BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015469
Article Type:	Protocol
Date Submitted by the Author:	12-Dec-2016
Complete List of Authors:	de Lusignan, Simon; University of Surrey, Department of Clinical and Experimental Medicine Dos Santos, Gaël; GlaxoSmithKline Vaccines Correa, Ana; University of Surrey, Department of Clinical and Experimental Medicine Haguinet, François; GlaxoSmithKline Vaccines Yonova, Ivelina; University of Surrey, Department of Clinical and Experimental Medicine Lair, Florence; GlaxoSmithKline Vaccines Byford, Rachel; University of Surrey, Department of Clinical and Experimental Medicine Ferreira, Filipa; University of Surrey, Department of Clinical and Experimental Medicine Stuttard, Karen; GlaxoSmithKline Vaccines Chan, Tom; University of Surrey, Department of Clinical and Experimental Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Epidemiology, Research methods, Health policy
Keywords:	EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, BIOTECHNOLOGY & BIOINFORMATICS, PREVENTIVE MEDICINE, PRIMARY CARE, Adverse events < THERAPEUTICS

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

Simon de Lusignan
(Principal Investigator)*[1]
Professor of Primary Care and Clinical Informatics
Chair in Health Care Management,
University of Surrey
s.lusignan@surrey.ac.uk
+44 0 1483 684802

Gaël Dos Santos
Epidemiologist, Global Epidemiology[2]
GAEL.X.DOS-SANTOS@GSK.COM

Ana Correa
Primary Care Scientist[1]
Department of Clinical and Experimental Medicine, University of Surrey
a.correa@surrey.ac.uk

François Haguinet
Bio-Statistician, Global Epidemiology[2]
FRANCOIS.F.HAGUINET@GSK.COM

Ivelina Yonova
Practice Liaison Officer[1]
Department of Clinical and Experimental Medicine, University of Surrey
i.yonova@surrey.ac.uk

Florence Lair
Study Delivery Lead[2]
FLORENCE.X.LAIR@GSK.COM

Rachel Byford
Senior Database Developer[1]
Department of Clinical and Experimental Medicine, University of Surrey
r.byford@surrey.ac.uk

Filipa Ferreira
Programme Manager[1]
Department of Clinical and Experimental Medicine, University of Surrey
f.ferreira@surrey.ac.uk

Karen Stuttard
Local Delivery Lead[2]
KAREN.E.STUTTARD@GSK.COM

Tom Chan
Senior Research Fellow[1]
Department of Clinical and Experimental Medicine, University of Surrey
t.chan@surrey.ac.uk

[1]Department of Clinical and Experimental Medicine
University of Surrey
Guildford
Surrey GU2 7XH
UK
W: www.clininf.eu

[2]GSK Vaccines
Rue de l'Institut 89
1330 Rixensart
Belgium

Word count: 3938

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

ABSTRACT

Aim:
To pilot enhanced safety surveillance of seasonal influenza vaccine meeting the European Medicines Agency (EMA) requirement to rapidly detect a significant increase in the frequency or severity of expected reactions. These local, systemic or allergic reaction are termed Adverse Events of Interest (AEI)) by EMA and may indicate risk from the new season's vaccine.

Study design: A prospective passive enhanced safety surveillance combining data collection from adverse drug reaction (ADR) cards with automated collection of pseudonymised routinely collected electronic health record (EHR) data. This study builds on a feasibility study carried out at the start of the 2015/2016 flu season. We will report flu vaccine exposure and any AEIs reported via ADR card or recorded directly into the EHR; from the commencement of influenza vaccination and ends as specified by EMA (30th November 2016).

Setting: 10 volunteer English general practices, primarily using the GSK influenza vaccines. They had selected this vaccine in advance of the study.

Participants: People who receive a GSK brand influenza vaccine. At least 100 vaccinees in each age-group defined in EMA interim guidance: 6months to 5years; 6-12 years; 13-17 years; 18-64 years; and ≥65years old.

Outcome measures:
The primary outcome measure is the rate of AEIs occurring within 7 days post-vaccination.
The secondary outcome measures are: (1) Weekly analysis of influenza vaccination and uptake by different age and by at-risk group. In the UK the Chief Medical Officer (CMO) specifies those at high risk from flu, predominantly older people and those with chronic conditions. (2) As many of the AEIs are common conditions, we will simultaneously report AEIs rates in the unvaccinated population, calling these illness-disease episodes (IDE). (3) Any difference in our practice population profile and representative national data.

We will produce an interim analysis within eight weeks, and an end of study report.

STRENGTHS AND LIMITATIONS

Strengths

- This study sets out the first methods for near real time enhanced passive surveillance of seasonal influenza vaccine using routinely collected data.
- The methods outlined in this study have the potential to be expanded to other brands.
- The practice recruitment is intended to have wide and representative coverage of England.
- The data of the participating patients will be thoroughly protected by means of a pseudonymising algorithm.

Limitations

- As we are still exploring feasibility, this study has not been powered to detect significant statistical differences of adverse event rates across brands.
- We are continuing to explore the feasibility of using rates of adverse events in non-vaccinated patients to establish a baseline for comparison.

INTRODUCTION

EMA guidance

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.

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

- *Enhanced Active surveillance (post authorisation safety studies (PASS)):* Active follow-up

of a cohort of children and adults for 7 days after immunisation for reactogenicity endpoints/adverse events.

- *Enhanced Passive Surveillance:* Rapidly estimate vaccine usage and facilitate adverse drug reaction (ADR) reporting, in order to determine reporting rate as a surrogate of incidence of the adverse events of interest (AEIs).
- *Data mining* or other use of electronic health record/ computerized medical record.

The present collaborative pilot study between MAH GlaxoSmithKline Biologicals (GSK) and the Clinical Informatics and Health Outcomes Research Group at the University of Surrey builds on the lessons learned from the pilot study (EPI-FLU-045 VS UK) implemented during the 2014/2015 influenza season and aims to address the EMA commitment for enhanced safety surveillance of seasonal vaccines in Europe. We will begin data collection on September 1st, 2016, and the analysis will be completed on March 31st, 2017.

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. The primary purpose of the 2016/17 pilot study is to improve the combination of an ADR card-based system and the use of routine data to collect adverse events following vaccination with seasonal influenza vaccines.

The RCGP RSC network

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 representative coverage of 1.5%-2% of the English population[iii]. The RCGP RSC has been described as the gold standard sentinel network.

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 vaccination in England

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. In the UK, the 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.
- People who are in receipt of a carer's allowance, or those who are the main carer of an older or disabled person.
- Household contacts of immunocompromised individuals.

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-wide programme of enhanced safety surveillance for seasonal influenza vaccines.

