GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England 2017/18
eTrack study number and Abbreviated Title	EPI-FLU-055 VS UK (207781)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 11-DEC-2017
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Epidemiologist) PPD (Lead Statistician Epidemiology) PPD (Safety representative) PPD (SERM Head) PPD (Regulatory Affair) PPD (Clinical and Epidemiology Project Lead) PPD (Lead Scientific Writer) PPD (Lead statistical analyst) PPD (Statistical analyst) PPD (peer reviewer statistician) PPD (Programme Manager, University of Surrey) Prof PPD (Principal Investigator, University of Surrey)
Approved by:	PPD (Epidemiologist) PPD (Lead Statistician Epidemiology) PPD (Clinical and Epidemiology Project Lead) PPD (Lead statistical analyst) PPD (Lead Scientific Writer)
Principal Investigator	Name Prof PPD PPD Signature dd-mmm-yyyy

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AEI	Adverse events of interest as defined by EMA
CI	Confidence interval
CMO	Chief Medical Officer at Department of Health, London
CTR	Clinical Trial Registry
CTV3	Clinical Terms Read version 3
DE	Design effect
EHR	Electronic Health Record
EMA	European Medicines Agency
EPI-FLU-046	The second pilot to monitor EMA defined AEIs (season 2016/2017)
GIS	Geographical Information System
GP	General Practitioner - A family physician providing NHS care to a registered list of patients
GSK	GlaxoSmithKline
ICC	Intra-cluster correlation
IMD	Index of Multiple Deprivation
ISO	International Organization for Standardization
LAIV	Live attenuated influenza vaccine
LL	Lower limit of the confidence interval
NHS	National Health Service
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TFL	Tables Figures and Listing template annexed to SAP
UK	United Kingdom
UL	Upper limit of the confidence interval
VS	Vaccine safety

1. INTRODUCTION

The complete statistical analysis plan and results presentation is divided into 2 parts: the first part detailing the analyses to be performed (known as SAP, current document) and a second part, annex (called TFL) describing the flow and format of tables, figures and listings to be annexed to the Study Report.

This SAP describes the final analysis to be performed after the end of the observation period on all data pertaining to the above study.

2. DOCUMENT HISTORY

Date	Description	Protocol Version
11-DEC-2017	First version	Final protocol: 30 June 2017

3. STUDY DESIGN

3.1. Study design overview

- Type of design: prospective post-authorisation passive enhanced safety surveillance study in the United Kingdom (UK).
- Co-Sponsors: GSK and the University of Surrey, Guildford UK.
- Study vaccination period: intended to be from 01SEP2017 (start of the seasonal influenza vaccination) up to 30N0V2017.
- Study period: intended to be from 01SEP2017 (start of the seasonal influenza vaccination) up to 7 days after last study participant vaccinated.
- Study General Practitioner (GP) practices: 10 GP practices ordering mainly GSK's Fluarix Tetra vaccine for the 2017/18 season will be enrolled in the study before the start of the seasonal influenza immunisation season. These 10 GP practices will be selected based on their willingness to participate, their location (distributed across England (in London, a Northern city, and rural settings in the North and South)) and that the participating population spans different age strata, different levels of deprivation, different ethnic mix, different brand of computerised medical record systems, and different practice sizes. GP practices will also be included based on their ability to comply with the study protocol requirements.
- Study participants: subjects who receive influenza vaccination between 01SEP2017 and 30N0V2017 in the 10 enrolled GP practices and who have not opted-out of data sharing.
- Number of subjects: according to the sample size assumption (conservative approach), it was estimated to be able to reach a number of 50,000 subjects registered in the 10 enrolled GP practices with an estimate of 5,000 vaccinated subjects with 7 days of follow-up after vaccination.
- **Type of study:** self-contained.

