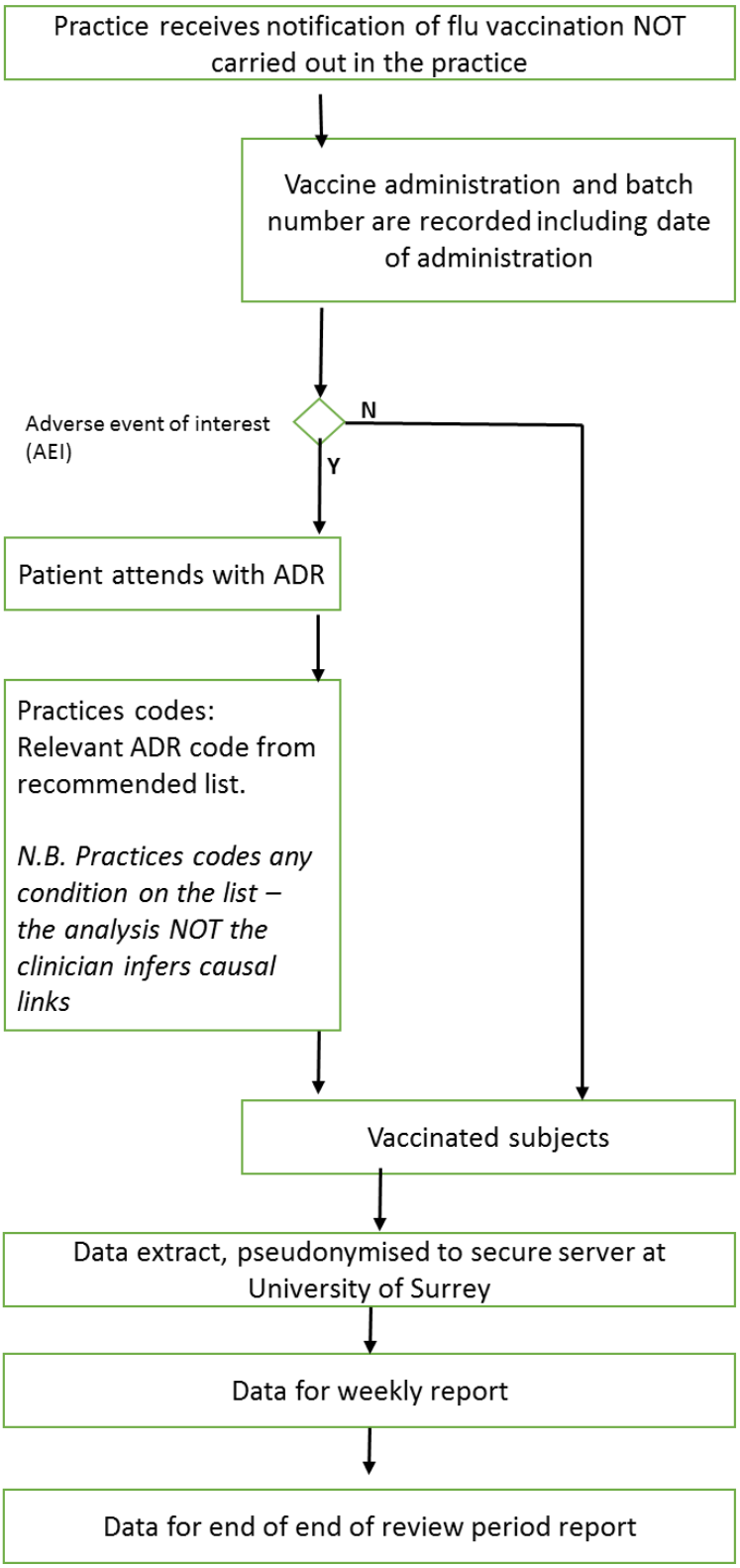
Flow chart 3: Visits during study linked to data quality



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



In this passive enhanced safety surveillance, there are two data sources. General practice EHR data, providing passive surveillance, with ADR cards completed by patients providing the enhanced component. The ADR cards are being returned to the patient's own practice to ensure confidentiality. The data from these cards we also be 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 practice on an ADR by a vaccinated patient.