RESEARCH METHODS

This published protocol is a summary of the full protocol, submitted for ethical approval, the long version is available as a supplementary file.

Objectives and endpoints

Primary objective:

- 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 electronic health record (HER) 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.

Primary endpoints:

- Occurrence and onset dates of AEIs 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.)

Study Design

Study setting and population

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.

Invitation letters will be sent to GP practices ordering mainly GSK's Fluarix Tetra vaccine for the 2016/17 season, and evenly representative of geographical locations and systems. Practices will be reimbursed for their involvement in this study, according to the National Institute of Health Research (NIHR) guidelines for industry sponsored studies[vi].

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. In last year's study the card-based ADR reporting system, used the Yellow Card developed by the UK Medicines and

Healthcare products Regulation Agency (MHRA). We have developed a more specific ADR card, for use in this study, which will be distributed to practices.

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[vii]. 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.

Inclusion criteria

All patients receiving a seasonal influenza vaccine between 01/09/2016 and 30/11/2016 in one of the 10 volunteer practices are eligible for inclusion in the analysis. The main inclusion criteria for practices is that practices state their principal vaccine supplier will be GSK.

Exclusion criteria

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.

Sample size calculation

The average practice size in England and Wales is 7,034[viii], 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)[ix].

The minimum needed target population to be medically followed by the GPs is estimated at 50,000 subjects (approximately 5,000 per practice). We expect to enrol at least 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. Similarities, or homogeneity, between subjects in clusters reduces the variability of their responses, compared with that expected from a random sample. The cluster effect has not been 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[x]. 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 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%
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 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.

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%

Data sources

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 would also be coded into the EHR and uploaded weekly (Figure 1).

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.

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. In addition to the adverse event data, we will extract demographics, vaccination status, and relevant comorbidities.

We will only extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the EHR system[xi]. The overwhelming majority of the large volume of research that has come out of UK primary care is based on coded data[xii]. The richness of primary care data are such that we anticipate being able to detect important AEIs[xiii]. 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).

Data analyses

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. All statistical analysis will be conducted using R Studio.

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

ETHICS AND DISSEMINATION

Ethical review

'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 sought 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. Ethical approval was granted by the Proportionate Review Sub-committee of the North East - Newcastle & North Tyneside 2 REC on 05/08/2016 (REC reference: 16/NE/0271). Section 251 application was not deemed necessary by the Health Research Authority (HRA) and the study received approval on 01/09/2016 (IRAS ID: 211560).

Data extraction and data management

The method and governance procedure has been developed by the University of Surrey, using an approved provider, Apollo Medical Software Solutions Ltd. 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.

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. Data are pseudonymised as near to source as possible. 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.

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[xiv]. 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[xv] on the recommendation of the European Data Protection Supervisor (EDPS)[xvi].

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[xvii]. 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 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

[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

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. 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.

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. 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. An SAE is defined as any untoward medical occurrence that:

- Results in death,
- Life-threatening (where the participant is at risk of death),
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity (where there is a substantial disruption of a person's ability to conduct normal life functions)..
- 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.

Dissemination and Public Register Disclosure

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[xviii xix]. 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.

AUTHOR CONTRIBUTIONS

SdeL
Simon de Lusignan developed the study design, and is the main writer of the protocol.

GDS
Gaël Dos Santos helped with the study design development, and contributed to the writing.

AC
Ana Correa contributed to the methods and analysis section of this protocol.

FH
François Haguinet contributed to the sample size and analysis section of this protocol.

IY
Ivelina Yonova helped develop the practice recruitment methods, and contributed to writing the protocol.

FL
Florence Lair reviewed the protocol, and contributed to the writing.

RB
Rachel Byford helped develop the data flow structure, and contributed to writing the protocol.

FF
Filipa Ferreira extensively reviewed the protocol, and contributed to the writing.

KS
Karen Stuttard reviewed the protocol, and contributed to the writing.

TC
Tom Chan contributed to the ethical implications and background section of this protocol.

FUNDING STATEMENT

This work was supported by GlaxoSmithKline Vaccines, study number 202056.

COMPETING INTERESTS STATEMENT

SdeL and AC participate in a European consortium called IMOVE+ funded by Horizon 2020 to monitor seasonal influenza vaccine effectiveness across Europe.

DATA SHARING STATEMENT

Once the study is completed, we will publish all relevant aggregated results. Unpublished aggregated results could be made available, upon request, by the authors.

REFERENCES

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

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

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

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

[v] Public Health England, Department of Health, NHS England. Flu plan Winter 2015/16. 2015. PHE publications gateway number: 2014833. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/418038/Flu_Plan_Winter_2015_to_2016.pdf

[vi] National Institute for Health Research Clinical Research Network. Guide to the NIHR CRN Industry Costing Template: Costing Industry Sponsored Studies (version: April 2014). URL: https://www.crn.nihr.ac.uk/wp-Content/uploads/Industry/GUIDE%20to%20Industry%20Costing%20Template-APRIL2014.pdf

[vii] David A. Asch M.Kathryn Jedrziewski, Nicholas A. Christakis, Response rates to mail surveys published in medical journals Journal of Clinical Epidemiology Volume 50, Issue 10, October 1997, Pages 1129–1136

[viii] Workforce and Facilities Team, Health and Social Care Information Centre. General and Personal Medical Services: England 2003-13. 25 March 2014. URL: http://www.hscic.gov.uk/catalogue/PUB13849/nhs-staf-2003-2013-gene-prac-rep.pdf

[ix] Public Health England. Vaccine uptake guidance and the latest coverage data. https://www.gov.uk/government/collections/vaccine-uptake#seasonal-flu-vaccine-uptake

[x] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934; 26:404-413

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

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

[xiii] de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. Fam Pract. 2006;23(2):253-63.