3.2. Risk groups for influenza vaccination

As mentioned in the protocol, the 2017/2018 influenza plan recommends the following groups to be vaccinated in the UK:

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

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

3.3. Safety surveillance methods of study subjects

Two different surveillance approaches will be used to provide information about the seasonal influenza vaccine safety:

- Passive surveillance: data collected routinely and recorded in the Electronic Health Record (EHR) system by GP practices.
- Enhanced component: adverse drug reaction (ADR) cards completed by subjects vaccinated with a seasonal influenza vaccine and recorded subsequently in EHR by GP practices.

3.3.1. EHR data from passive surveillance

All 10 enrolled GP practices will be asked to record data into each subject's EHR in the usual way, using a preferred codes list (refer to Annex 2).

3.3.2. Adverse Drug Reaction card

In order to facilitate the coding of data using a standardised approach, the 10 enrolled GP practices will also distribute an ADR card to their subjects receiving seasonal influenza vaccine or, as appropriate, to their parent or carer.

Subjects will be instructed to record adverse events (refer to Annex 3) within 7 days following vaccination and to return the card to their GP practice not later than 14 days post-vaccination. Data recorded on these cards will then be recorded by the GP staff into the subject's EHR. The coding will follow a standardised approach to data recording (refer to Annex 2) and will include a specific code to indicate that the information is derived from those cards.

Of note, the intent will be to issue cards to all vaccinated patients belonging to the enrolled GP practices, however, considering the UK influenza vaccination plan, some vaccinations are expected to occur outside of the GP settings. These are described as opportunistic vaccination, performed by third parties including pharmacists and thus it cannot be excluded that for some patients, ADR cards will not be distributed. These vaccinations will still be encoded in the EHR and those subjects will be included in the study. The adverse events (AEs) will be captured through the routine data collection process (refer to Section 3.3.1).

3.4. Data extract from EHR

The following data from subjects in the 10 enrolled GP practices will be imported (anonymised) into the secure servers of the University of Surrey:

- Demographic information: age, gender, ethnicity, date of registration
- Seasonal influenza vaccine information: date of administration, brand and batch number when available
- Postcode: to understand any inequities in access according to level of social deprivation using Geographical Information System (GIS) methods. Full postcodes will be immediately transformed into deprivation scores, using the Index of Multiple Deprivation (IMD), within GP computer systems upon extraction
- Primary care consultations following vaccination, any other markers of health care utilisation, and referral to further care.
- Pre-specified European Medicines Agency (EMA) adverse events of interest (AEIs) (Annex 2) or any other reported AE recorded in the EHR. Only coded data (Read code and CTV3), i.e. where the GP codes a disease or symptom into the EHR system, will be extracted
- Data from at least one year prior to the start of the study to determine the category of UK Chief Medical Officer (CMO)-specified risk group for influenza vaccination the subjects belong to:
  - Life-style/risk factors – e.g. body mass index, smoking status
  - Records of other diseases and long term conditions – e.g. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, immunosuppression, pneumonia, etc
- Pregnancy status during the course of the study period

No individual patient level data will be released to GSK.

GSK will be blind to GP practice identities, and the locality at which any AE occurs.

3.5. Summary of different groups

The following groups will be used for the statistical analyses.

Vaccine groups for vaccinated subjects:

Group name	Group order in tables	Group label in tables
Vaccine	1	Vaccinated (GSK's Fluarix Tetra)
	2	Vaccinated (Non-GSK)
	3	Vaccinated (Unknown)
	4	Vaccinated (All)

Age groups (categories recommended by EMA):

Group name	Group order in tables	Group label in tables
Age	1	6 months to 5 years
	2	6-12 years
	3	13-17 years
	4	18-65 years
	5	>65 years

UK CMO-specified risk groups*; note that subjects may be assigned in more than one specified risk group:

Group name	Group order in tables	Group label in tables
UK CMO-specified risk groups	1	Any risk group
	2	Asthma
	3	Chronic Respiratory Disease
	4	Chronic Heart Disease
	5	Chronic Kidney Disease
	6	Chronic Liver Disease
	7	Diabetes
	8	Immunosuppression (includes relevant cancer treatment)
	9	Chronic Neurological Disease
	10	Asplenia
	11	Carer
	12	Pregnancy
	13	2 to 8 years old
	14	65 years old and over
	15	Not at risk

* Some high risk groups e.g. in residential care are not well recorded in GP data

UK CMO-specified risk status:

Group name	Group order in tables	Group label in tables
UK CMO-specified risk status	1	At risk
	2	Not at risk

4. OBJECTIVES

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

4.1. Primary objectives

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

4.2. Secondary objectives

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

4.3. Tertiary objectives

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

5. ENDPOINTS

5.1. Primary endpoints

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

5.2. Secondary endpoints

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

5.3. Tertiary endpoints

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

6. ANALYSIS SETS

The following cohorts will be evaluated.