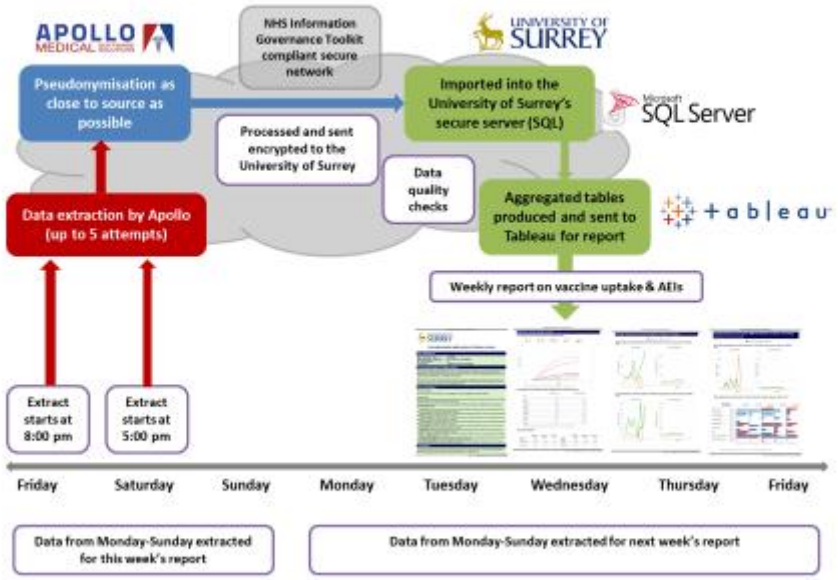
2. ADR cards completed by patients. Among the 10 participating GP practices, patients who are vaccinated against influenza will be provided ADR cards. These ADR cards, customised following practice feedback to match EMA requirements, to collect AEIs reported after the receipt of influenza vaccination.

The ADR cards completed by patients will be returned to that patient's general practitioner. Any outcomes (including no AEIs) recorded on these cards will be coded into their GP's EHR system. This coding will include a specific code to indicate that the information is derived from those cards, as well as coding any ADR detected. The coding will follow a standardised approach to data recording (appendix 2).

In addition, among the participating sites, we will extract routinely recorded data from the practices EHR system. The data collected will include demographics, comorbidities and other data required to further define the risk groups recommended for vaccination. In addition the practice will code AEI data returned from the orange ADR card to the EHR system.

These data, originating from the two sources (patient completed ADR card, or practice recorded) will be then imported (anonymised) into the secure servers of the University of Surrey. The final dataset will therefore combine data routinely collected for all patients registered with the 10 participating sites and data collected form the ADR cards and encoded during the 2016/17 influenza season.

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



Analyses of the primary objective

All analyses will be carried out by overall, by brand (Fluarix tetra vs. others), by age strata (6 months to 5 years; 6 to 12 years; 13 to 18 years; ≥18-65 years; >65), and CMO-specified risk groups.

To estimate on a weekly basis the crude incidence rate of AEIs within 7 days

- The denominator will consist of the number vaccinated subjects receiving a vaccination card and reaching 7 days of follow-up post vaccination during the week of interest and cumulatively since the beginning of the study.
- The numerator will encompass all vaccinated subjects reporting at least one AEI within 7 days following vaccination with a seasonal influenza vaccine

Analyses of the secondary objective

To estimate on a weekly basis the crude incidence rate of AEIs within 7 days

- The denominator will consist of the number vaccinated subjects with a seasonal influenza vaccine recorded in the CMR system and reaching 7 days of follow-up post vaccination during the week of interest and cumulatively since the beginning of the study.
- The numerator will encompass all vaccinated subjects reporting at least one AE within 7 days following vaccination with a seasonal influenza vaccine (on either the CMR system or card based system).

Analyses of the tertiary objective

To estimate on a weekly basis the vaccine uptake, by age strata (6 months to 5 years; 6 to 12 years; 13 to 18 years; ≥18-65 years; >65), and CMO-specified risk groups.

- The denominator will consist of all subjects registered in the GP practice and active within the last 12 months prior to the study start (i.e., 01 September 2016).
- The numerator will consist of all subjects vaccinated with a seasonal influenza vaccine during the 2016/17 influenza season recorded in the CMR system

To assess the completeness of vaccination data in the CMR

- Among vaccinated subjects, assess the proportion of subjects for who the complete information on vaccination will be reported. Key information includes the date of vaccination (event date), the brand, batch number, number of dose

To assess the timeliness of vaccination data in the CMR

Summarize the time interval between the vaccination date and the date at which the record was encoded in the system and the date at which the record is available to be included in the dataset.