[xiv] National Health Service (NHS). Pseudonymisation and anonymisation of data policy (last reviewed: 27 April 2015), accessed 09/06/2016. URL: http://www.google.fr/url?url=http://www.nhsbsa.nhs.uk/Documents/NHSBSACorporatePoliciesandProcedures/Pseudonymisation_and_Anonymisation_of_Data_Policy.doc&rct=j&frm=1&q=&esrc=s&sa=U&ved=0ahUKEwjZrqPvz4fNAhWEB8AKHU0IBz4QFggUMAA&usg=AFQjCNF-JPX5zueirRlBylzoF-WAEDNkmg

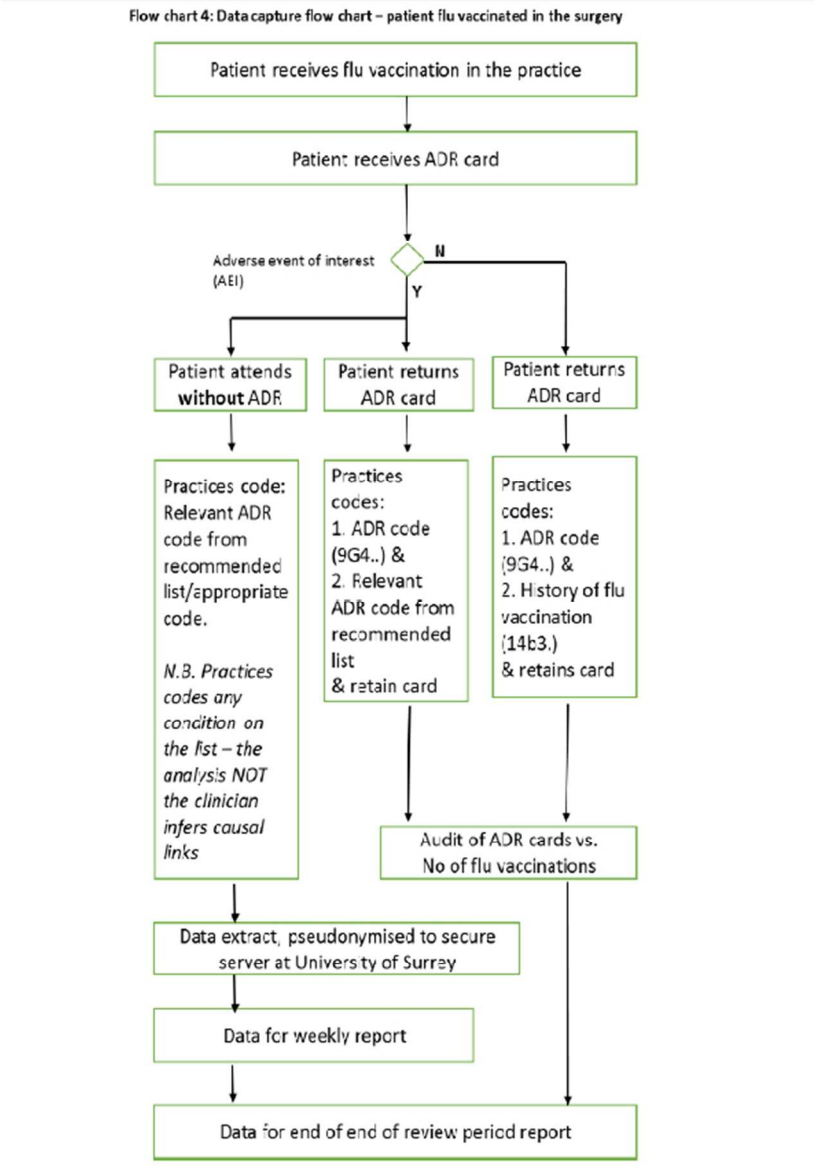
[xv] European Union. Justice. Reform of EU data protection rules. URL: http://ec.europa.eu/justice/data-protection/reform/index_en.htm

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

[xvii] Health and Social Care Information Centre (HSCIC). Information Governance Toolkit (IGT). URL: https://www.igt.hscic.gov.uk/

[xviii] MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies (Sept 2011) http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/Policy/index.htm

[xix] Economic Co-operation and Development (OECD). "Promoting Access to Public Research Data for Scientific, Economic and Social Development" 2007 http://www.oecd.org/sti/sci-tech/38500813.pdf



156x231mm (96 x 96 DPI)

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015469.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Mar-2017
Complete List of Authors:	de Lusignan, Simon; University of Surrey, Department of Clinical and Experimental Medicine Dos Santos, Gaël; GlaxoSmithKline Vaccines Correa, Ana; University of Surrey, Department of Clinical and Experimental Medicine Haguinet, François; GlaxoSmithKline Vaccines Yonova, Ivelina; University of Surrey, Department of Clinical and Experimental Medicine Lair, Florence; GlaxoSmithKline Vaccines Byford, Rachel; University of Surrey, Department of Clinical and Experimental Medicine Ferreira, Filipa; University of Surrey, Department of Clinical and Experimental Medicine Stuttard, Karen; GlaxoSmithKline Vaccines Chan, Tom; University of Surrey, Department of Clinical and Experimental Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Epidemiology, Research methods, Health policy
Keywords:	EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, BIOTECHNOLOGY & BIOINFORMATICS, PREVENTIVE MEDICINE, PRIMARY CARE, Adverse events < THERAPEUTICS

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

Simon de Lusignan
(Principal Investigator)*[1]
Professor of Primary Care and Clinical Informatics
Chair in Health Care Management,
University of Surrey
s.lusignan@surrey.ac.uk
+44 0 1483 684802

Gaël Dos Santos
Epidemiologist, Global Epidemiology[2]
gael.x.dos-santos@gsk.com

Ana Correa
Primary Care Scientist[1]
Department of Clinical and Experimental Medicine, University of Surrey
a.correa@surrey.ac.uk

François Haguinet
Bio-Statistician, Global Epidemiology[2]
francois.f.haguinet@gsk.com

Ivelina Yonova
Practice Liaison Officer[1]
Department of Clinical and Experimental Medicine, University of Surrey
i.yonova@surrey.ac.uk

Florence Lair
Study Delivery Lead[2]
florence.x.lair@gsk.com

Rachel Byford
Senior Database Developer[1]
Department of Clinical and Experimental Medicine, University of Surrey
r.byford@surrey.ac.uk

Filipa Ferreira
Programme Manager[1]
Department of Clinical and Experimental Medicine, University of Surrey
f.ferreira@surrey.ac.uk

Karen Stuttard
Local Delivery Lead[2]
karen.e.stuttard@gsk.com

Tom Chan
Senior Research Fellow[1]
Department of Clinical and Experimental Medicine, University of Surrey
t.chan@surrey.ac.uk

[1]Department of Clinical and Experimental Medicine
University of Surrey
Guildford
Surrey GU2 7XH
UK
W: www.clininf.eu

[2]GSK Vaccines
Rue de l'Institut 89
1330 Rixensart
Belgium

Word count: 4106

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

ABSTRACT

Aim:
To pilot enhanced safety surveillance of seasonal influenza vaccine meeting the European Medicines Agency (EMA) requirement to rapidly detect a significant increase in the frequency or severity of expected reactions. These local, systemic or allergic reactions are termed Adverse Events of Interest (AEI) by EMA and may indicate risk from the new season's vaccine.