6.1. Total registered population

The Total registered population will include all subjects registered in EHR at any time point during the study vaccination period in the 10 enrolled GP practices who had not opted-out of data sharing.

Note that subjects may have left or joined the GP practices during the study period.

6.2. Total eligible registered population

The Total eligible registered population will include all subjects from the Total registered population

- who have a valid NHS number recorded in EHR
- with date of birth recorded in EHR
- with gender recorded in EHR

6.3. Weekly vaccinated cohorts

The Weekly vaccinated cohorts (for each ISO Week 35 to 48) will include all subjects from the Total eligible registered population

- who are vaccinated with a seasonal influenza vaccine during the week of interest
- who are registered in EHR during the safety follow-up period (from vaccination up to 7 days post vaccination)

Refer to Annex 4 for details of the ISO weeks.

For example, the Weekly vaccinated cohort Week 40 will include all subjects from the Total eligible registered population:

- who are vaccinated with a seasonal influenza vaccine during Week 40
- who are registered in EHR during the safety follow-up period (from vaccination up to 7 days post vaccination)

6.4. Cumulative vaccinated cohorts

The Cumulative vaccinated cohorts (for each ISO Week 35 to 48, denoted as Weeks 35-35 to Weeks 35-48) will include all subjects from the Total eligible registered population

- who are vaccinated with a seasonal influenza vaccine at any point from study start up (i.e. 01SEP2017) up to the end of the week of interest (i.e. cumulatively since the beginning of the study)
- who are registered in EHR during the safety follow-up period (from vaccination up to 7 days post vaccination)

For example, the Cumulative vaccinated cohort Weeks 35-40 will include all subjects from the Total eligible registered population:

- who are vaccinated with a seasonal influenza vaccine at any point from study start up (i.e. 01SEP2017) up to the end of Week 40 (i.e. cumulatively since the beginning of the study)
- who are registered in EHR during the safety follow-up period (from vaccination up to 7 days post vaccination)

7. STATISTICAL ANALYSES FOR THE FINAL ANALYSIS AFTER STUDY COMPLETION

All data processing and statistical analysis will be performed within the secure IT environment of the Clinical Informatics Research Group, at the University of Surrey. R and SAS will be used for the statistical analyses.

Note that statistical methods and data derivation rules are described in Annex 1 and will not be repeated below.

7.1. Analysis of demographics/baseline characteristics

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

The number of subjects in the Total registered population as well as the number excluded from the Total eligible registered population and from the Cumulative vaccinated cohorts will be tabulated, with reasons for exclusion

Demographic characteristics will be summarized for the 2012 Census population, the Total eligible registered population and the Cumulative vaccinated cohorts using descriptive statistics:

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

7.2. Analysis of vaccine exposure

The percentage of subjects vaccinated with a seasonal influenza vaccine during the study vaccination period will be tabulated by Vaccine, Age and UK CMO-specified risk group for the Total eligible registered population as follows:

- The denominator will be the number of subjects in the Total eligible registered population
- The numerator will be the number of subjects from the denominator who were vaccinated with a seasonal influenza vaccine during the study vaccination period

Cumulative percentage of subjects vaccinated with a seasonal influenza vaccine will be graphically displayed by ISO week for the Total eligible registered population.

The number of vaccinated subjects will be tabulated, for the Cumulative vaccinated cohort Weeks 35-48, by GP practice and:

- Vaccine batch number for the group Vaccinated (GSK's Fluarix Tetra)
- Vaccine brand code (A, B, C,…) for the group Vaccinated (Non-GSK) in order to not disclose the detailed information from other manufacturers.