To assess the timeliness of AEI reporting in the CMR (medically attended AEs) and from card based ADR reporting system

Summarize the time interval between the onset date of AE and the date at which the record was encoded in the system presented by source (medically attended and derived from the card based system) and also time at which data become available for review for GSK

Safety reporting, including routine pharmacovigilance

This study's primary endpoints are safety-related. However, it will be clearly communicated to participating practices that the study does not replace AEI reporting that would occur as part of routine practice. If a GP felt an AEI merited reporting they should do so in whatever way they would generally do so.

The reporting within this study is supplemental and their participation is not expect to alter routine safety reporting practices to either the appropriate authorities or MAHs in any way. On a routine basis, patients are usually encouraged to contact their GP or pharmacist to obtain guidance on how to report suspected side effects (including adverse events following immunization). The process to report an adverse event following vaccination with a seasonal influenza vaccine will be maintained. Any AE that a health care professional feels important to be communicated to the MHRA will be communicated according to routine practice. We expect however that the reporting rate might increase for the participating sites, give that all vaccinees receiving their vaccination during the study period will be provided with an ADR cards to complete and return to their GP. GPs will be trained and supported to ensure such reports are also coded into their practice EHR record system.

The team at the University of Surrey will review the data submitted weekly as part of the study. If the team at the University of Surrey becomes aware of a serious adverse event (SAE) experienced by

a study participant, the SAE should be reported to GSK within 24 hours of awareness, in writing. If GSK deems additional information necessary, request of additional information will be sent through the team at the University of Surrey. An SAE is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
  NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity.
  NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Important medical events - events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

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. Our 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 events 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 (TBD)	**Role and Organisation**
Prof Simon de Lusignan	Principal Investigator, University of Surrey
Dr Gaël Dos Santos	Research Representative, GSK
François Haguinet	Domain Expert, GSK
TBC – after practice recruitment	GP/Practice representative
TBC – after practice recruitment	Patient Representative
Dr Filipa Ferreira	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 Simon de Lusignan	Senior Clinical Lead, University of Surrey
Dr Filipa Ferreira	Project Manager, University of Surrey
Dr Gaël Dos Santos	Research Representative, GSK
Rachel Byford	Senior Database developer, University of Surrey
Dr Tom Chan	Senior Research Fellow, University of Surrey
Ana Correa	Research Fellow, University of Surrey
Ivelina Yonova	Practice Liaison Officer

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

Patient involvement

Patients will be involved in the protocol review. Their comments will be taken into consideration in the development of the protocol to help ensure its acceptability to patients. A patient representative will be part of the steering committee.

Practitioner involvement

Invitation letters, to participate in this study, will be sent to general practices who have ordered Fluarix tetra vaccine for the 2016/17 season; This may also include existing research contacts and networks of the University of Surrey. The intent is to look for practices purposefully to represent different levels of deprivation and ethnic mix, brand of computerised medical record systems, and practice size. However, this will be tempered by our need to recruit before the start of the influenza immunisation season.

Peer review of the study protocol

The study protocol has been review by GSK's peer review committee.

The study protocol will be sent for peer review by pharmacologists, general practitioners and lay advisors.

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 proposed study starts with an exploration of routinely collected primary care data from up to ten volunteer GP practices to assess if the data is fit for the purpose of realising the EMA requirement for enhanced surveillance of seasonal influenza vaccination. We will recommend whether additional data collection in primary care is needed to meet EMA standards for enhanced surveillance of seasonal influenza vaccination.

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[xxi]. 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. We do not believe that such enhanced surveillance requires 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 pilot study last year, we anticipate that this investigation meets the Health Research Authority's definition of Service Evaluation[xxii]. We anticipate this enhanced passive surveillance project will feel the same criteria[xxii].

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 Information Governance Toolkit (IGT) for Hosted Secondary Use Team/ Project, Version 12[xxiii]. 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. We will respect the codes in the data indicating that a patient does not wish to have their record available for research; we will, however, seek to report the number of patients within a practice who have chosen to opt out.

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 will be published in a peer review open access journal.
The outputs from the research will be disseminated primarily through peer review papers in high impact journals within the domains of primary care, surveillance, vaccines, and infectious diseases[xxiv] [xxv]. We will present findings at relevant seminars and conferences.

The University of Surrey, in accordance with GSK policy, will post a summary of the study protocol and 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. SIGN OFF PAGE

For and on behalf of

GLAXOSMITHKLINE BIOLOGICALS S.A.