Study design: A prospective passive enhanced safety surveillance combining data collection from adverse drug reaction (ADR) cards with automated collection of pseudonymised routinely collected electronic health record (EHR) data. This study builds on a feasibility study carried out at the start of the 2015/2016 flu season. We will report flu vaccine exposure and any AEIs reported via ADR card or recorded directly into the EHR, from the commencement of influenza vaccination and ends as specified by EMA (30th November, 2016).

Setting: Ten volunteer English general practices, primarily using the GSK influenza vaccines. They had selected this vaccine in advance of the study.

Participants: People who receive a GSK brand influenza vaccine. At least 100 vaccinees in each age-group defined in EMA interim guidance: 6months to 5years; 6-12 years; 13-17 years; 18-65 years; and >65years old.

Outcome measures:
The primary outcome measure is the rate of AEIs occurring within 7 days post-vaccination, using passive surveillance of GP electronic health record (HER) 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.

We will produce an interim analysis within 8 weeks, and an end of study report.

STRENGTHS AND LIMITATIONS

Strengths

- This study sets out the first methods for near real time enhanced passive surveillance of seasonal influenza vaccine using routinely collected data.
- Customised adverse drug reaction cards may enhance reporting over standard passive surveillance, which may result in under-reporting of less severe symptoms not requiring medical attendance.
- The methods outlined in this study have the potential to be expanded to other brands.
- The practice recruitment is intended to have wide and representative coverage of England.
- The data of the participating patients will be thoroughly protected by means of a pseudonymising algorithm that allowed removal of strong identifiers.

Limitations

- This feasibility study has not been powered or designed to detect rare events or detect significant statistical differences of adverse event rates across brands.
- We are also exploring the feasibility of using rates of adverse events in non-vaccinated patients as a basis for comparison.

INTRODUCTION

EMA guidance

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 [1]. 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.

Since 2015, European regulatory requirements to evaluate the safety and immunogenicity of seasonal influenza vaccines in small scale clinical trials were withdrawn[2]. 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 EMA Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU suggested that there would be 3 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/ computerised medical record.

We opted for enhanced passive surveillance because, whilst highly computerised medical records system maximise the likelihood of reliably capturing the AEIs, we felt this needed enhancement through the use of customised ADR cards. These cards were pre-printed with the categories of possible adverse events to facilitate the reporting and the subsequent coding of events. They also contained a specific tick box when no AEIs where experienced leading to a reasonably acceptable return rate.

We expect that, by enhancing surveillance with a customised card and encouraging patients to directly report their symptoms, we will more reliably detect a greater number of events. The

proposed approach was designed to meet the EMA enhanced passive surveillance definition.

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 season and aims to address the EMA commitment for enhanced safety surveillance of seasonal vaccines in Europe. We will begin data collection on September 1st, 2016, and the analysis will be completed on March 31st, 2017.

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. The primary purpose of the 2016/17 pilot study is to improve the combination of an ADR card-based system and the use of routine data to collect adverse events following vaccination with seasonal influenza vaccines.

The RCGP RSC network

The Clinical Informatics Research Group, in the Department of Clinical and Experimental Medicine (DCEM) at the University of Surrey is the 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 representative coverage of 1.5%-2% of the English population[3]. The RCGP RSC has been described as the gold standard sentinel network.

The most important work of the RCGP RSC network is its influenza surveillance; many practices have been involved in this work for decades[4]. 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 vaccination in England

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. In the UK, the 2015/2016 influenza plan recommended the following groups to be vaccinated[5]:

- 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 medical condition:

- 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, stages 3-5
- chronic liver disease
- chronic neurological disease, such as Parkinson's disease or motor neurone disease, or a learning disability
- diabetes
- splenic dysfunction
- immunocompromised 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 2, 3, and 4 years (but not 5 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.
- People who are in receipt of a carer's allowance, or those who are the main carer of an older or disabled person.
- Household contacts of immunocompromised individuals.

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-wide programme of enhanced safety surveillance for seasonal influenza vaccines.

RESEARCH METHODS

This published protocol is a summary of the full protocol, submitted for ethical approval, the long version is available as a supplementary file.

Objectives and endpoints

Primary objective:

- 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 electronic health record (HER) 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.

Primary endpoints:

- Occurrence and onset dates of AEIs 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 17 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.)

Study Design

Study setting and population

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. The final data collection will occur on 10/01/2017 to allow for any delays in records of up to 6 weeks.

Invitation letters will be sent to GP practices ordering mainly GSK's Fluarix Tetra vaccine for the 2016/17 season, and evenly representative of geographical locations and systems. Practices will be reimbursed for their involvement in this study, according to the National Institute of Health Research (NIHR) guidelines for industry sponsored studies[6].

For this pilot project, routinely collected primary care data from up to 10 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. In last year's study the card-based ADR reporting system, used the Yellow Card developed by the UK Medicines and Healthcare products Regulation Agency (MHRA). We have developed a more specific ADR card for use in this study, which will be distributed to practices. The new ADR card is pre-printed with the categories of likely AEIs the EMA require surveillance for, to facilitate the recording of AEIs and to make their coding into the GP EHR system easier. There was also a tick box for no AEI.

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[7]. 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.

Inclusion criteria

All patients receiving a seasonal influenza vaccine between 01/09/2016 and 30/11/2016 in 1 of the 10 volunteer practices are eligible for inclusion in the analysis. The main inclusion criteria for practices is that they state their principal vaccine supplier will be GSK.

Exclusion criteria

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.

Sample size calculation

The average practice size in England and Wales is 7,034[8], and 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)[9].

The minimum needed target population to be medically followed by the GPs is estimated at 50,000 subjects (approximately 5,000 per practice). We expect to enrol at least 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. Similarities, or homogeneity, between subjects in clusters reduces the variability of their responses, compared with that expected from a random sample.

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%
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%

The cluster effect has not been 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 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[10]. 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.

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

Data sources

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 would also be coded into the EHR and uploaded weekly (Figure 1).

1. General Practice EHR data recorded by the practice team. Weekly data about vaccine exposure, and any subsequent AEIs will be uploaded (anonymised) to the 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.

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. In addition to the adverse event data, we will extract demographics, vaccination status, and relevant comorbidities.

We will only extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the EHR system[11]. The overwhelming majority of the large volume of research that has come out of UK primary care is based on coded data[12]. The richness of primary care data are such that we anticipate being able to detect important AEIs[13]. 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).

Data analyses

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 considerable 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. All statistical analysis will be conducted using

R Studio.

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 17 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

ETHICS AND DISSEMINATION

Ethical review

'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 sought 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. Ethical approval was granted by the Proportionate Review Sub-committee of the North East - Newcastle & North Tyneside 2 REC on 05/08/2016 (REC reference: 16/NE/0271). Section 251 application was not deemed necessary by the Health Research Authority (HRA) and the study received approval on 01/09/2016 (IRAS ID: 211560).