In addition, the list of GSK's Fluarix Tetra vaccine batch numbers administered during the study vaccination period will be provided by Region and Week.

7.3. Analysis of safety

The analyses will be descriptive and will be presented by Vaccine group.

7.3.1. ADR compliance

The percentage of subjects who received and who returned the ADR card will be tabulated by Vaccine group for the Cumulative vaccinated cohort Weeks 35-48.

7.3.2. Analyses of primary objectives

The weekly incidence rate (per 100 subjects) of any AEIs within 7 days* post-vaccination period reported via ADR card will be estimated by Vaccine group as follows in the Weekly vaccinated cohorts restricted to subjects who received the ADR card:

- The denominator will be the number of subjects in the Weekly vaccinated cohort for the week of interest who received the ADR card
- The numerator will be the number of subjects from the denominator who reported any AEIs on the ADR card within 7 days following vaccination with the seasonal influenza vaccine

**Day of vaccination plus the following 7 days*

The cumulative incidence rate (per 100 subjects) of any AEIs within 7 days post-vaccination period reported via ADR card will be estimated by Vaccine group as follows in the Cumulative vaccinated cohorts restricted to subjects who received the ADR card:

- The denominator will be the number of subjects in the Cumulative vaccinated cohort up to the week of interest who received the ADR card
- The numerator will be the number of subjects from the denominator who reported any AEIs on the ADR card within 7 days following vaccination with the seasonal influenza vaccine

Similarly, weekly and cumulative incidence rates will be estimated for the following AEIs within 7 days post-vaccination period reported via ADR card:

- Fever/pyrexia
- Fever >38.5°C and >39.5°C (with a temperature measurement recorded in EHR; independent of route of measurement)
- Local symptoms (i.e. local erythema)
- Any and each general non-specific symptom: drowsiness, fatigue, headache, irritability and malaise
- Any and each respiratory AE: conjunctivitis, coryza, cough, epistaxis, hoarseness, nasal congestion, oropharyngeal pain, rhinorrhoea, wheezing
- Any and each gastrointestinal AE: decreased appetite, diarrhea, nausea, vomiting
- Any and each sensitivity/anaphylaxis AE: anaphylactic reactions, facial oedema, hypersensitivity reactions
- Rash
- Any and each musculoskeletal AE: arthropathy, muscle aches / myalgia
- Any and each neurological AE: Bell's palsy, Guillain-Barre syndrome, peripheral tremor, seizure / febrile convulsions

Similarly, weekly and cumulative incidence rates of any SAEs within 7 days post-vaccination period reported via ADR card will also be generated.

In addition, weekly and cumulative incidence rates of any AEIs, each AEIs category (i.e. fever/pyrexia, local symptoms, any general non-specific symptom, any respiratory, any gastrointestinal, any sensitivity/anaphylaxis, rash, any musculoskeletal and any neurological AEs) and SAEs within 7 days post-vaccination period reported via ADR card will also be generated by Age group (6 months to 5 years; 6 to 12 years; 13 to 17 years; 18-65 years; >65 years) and by UK CMO-specified risk status (at risk, not at risk).

95% confidence interval (CI) adjusted for clustering effect of GP practices will be computed on all estimated incidence rates (Clopper-Pearson exact CI modified for cluster data as described in Annex 1).

The design effects and the intra-cluster correlation coefficients will also be estimated as described in Annex 1 for the estimated cumulative incidence rates of AEIs reported on the ADR card within the 7 days post-vaccination period for the Cumulative vaccinated cohort Weeks 35-48 restricted to subjects who received the ADR card.

7.3.3. Analyses of secondary objectives

All analyses described for the primary objectives (refer to Section 7.3.2) will also be generated by Vaccine group for all subjects included in the Weekly vaccinated cohorts and the Cumulative vaccinated cohorts (i.e. whether or not they received the ADR card).