Date : 9 JUNE 2016

Name :

Anne Schuind

Title :
Clinical and Epidemiology Project Lead, Influenza Vaccines, Clinical R&D

For and on behalf of

UNIVERSITY OF SURREY

Date : 12th June 2016

Name : Simon de Lusignan

Simon de Lusignan

Title :
Professor of Primary Care and Clinical Informatics
Chair in Health Care Management, University of Surrey

11. 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	
Rhinorrhoea	1C83.	XM00h	
Nasal congestion	H1y1z	X77Gp	
Epistaxis	R047.	Xa96W	
Coryza	H00..	XE0Xl	
Cough	171..	XM0Ch	
Oropharyngeal pain	1922. 1CB3.	1922. 1CB3.	
Hoarseness	1CA2.	1CA2.	
Wheezing	1737.	XE0qs	
Gastrointestinal			
Decreased appetite	R0300	XM07Y	
Nausea	198..	X75qw	
Vomiting	199..	XE0rA	
Diarrhoea	19F..	19F2.	
Fever/pyrexia			
Fever	165..	X76Dl	
Mild fever (<38.5° C rectal)	**2E3..**	2E3..	Please include level of temperature, to help us classify the fever
Moderate fever (38.6-39.5°C)			
High fever (>39.5°C)			
Sensitivity/anaphylaxis			
Hypersensitivity reactions	SN52.	Xa5uf	
Anaphylactic reactions	SN501	X70vr	
Facial oedema	16J5.	Xa0ls	
Rash			
Rash	M130.	X50Ge	
Generalised rash	2I14.	XM07J	
General non-specific symptoms			
Irritability	225A.	225A.	
Drowsiness	1B67.	XM06R	
Fatigue	168..	1682.	
Neurological			
Bell's palsy	F310.	F310.	
Peripheral tremor	1B22.	XE0rn	
Guillain-Barre Syndrome (GBS)	F3700	F3700	
Seizure/ Febrile convulsions	1B64. 1B6B.	XaDbE XM03l	
Headache	1B1G.	XM0CV	
Musculoskeletal			
Muscle aches/ myalgia	N2410	X75rs	
Arthropathy	N037.	X701f	
Local Symptoms			
Local erythema	SP3y4 SP3y5 SP3y6 SP3y7	X75ty	

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

Principal Investigator: Professor Simon de Lusignan
Practice Liaison Officer: Ivelina Yonova i.yonova@surrey.ac.uk

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	
Rhinorrhoea	1C83.	XM00h	
Nasal congestion	H1y1z	X77Gp	
Epistaxis	R047.	Xa96W	
Coryza	H00..	XE0Xl	
Cough	171..	XM0Ch	
Oropharyngeal pain	1922. 1CB3.	1922. 1CB3.	
Hoarseness	1CA2.	1CA2.	
Wheezing	1737.	XE0qs	
Gastrointestinal			
Decreased appetite	R0300	XM07Y	
Nausea	198..	X75qw	
Vomiting	199..	XE0rA	
Diarrhoea	19F..	19F2.	
Fever/pyrexia			
Fever	165..	X76Dl	
Mild fever (<38.5° C rectal)	2E3..	2E3..	Please include level of temperature, to help us classify the fever
Moderate fever (38.6-39.5°C)			
High fever (>39.5°C)			
Sensitivity/anaphylaxis			
Hypersensitivity reactions	SN52.	Xa5uf	
Anaphylactic reactions	SN501	X70vr	
Facial oedema	16J5.	Xa0ls	
Rash			
Rash	M130.	X50Ge	
Generalised rash	2I14.	XM07J	
General non-specific symptoms			
Irritability	225A.	225A.	
Drowsiness	1B67.	XM06R	
Fatigue	168..	1682.	
Neurological			
Bell's palsy	F310.	F310.	
Peripheral tremor	1B22.	XE0rn	
Guillain-Barre Syndrome (GBS)	F3700	F3700	
Seizure/ Febrile convulsions	1B64. 1B6B.	XaDbE XM03l	
Headache	1B1G.	XM0CV	
Musculoskeletal			
Muscle aches/ myalgia	N2410	X75rs	
Arthropathy	N037.	X701f	
Local Symptoms			
Local erythema	SP3y4 SP3y5 SP3y6 SP3y7	X75ty	