Data extraction and data management

The method and governance procedure has been developed by the University of Surrey, using an approved provider, Apollo Medical Software Solutions Ltd. 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.

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

[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.

key pairs unique to each project. Data are pseudonymised as near to source as possible. 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.

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[14]. 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[15] on the recommendation of the European Data Protection Supervisor (EDPS)[16].

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[17]. 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 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. 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 blinded 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.

Safety reporting, including routine pharmacovigilance

[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.

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. 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. An SAE is defined as any untoward medical occurrence that:

- Results in death,
- Life-threatening (where the participant is at risk of death),
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity (where there is a substantial disruption of a person's ability to conduct normal life functions)..
- 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.

Dissemination and Public Register Disclosure

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[18 19]. 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.

AUTHOR CONTRIBUTIONS

SdeL

Simon de Lusignan developed the study design, and is the main writer of the protocol.

GDS

Gaël Dos Santos helped with the study design development, and contributed to the writing.

AC

Ana Correa contributed to the methods and analysis section of this protocol.

FH

François Haguinet contributed to the sample size and analysis section of this protocol.

IY

Ivelina Yonova helped develop the practice recruitment methods, and contributed to writing the protocol.

FL

Florence Lair reviewed the protocol, and contributed to the writing.

RB

Rachel Byford helped develop the data flow structure, and contributed to writing the protocol.

FF

Filipa Ferreira extensively reviewed the protocol, and contributed to the writing.

KS

Karen Stuttard reviewed the protocol, and contributed to the writing.

TC

Tom Chan contributed to the ethical implications and background section of this protocol.

FUNDING STATEMENT

GlaxoSmithKline Biologicals SA was the funding source and was involved in study design and interpretation, study number 202056.

COMPETING INTERESTS STATEMENT

SdeL and AC participate in a European consortium called IMOVE+ funded by Horizon 2020 to monitor seasonal influenza vaccine effectiveness across Europe.

GDS reports he was employed by Business & Decision Life Sciences on behalf of GSK Vaccines at the time of the study and is now employed by the GSK group of companies. NM and FH are employees of the GSK group of companies. GDS and NM hold shares in the GSK group of companies as part of their employee remuneration.

DATA SHARING STATEMENT

Once the study is completed, we will publish all relevant aggregated results. Unpublished aggregated results could be made available, upon request, by the authors.

REFERENCES

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

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

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

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

[5] Public Health England, Department of Health, NHS England. Flu plan Winter 2015/16. 2015. PHE publications gateway number: 2014833. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/418038/Flu_Plan_Winter_2015_to_2016.pdf

[6] National Institute for Health Research Clinical Research Network. Guide to the NIHR CRN Industry Costing Template: Costing Industry Sponsored Studies (version: April 2014). URL: https://www.crn.nihr.ac.uk/wp-Content/uploads/Industry/GUIDE%20to%20Industry%20Costing%20Template-APRIL2014.pdf

[7] David A. Asch M.Kathryn Jedrziewski, Nicholas A. Christakis, Response rates to mail surveys published in medical journals Journal of Clinical Epidemiology Volume 50, Issue 10, October 1997, Pages 1129–1136

[8] Workforce and Facilities Team, Health and Social Care Information Centre. General and Personal Medical Services: England 2003-13. 25 March 2014. URL: http://www.hscic.gov.uk/catalogue/PUB13849/nhs-staf-2003-2013-gene-prac-rep.pdf

[9] Public Health England. Vaccine uptake guidance and the latest coverage data. https://www.gov.uk/government/collections/vaccine-uptake#seasonal-flu-vaccine-uptake

[10] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934; 26:404-413

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

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

[13] de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. Fam Pract. 2006;23(2):253-63.

[14] National Health Service (NHS). Pseudonymisation and anonymisation of data policy (last reviewed: 27 April 2015), accessed 09/06/2016. URL: http://www.google.fr/url?url=http://www.nhsbsa.nhs.uk/Documents/NHSBSACorporatePoliciesandProcedures/Pseudonymisation_and_Anonymisation_of_Data_Policy.doc&rct=j&frm=1&q=&esrc=s&sa=U&ved=0ahUKEwjZrqPvz4fNAhWEB8AKHU0IBz4QFggUMAA&usg=AFQjCNF-JPX5zueirRlBylzoF-WAEDNkmg

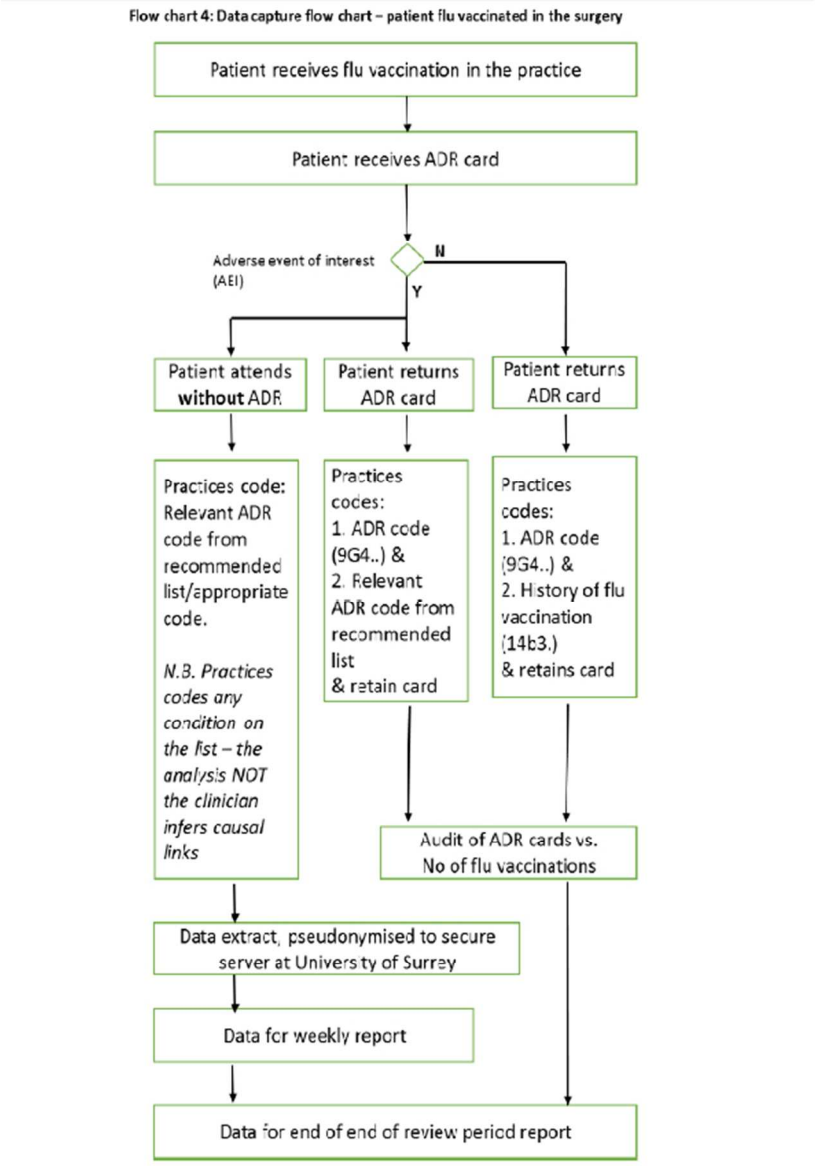
[15] European Union. Justice. Reform of EU data protection rules. URL: http://ec.europa.eu/justice/data-protection/reform/index_en.htm