For the weekly incidence rates (per 100 subjects):

- The denominator will be the number of subjects in the Weekly vaccinated cohort for the week of interest
- The numerator will be the number of subjects from the denominator who reported the specified AEI within 7 days following vaccination with the seasonal influenza vaccine using data entered in the EHR (i.e. AEIs derived from ADR card and medically attended AEIs)

For the cumulative incidence rates (per 100 subjects):

- The denominator will be the number of subjects in the Cumulative vaccinated cohort up to the week of interest
- The numerator will be the number of subjects from the denominator who reported the specified AEI within 7 days following vaccination with the seasonal influenza vaccine using data entered in the EHR (i.e. AEIs derived from ADR card and medically attended AEIs)

7.3.4. Analyses of tertiary objectives

The analysis on vaccine uptake is described in Section 7.2.

Completeness of seasonal influenza vaccination data in the EHR will be assessed by computing the percentage of subjects from the Cumulative vaccinated cohort Weeks 35-48 with data on influenza vaccines recorded in EHR, by Vaccine group:

- The denominator will be the number of subjects in the Cumulative vaccinated cohort Weeks 35-48
- The numerator will include all subjects from the denominator with the following respective data recorded in EHR:
    - Complete date of vaccination
    - Vaccine batch number
    - Both complete date of vaccination and vaccine batch number

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

- Time interval in days between the seasonal influenza vaccination dates and the dates at which the records were encoded in EHR will be summarized by Vaccine group using descriptive statistics (mean, standard deviation, median, range, first and third quartile) for the Cumulative vaccinated cohort Weeks 35-48. This time interval in days will also be graphically displayed.

Compliance in returning ADR cards is described in Section 7.3.1.

Timeliness of AEI reporting in EHR will be assessed as follows:

- Time interval in days between the first onset date of AEIs within the 7 days post-vaccination period and the dates at which the records were encoded in EHR will be summarized by Vaccine group and ADR cards returned status using descriptive statistics (mean, standard deviation, median, range, first and third quartile) for the Cumulative vaccinated cohort of Weeks 35-48. This time interval in days will also be graphically displayed.

7.3.5. Analyses of serious adverse events

The cumulative incidence rates (per 100 subjects) of serious adverse events (SAEs) within the study period will be estimated by Vaccine group, with 95%CI, for the Cumulative vaccinated cohort Weeks 35-48.

7.3.6. Sensitivity analyses

7.3.6.1. Not accounting for clustering effect

To assess the impact of cluster data on the estimated 95%CI, the 95%CI will also be computed for the incidence rates described below using the Clopper-Pearson exact CI method not taken into account the clustering effect.

The cumulative incidence rates (per 100 subjects) of each AEIs within the 7 days post-vaccination period reported via ADR card, with exact 95%CI not accounting for cluster effect of GP practices (Clopper-Pearson exact CI method as described in Annex 1), will be estimated by Vaccine group for the Cumulative vaccinated cohort Weeks 35-48 restricted to subjects who returned the ADR card.

The cumulative incidence rates (per 100 subjects) of each AEIs within the 7 days post-vaccination period using data entered in the EHR (i.e. AEIs derived from ADR card and medically attended AEIs), with exact 95%CI not accounting for cluster effect of GP practices (Clopper-Pearson exact CI method as described in Annex 1), will be estimated by Vaccine group for the Cumulative vaccinated cohort Weeks 35-48.

7.3.6.2. Subjects who returned the ADR card

The cumulative incidence rates (per 100 subjects) of each AEIs within the 7 days post-vaccination period reported via ADR card, with 95%CI, will be estimated by Vaccine group for the Cumulative vaccinated cohort Weeks 35-48 restricted to subjects who returned the ADR card:

- The denominator will be the number of subjects in the Cumulative vaccinated cohort Weeks 35-48 who returned the ADR card
- The numerator will be the number of subjects from the denominator who reported the AEI on the ADR card within 7 days following vaccination with the seasonal influenza vaccine

7.3.7. Analysis on the RCGP RSC network of practices

The Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) network of practices includes approximately 170 GP practices.