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

Principal Investigator: Professor Simon de Lusignan
Practice Liaison Officer: Ivelina Yonova i.yonova@surrey.ac.uk

Appendix 3: ADR form

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 ___ /____ /2016

***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 ___ /____ /2016

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 car in the envelope provide 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 car in the envelope provide 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

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Enhanced safety surveillance of seasonal influenza vaccine

Possible side effect or Condition in the 7 days after influenza vaccination	Present	Date	Mild	Unpleasant no effect on daily activities	Bad Affecting daily activities	Bad Enough to see a doctor	Bad Enough to go to a hospital	Severe Caused very serious illness	Still present
Conjunctivitis – Sticky eyes	☐	___/___/16							☐
Runny nose	☐	___/___/16							☐
Blocked nose	☐	___/___/16							☐
Epistaxis – Nose bleed	☐	___/___/16							☐
Common cold	☐	___/___/16							☐
Cough	☐	___/___/16							☐
Sore throat	☐	___/___/16							☐
Hoarse voice	☐	___/___/16							☐
Wheezing	☐	___/___/16							☐
Decreased appetite	☐	___/___/16							☐
Nausea – feeling sick	☐	___/___/16							☐
Vomiting – being sick	☐	___/___/16							☐
Diarrhoea	☐	___/___/16							☐
Fever	☐	___/___/16							☐
Temperature if measured	☐	____ celsius	___/___/16						☐
Allergic reaction rash	☐	___/___/16							☐
Other allergic reactions	☐	___/___/16							☐
Facial oedema	☐	___/___/16							☐
Local reaction to vaccine	☐	___/___/16							☐
Rash	☐	___/___/16							☐
Irritability	☐	___/___/16							☐
Drowsiness	☐	___/___/16							☐
Fatigue	☐	___/___/16							☐
Tremor / shaking	☐	___/___/16							☐
Seizure / fits	☐	___/___/16							☐
Headache	☐	___/___/16							☐
Muscle aches	☐	___/___/16							☐
Joint pain	☐	___/___/16							☐
Other	☐	___/___/16							☐
1. _____		___/___/16							
2. _____		___/___/16							
3. _____		___/___/16							
Add below if more									

Appendix 4: GP surgery Poster

ARE YOU HAVING A FLU VACCINE?

PATIENT INFORMATION: RESEARCH PROJECT IN THIS SURGERY

It is important to maintain a strong process to monitor vaccine safety, particularly for frequent vaccines such as the influenza vaccine. This surgery is taking part in a research programme to explore how influenza vaccine safety could be monitored using primary care data. This study is funded by GlaxoSmithKline Biologicals, and is conducted by the Department of Clinical and Experimental Medicine, University of Surrey.

The main objective is to conduct a pilot **assessing 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.

How will it be carried out?

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. **Patient identifiable information (name & date of birth) will be converted in your surgery to an anonymous and encrypted format. No patient identifiable information will actually leave the surgery.**

How will it affect me?

This project does not affect patients directly. No additional treatment or assessments will be needed. **The information provided by the surgery is treated in the strictest confidence, and it is not possible to relate any results to you personally.**

Who has reviewed this information?

This study has been reviewed and approved for conduct by the National Research Ethics Committee. This committee reviews research studies to protect the rights and wellbeing of the patients taking part.

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 Simon de Lusignan
Professor of Primary Care & Clinical Informatics
Phone: +44 (0) 1483 684802
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Appendix 5: Information Sheet – GP

INFORMATION SHEET FOR GP PRACTICES

Enhanced safety surveillance of seasonal influenza vaccine

Full 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 2016.

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 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 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 Simon de Lusignan. 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?

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

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Appendix 6: Information Sheet - Patients

Practice logo to be added

INFORMATION SHEET FOR PATIENTS

Enhanced safety surveillance of seasonal flu vaccine

Full 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 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?

We have recruited ten practices representing urban and rural localities across England. 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.

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. Patient identifiable information (name & date of birth) will be converted in your surgery to an anonymous and encrypted format. No patient identifiable information will actually leave the surgery. In addition, patients who have received the vaccine will be asked to complete a reporting card with details of any AEIs.

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 within 7-14 days after vaccination. 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 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.

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:

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

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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.