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

[17] Health and Social Care Information Centre (HSCIC). Information Governance Toolkit (IGT). URL: https://www.igt.hscic.gov.uk/

[18] MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies (Sept 2011) http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/Policy/index.htm

[19] Economic Co-operation and Development (OECD). "Promoting Access to Public Research Data for Scientific, Economic and Social Development" 2007 http://www.oecd.org/sti/sci-tech/38500813.pdf



156x231mm (96 x 96 DPI)

BMJ Open

Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Protocol of a pilot study in England

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015469.R2
Article Type:	Protocol
Date Submitted by the Author:	24-Mar-2017
Complete List of Authors:	de Lusignan, Simon; University of Surrey, Department of Clinical and Experimental Medicine Dos Santos, Gaël; GlaxoSmithKline Vaccines Correa, Ana; University of Surrey, Department of Clinical and Experimental Medicine Haguinet, François; GlaxoSmithKline Vaccines Yonova, Ivelina; University of Surrey, Department of Clinical and Experimental Medicine Lair, Florence; GlaxoSmithKline Vaccines Byford, Rachel; University of Surrey, Department of Clinical and Experimental Medicine Ferreira, Filipa; University of Surrey, Department of Clinical and Experimental Medicine Stuttard, Karen; GlaxoSmithKline Vaccines Chan, Tom; University of Surrey, Department of Clinical and Experimental Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Epidemiology, Research methods, Health policy
Keywords:	EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, BIOTECHNOLOGY & BIOINFORMATICS, PREVENTIVE MEDICINE, PRIMARY CARE, Adverse events < THERAPEUTICS

Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Protocol of a pilot study in England

Simon de Lusignan
(Principal Investigator)*[1]
Professor of Primary Care and Clinical Informatics
Chair in Health Care Management,
University of Surrey
s.lusignan@surrey.ac.uk
+44 0 1483 684802

Gaël Dos Santos
Epidemiologist, Global Epidemiology[2]
gael.x.dos-santos@gsk.com

Ana Correa
Primary Care Scientist[1]
Department of Clinical and Experimental Medicine, University of Surrey
a.correa@surrey.ac.uk

François Haguinet
Bio-Statistician, Global Epidemiology[2]
francois.f.haguinet@gsk.com

Ivelina Yonova
Practice Liaison Officer[1]
Department of Clinical and Experimental Medicine, University of Surrey
i.yonova@surrey.ac.uk

Florence Lair
Study Delivery Lead[2]
florence.x.lair@gsk.com

Rachel Byford
Senior Database Developer[1]
Department of Clinical and Experimental Medicine, University of Surrey
r.byford@surrey.ac.uk

Filipa Ferreira
Programme Manager[1]
Department of Clinical and Experimental Medicine, University of Surrey
f.ferreira@surrey.ac.uk

Karen Stuttard
Local Delivery Lead[2]
karen.e.stuttard@gsk.com

Tom Chan
Senior Research Fellow[1]
Department of Clinical and Experimental Medicine, University of Surrey
t.chan@surrey.ac.uk

[1]Department of Clinical and Experimental Medicine
University of Surrey
Guildford
Surrey GU2 7XH
UK
W: www.clininf.eu

[2]GSK Vaccines
Rue de l'Institut 89
1330 Rixensart
Belgium

Word count: 4106

Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Protocol of a pilot study in England

ABSTRACT

Aim:
To pilot enhanced safety surveillance of seasonal influenza vaccine meeting the European Medicines Agency (EMA) requirement to rapidly detect a significant increase in the frequency or severity of adverse events of interest (AEIs), which may indicate risk from the new season's vaccine.

Study design: A prospective passive enhanced safety surveillance combining data collection from adverse drug reaction (ADR) cards with automated collection of pseudonymised routinely collected electronic health record (EHR) data. This study builds on a feasibility study carried out at the start of the 2015/2016 flu season. We will report flu vaccine exposure and any AEIs reported via ADR card or recorded directly into the EHR, from the commencement of influenza vaccination and ends as specified by EMA (30th November, 2016).

Setting: Ten volunteer English general practices, primarily using the GSK influenza vaccines. They had selected this vaccine in advance of the study.

Participants: People who receive a seasonal influenza vaccine, in each age-group defined in EMA interim guidance: 6months to 5years; 6-12 years; 13-17 years; 18-65 years; and >65years old.

Outcome measures:
The primary outcome measure is the rate of AEIs occurring within 7 days post-vaccination, using passive surveillance of GP electronic health record (EHR) systems enhanced by a card-based ADR reporting system. Extracted data will be presented overall, by brand (Fluarix Tetra vs. others), by age strata, and risk groups. The secondary outcome measure is the vaccine uptake among the subjects registered in the enrolled GP practices.

Ethics and dissemination:
Ethical approval was granted by the Proportionate Review Sub-committee of the North East - Newcastle & North Tyneside 2 on 05/08/2016. The study received approval from the Health Research Authority on 01/09/2016. We will produce an interim analysis within 8 weeks, and an end of study report, which will submitted to peer-reviewed journals.

STRENGTHS AND LIMITATIONS

Strengths

- This study sets out the first methods for near real time enhanced passive surveillance of seasonal influenza vaccine using routinely collected data.
- Customised adverse drug reaction cards may enhance reporting over standard passive surveillance, which may result in under-reporting of less severe symptoms not requiring medical attendance.
- The methods outlined in this study have the potential to be expanded to other brands.
- The practice recruitment is intended to have wide and representative coverage of England.
- The data of the participating patients will be thoroughly protected by means of a pseudonymising algorithm that allowed removal of strong identifiers.