The RCGP RSC network will be used to observe the trend of AEI rates using a larger sample of GPs.

The 2017 RSCGP RSC vaccinated cohort will include all subjects from the RSCGP RSC population

- who have not opted-out of data sharing
- who will be vaccinated against influenza at any point during the study vaccination period
- who have a valid NHS number recorded in EHR
- with date of birth recorded in EHR
- with gender recorded in EHR
- who are registered in EHR during the 7 days post vaccination period

The cumulative incidence rate (per 100 subjects) of each AEI within the 7 days post-vaccination period, with 95%CI, will be estimated by Vaccine group as follows:

- The denominator will be the number of subjects from the 2017 RCGP RSC vaccinated cohort
- The numerator will be the number of subjects from the denominator who reported the specified AEI during the 7 days following vaccination with the seasonal influenza vaccine using data entered in the EHR

8. ANALYSIS INTERPRETATION

All analyses are descriptive.

9. CONDUCT OF ANALYSES

9.1. Sequence of analyses

Interim weekly safety reports and a final analysis after study end will be done.

Description	Analysis ID	Disclosure Purpose	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis after study end	E1_01	Study report, CTRS	No	Yes	Refer to EPI-FLU-055 VS UK (207781) TFL .docx
Interim analyses	E1_02	Safety monitoring	No	No	Weekly safety reports of EPI-FLU-046

9.1.1. Interim analyses

Weekly safety reports of influenza vaccination and uptake by different age and risk groups and the EMA listed AEIs reported by the vaccinated subjects will be generated during the study period. These analyses will be performed overall and by vaccine brand (*Fluarix Tetra* vs. others).

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

- The denominator will be the number of subjects vaccinated with a seasonal influenza vaccine during the week of interest
- The numerator will be the number of subjects from the denominator reporting the AEI within 7 days following vaccination with a seasonal influenza vaccine using data entered in the EHR

A safety report will be generated for each ISO week 35 to 48.

The safety report of a specific ISO week will be provided 3 weeks after that week to allow for data to be encoded in EHR.

9.1.2. Final analysis

A final analysis will be generated after study end and a final study report will be written.

9.2. Statistical considerations for interim analyses

Since there is no hypothesis testing, no adjustment of type I error will be needed.

10. CHANGES FROM PLANNED ANALYSES

The study cohorts and incidence rates were clarified.

11. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

Refer to the document entitled EPI-FLU-055 VS UK (207781) TFL.

12. ANNEX 1 STATISTICAL METHODS AND DATA DERIVATION RULES

12.1. Statistical Method

The recruitment will be performed by the GP practices and this may create a clustering effect.

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

Similarities (or homogeneity) between subjects in clusters reduce the variability of their responses, compared with that expected from a random sample. Not accounting for cluster effect would overestimate the precision of the estimated rates.

The two-sided 95% CI for a proportion within a group accounting for clustering effect will be estimated using the Clopper-Pearson exact CI modified for cluster data [Korn, E.L. and Graubard, B.I. (1998). Confidence Intervals for Proportions with Very Small Expected Number of Positive Counts Estimated from Survey Data. Survey Methodology, 24, 193–201].

The design effect (DE), assessing the impact of clustered data on the variance, will be estimated as follows (PROC SURVEYFREQ in SAS with CLUSTER statement):

> DE = actual variance (estimated using Taylor series linearization method) over the variance of a simple random sample with the same number of observations

The intra-cluster correlation (ICC) will be estimated as follows:

> ICC = (DE-1) / (m-1)
>
> Where DE is the design effect and m is the average number of subjects per cluster

The exact two-sided 95% CI for a proportion within a group not accounting for clustering effect will be calculated using the method described in Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

12.2. Data derivation

12.2.1. Date derivation

The date of birth will be modified during the extract from EHR to protect personally identifiable information. The modified date of birth will contain the exact month and year of birth of the subjects, but the exact day of birth will not be provided and will be set to '01' for all the subject's birth dates.