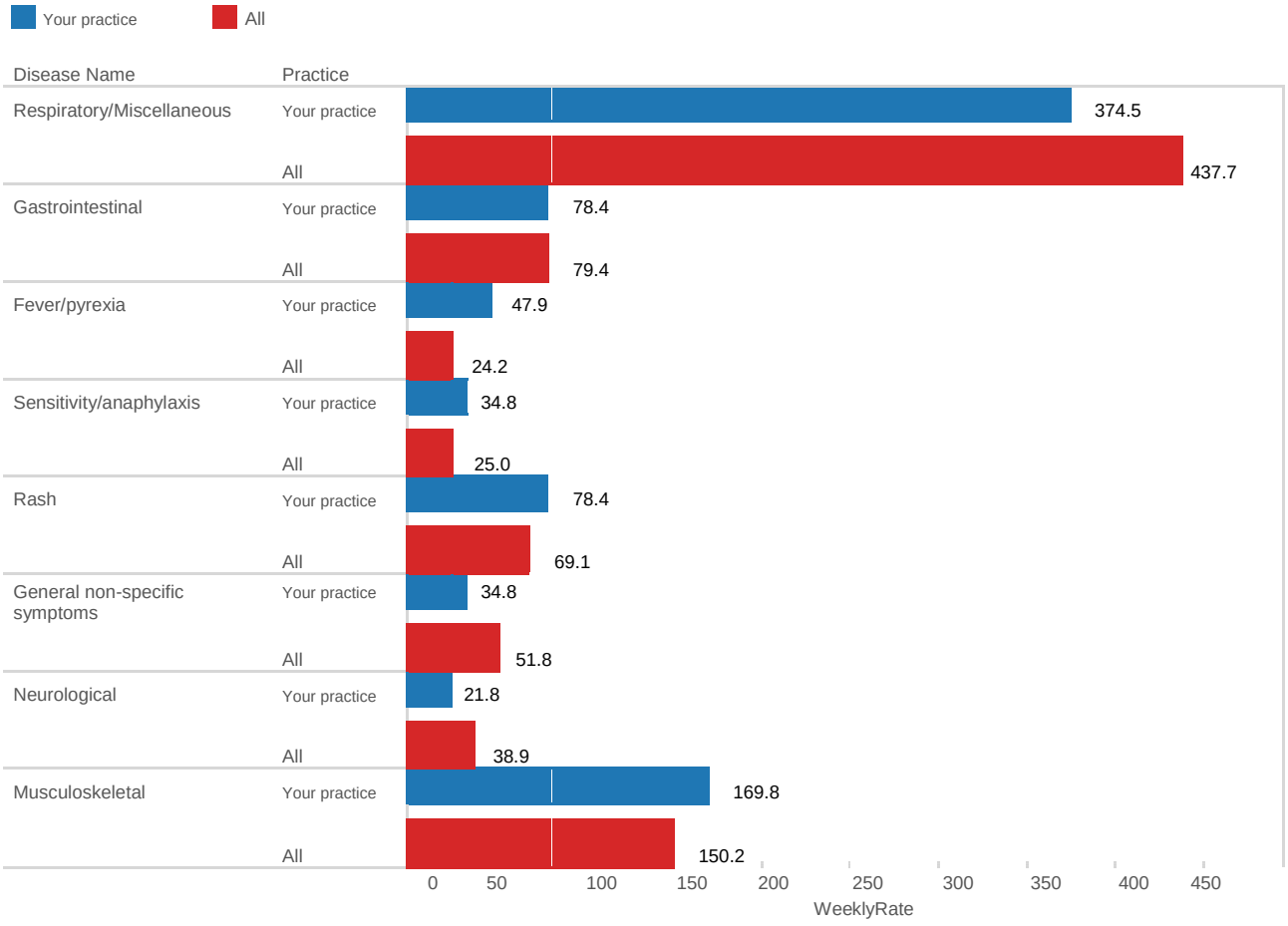
Data from will be used to monitor these possible adverse events, via twice-weekly data extract.

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: ADR card Information letter

Practice logo to be added

INFORMATION SHEET FOR PATIENTS

Enhanced safety surveillance of seasonal flu vaccine

Full 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 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?

We have recruited ten practices representing urban and rural localities across England. 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.

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. Patient identifiable information (name & date of birth) will be converted in your surgery to an anonymous and encrypted format. No patient identifiable information will actually leave the surgery. In addition, patients who have received the vaccine will be asked to complete a reporting card with details of any AEIs.

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 within 7-14 days after vaccination. 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 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.

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:

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

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