Limitations

- This feasibility study has not been powered or designed to detect rare events or detect significant statistical differences of adverse event rates across brands.
- We are also exploring the feasibility of using rates of adverse events in non-vaccinated patients as a basis for comparison.

INTRODUCTION

EMA guidance

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[1]. 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.

Since 2015, European regulatory requirements to evaluate the safety and immunogenicity of seasonal influenza vaccines in small scale clinical trials were withdrawn[2]. 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 EMA Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU suggested that there would be 3 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/ computerised medical record.

We opted for enhanced passive surveillance because, whilst highly computerised medical records system maximise the likelihood of reliably capturing the AEIs, we felt this needed enhancement through the use of customised ADR cards. These cards were pre-printed with the categories of possible adverse events to facilitate the reporting and the subsequent coding of events. They also contained a specific tick box when no AEIs where experienced leading to a reasonably acceptable return rate.

We expect that, by enhancing surveillance with a customised card and encouraging patients to directly report their symptoms, we will more reliably detect a greater number of events. The

proposed approach was designed to meet the EMA enhanced passive surveillance definition.

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 season and aims to address the EMA commitment for enhanced safety surveillance of seasonal vaccines in Europe. We will begin data collection on September 1st, 2016, and the analysis will be completed on March 31st, 2017.

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. The primary purpose of the 2016/17 pilot study is to improve the combination of an ADR card-based system and the use of routine data to collect adverse events following vaccination with seasonal influenza vaccines.

The RCGP RSC network

The Clinical Informatics Research Group, in the Department of Clinical and Experimental Medicine (DCEM) at the University of Surrey is the 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 representative coverage of 1.5%-2% of the English population[3]. The RCGP RSC has been described as the gold standard sentinel network.

The most important work of the RCGP RSC network is its influenza surveillance; many practices have been involved in this work for decades[4]. 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 vaccination in England

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. In the UK, the 2015/2016 influenza plan recommended the following groups to be vaccinated[5]:

- 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 medical condition:

- 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, stages 3-5
- chronic liver disease
- chronic neurological disease, such as Parkinson's disease or motor neurone disease, or a learning disability
- diabetes
- splenic dysfunction
- immunocompromised 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 2, 3, and 4 years (but not 5 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.
- People who are in receipt of a carer's allowance, or those who are the main carer of an older or disabled person.
- Household contacts of immunocompromised individuals.

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-wide programme of enhanced safety surveillance for seasonal influenza vaccines.

RESEARCH METHODS

This published protocol is a summary of the full protocol, submitted for ethical approval, the long version is available as a supplementary file.

Objectives and endpoints

Primary objective:

- 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 electronic health record (EHR) 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 objective:

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

Primary endpoints:

- Occurrence and onset dates of AEIs 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 17 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:

- 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

Study Design

Study setting and population

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. The final data collection will occur on 10/01/2017 to allow for any delays in records of up to 6 weeks.

Invitation letters will be sent to GP practices ordering mainly GSK's Fluarix Tetra vaccine for the 2016/17 season, and evenly representative of geographical locations and systems. Practices will be reimbursed for their involvement in this study, according to the National Institute of Health Research (NIHR) guidelines for industry sponsored studies[6].

For this pilot project, routinely collected primary care data from up to 10 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. In last year's study the card-based ADR reporting system, used the Yellow Card developed by the UK Medicines and Healthcare products Regulation Agency (MHRA). We have developed a more specific ADR card for use in this study, which will be distributed to practices. The new ADR card is pre-printed with the categories of likely AEIs the EMA require surveillance for, to facilitate the recording of AEIs and to make their coding into the GP EHR system easier. There was also a tick box for no AEI.

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[7]. 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.

Inclusion criteria

All patients receiving a seasonal influenza vaccine between 01/09/2016 and 30/11/2016 in 1 of the 10 volunteer practices are eligible for inclusion in the analysis. The main inclusion criteria for practices is that they state their principal vaccine supplier will be GSK.

Exclusion criteria

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.

Sample size calculation

The average practice size in England and Wales is 7,034[8], and 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)[9].

The minimum needed target population to be medically followed by the GPs is estimated at 50,000 subjects (approximately 5,000 per practice). We expect to enrol at least 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. Similarities, or homogeneity, between subjects in clusters reduces the variability of their responses, compared with that expected from a random sample.

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%
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%

The cluster effect has not been 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 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[10]. 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.

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

Data sources

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 would also be coded into the EHR and uploaded weekly (Figure 1).

Figure 1 – Data capture flowchart

1. General Practice EHR data recorded by the practice team. Weekly data about vaccine exposure, and any subsequent AEIs will be uploaded (anonymised) to the 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.

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. In addition to the adverse event data, we will extract demographics, vaccination status, and relevant comorbidities.

We will only extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the EHR system[11]. The overwhelming majority of the large volume of research that has come out of UK primary care is based on coded data[12]. The richness of primary care data are such that we anticipate being able to detect important AEIs[13]. 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).

Data analyses

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 considerable 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. All statistical analysis will be conducted using R Studio.

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 17 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

ETHICS AND DISSEMINATION

Ethical review

'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 sought 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. Ethical approval was granted by the Proportionate Review Sub-committee of the North East - Newcastle & North Tyneside 2 REC on 05/08/2016 (REC reference: 16/NE/0271). Section 251 application was not deemed necessary by the Health Research Authority (HRA) and the study received approval on 01/09/2016 (IRAS ID: 211560).

Data extraction and data management

The method and governance procedure has been developed by the University of Surrey, using an approved provider, Apollo Medical Software Solutions Ltd. 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.

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. Data are pseudonymised as near to source as possible. 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.

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[14]. 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[15] on the recommendation of the European Data Protection Supervisor (EDPS)[16].

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[17]. 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 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. 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 blinded 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

[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.

condition in line with best practice.

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. 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. An SAE is defined as any untoward medical occurrence that:

- Results in death,
- Life-threatening (where the participant is at risk of death),
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity (where there is a substantial disruption of a person's ability to conduct normal life functions).
- 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.

Dissemination and Public Register Disclosure

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[18 19]. 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.

AUTHOR CONTRIBUTIONS

SdeL

Simon de Lusignan developed the study design, and is the main writer of the protocol.

GDS

Gaël Dos Santos helped with the study design development, and contributed to the writing.

AC

Ana Correa contributed to the methods and analysis section of this protocol.

FH

François Haguinet contributed to the sample size and analysis section of this protocol.

IY

Ivelina Yonova helped develop the practice recruitment methods, and contributed to writing the protocol.

FL

Florence Lair reviewed the protocol, and contributed to the writing.

RB

Rachel Byford helped develop the data flow structure, and contributed to writing the protocol.

FF

Filipa Ferreira extensively reviewed the protocol, and contributed to the writing.

KS

Karen Stuttard reviewed the protocol, and contributed to the writing.

TC

Tom Chan contributed to the ethical implications and background section of this protocol.

FUNDING STATEMENT

GlaxoSmithKline Biologicals SA was the funding source and was involved in study design and interpretation, study number 202056.

COMPETING INTERESTS STATEMENT

SdeL and AC participate in a European consortium called IMOVE+ funded by Horizon 2020 to monitor seasonal influenza vaccine effectiveness across Europe.

GDS reports he was employed by Business & Decision Life Sciences on behalf of GSK Vaccines at the time of the study and is now employed by the GSK group of companies. NM and FH are employees of the GSK group of companies. GDS and NM hold shares in the GSK group of companies as part of their employee remuneration.

DATA SHARING STATEMENT

Once the study is completed, we will publish all relevant aggregated results. Unpublished

aggregated results could be made available, upon request, by the authors.

REFERENCES

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

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

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

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

[5] Public Health England, Department of Health, NHS England. Flu plan Winter 2015/16. 2015. PHE publications gateway number: 2014833. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/418038/Flu_Plan_Winter_2015_to_2016.pdf

[6] National Institute for Health Research Clinical Research Network. Guide to the NIHR CRN Industry Costing Template: Costing Industry Sponsored Studies (version: April 2014). URL: https://www.crn.nihr.ac.uk/wp-Content/uploads/Industry/GUIDE%20to%20Industry%20Costing%20Template-APRIL2014.pdf

[7] David A. Asch M.Kathryn Jedrziewski, Nicholas A. Christakis, Response rates to mail surveys published in medical journals Journal of Clinical Epidemiology Volume 50, Issue 10, October 1997, Pages 1129–1136

[8] Workforce and Facilities Team, Health and Social Care Information Centre. General and Personal Medical Services: England 2003-13. 25 March 2014. URL: http://www.hscic.gov.uk/catalogue/PUB13849/nhs-staf-2003-2013-gene-prac-rep.pdf

[9] Public Health England. Vaccine uptake guidance and the latest coverage data. https://www.gov.uk/government/collections/vaccine-uptake#seasonal-flu-vaccine-uptake

[10] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934; 26:404-413

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

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

[13] de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. Fam Pract. 2006;23(2):253-63.

[14] National Health Service (NHS). Pseudonymisation and anonymisation of data policy (last reviewed: 27 April 2015), accessed 09/06/2016. URL: http://www.google.fr/url?url=http://www.nhsbsa.nhs.uk/Documents/NHSBSACorporatePoliciesandProcedures/Pseudonymisation_and_Anonymisation_of_Data_Policy.doc&rct=j&frm=1&q=&esrc=s&sa=U&ved=0ahUKEwjZrqPvz4fNAhWEB8AKHU0IBz4QFggUMAA&usg=AFQjCNF-JPX5zueirRlBylzoF-WAEDNkmg

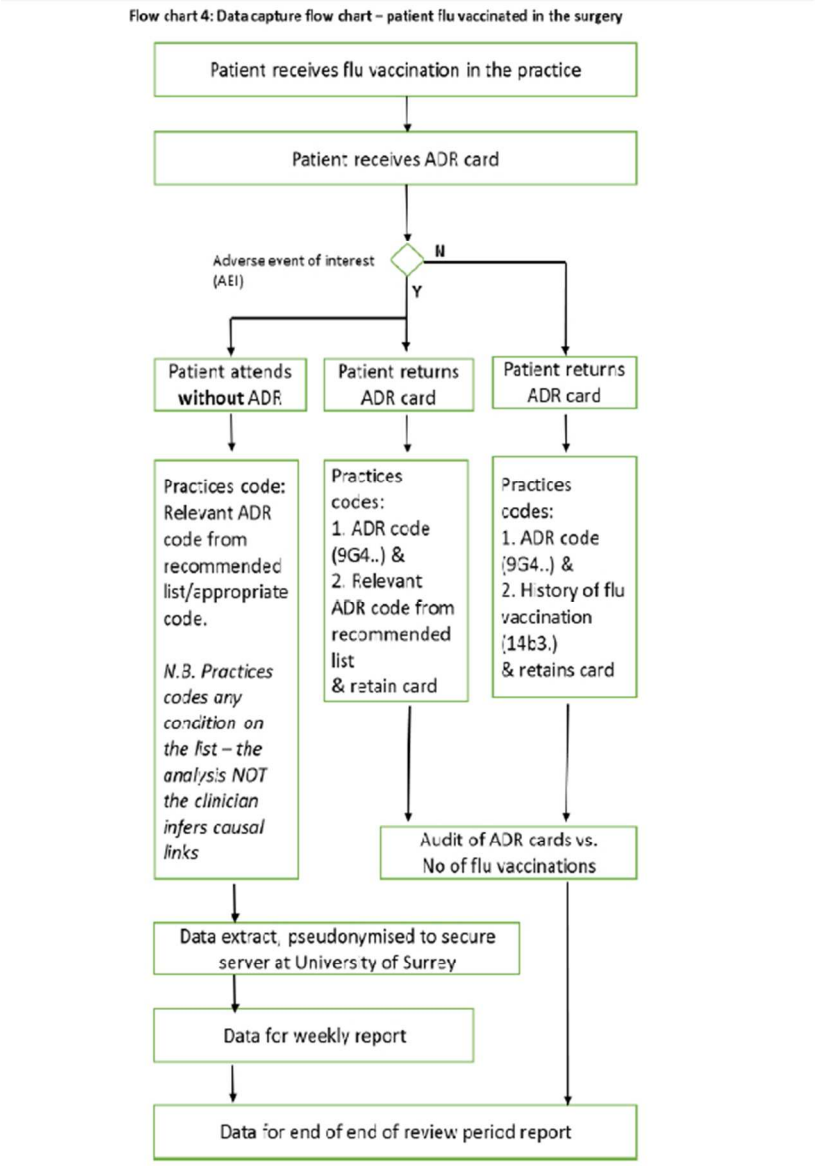
[15] European Union. Justice. Reform of EU data protection rules. URL: http://ec.europa.eu/justice/data-protection/reform/index_en.htm

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

[17] Health and Social Care Information Centre (HSCIC). Information Governance Toolkit (IGT). URL: https://www.igt.hscic.gov.uk/

[18] MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies (Sept 2011) http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/Policy/index.htm

[19] Economic Co-operation and Development (OECD). "Promoting Access to Public Research Data for Scientific, Economic and Social Development" 2007 http://www.oecd.org/sti/sci-tech/38500813.pdf



156x231mm (96 x 96 DPI)