If the vaccine administration date is incomplete or missing the following rule will be applied:

- Day missing: 15 is used (standard GSK imputation)
- Month or year is missing: vaccination not included in the statistical analysis

If the start date of the AEI is incomplete or missing, a conservative approach (worst case scenario) will be used for imputation for the vaccinated subjects. The rules for imputation are detailed below, the examples are given assuming 16OCT2017 as date of vaccine administration.

- Day missing:
  - Month of onset = month of administration: day of administration will be used (e.g. OCT2017 → 16OCT2017)
  - Month of onset > month of administration: first day of the month will be used (e.g. NOV2017 → 01NOV2017)
  - Month of onset < month of administration: AEI not included in the statistical analysis
- Month or year missing: AEI not included in the statistical analysis

12.2.2. Demography

For a given subject and a given demographic variable, a missing measurement will not be replaced.

Age: Age at the reference activity will be computed as the number of units (years, months, or days) between the date of birth and the reference activity.

12.2.3. Influenza vaccine exposure

For subjects who received more than one seasonal influenza vaccination during the study vaccination period, if any, only the first vaccination will be included in the analysis.

12.2.4. Safety

Subjects who did not report an adverse event will be considered as subjects who did not experience adverse event.

For the analysis of fever/pyrexia, all subjects with a fever/pyrexia Read code recorded will be considered as having fever/pyrexia regardless of what temperature had been recorded. For the analysis of fever >38.5C and 39.5C, all subjects with a fever/pyrexia Read code recorded within 7-day post vaccination and with a recorded temperature above the specified thresholds (>38.5C and >39.5C) within 7-day post vaccination, independent of route of measurement, will be considered as having fever above the specified thresholds.

The following process steps will be followed for the cleaning of temperature values:

- Every value recorded has a field for units, which can be left blank. If the units specified “Fahrenheit” or “F”, the value will be converted to Celsius, using this formula: (Value – 32) * 5/9.
- Otherwise, if the value is between 90 and 110, the value will be converted from Fahrenheit to Celsius, using the above formula.
- Otherwise, if the value is between 3.3 and 4.1, it'll be assumed a decimal place error, and the value will be multiplied by 10.
- Otherwise, if the value is between 330 and 410, it'll be assumed a decimal place error, and the value will be divided by 10.
- Otherwise, if the value is between 3300 and 4100, it'll be assumed a decimal place error, and the value will be divided by 100.

All temperature values below 37.5 or above 41.5 will be discarded.

12.3. Data presentation description

The following decimal description will be used for the analyses:

Display Table	Parameters	Number of decimal digits
Demographic characteristics, vaccine exposure	%	1
	Mean, median	1
	Standard deviation	1
Safety	%, LL & UL of CI	2

13. ANNEX 2 PREFERRED CODE LIST FOR ADVERSE EVENTS OF INTEREST

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

EMA surveillance condition	Read Code (5 Byte)	Read Code (CTV3)	Notes
Respiratory/Miscellaneous			
Conjunctivitis	F4C0.	XE16X	
Rhinorrhoea	1C83.	XM00h	
Nasal congestion	H1y1z	X77Gp	
Epistaxis	R047.	Xa96W	
Coryza	H00..	XE0XI	
Cough	171..	XM0Ch	
Oropharyngeal pain	1922. 1CB3.	1922. 1CB3.	
Hoarseness	1CA2.	1CA2.	
Wheezing	1737.	XE0qs	
Gastrointestinal			
Decreased appetite	R0300	XM07Y	
Nausea	198..	X75qw	
Vomiting	199..	XE0rA	
Diarrhoea	19F..	19F2.	
Fever/pyrexia			
Fever	165..	X76DI	
Mild fever (<38.5° C rectal)			Please include level of temperature, to help us classify the fever
Moderate fever (38.6-39.5°C)	2E3..	2E3..	
High fever (>39.5°C)			
Sensitivity/anaphylaxis			
Hypersensitivity reactions	SN52.	Xa3uf	
Anaphylactic reactions	SN501	X70wr	
Facial oedema	16J5.	Xa0ls	
Rash			
Rash	M130.	X50Ge	
Generalised rash	2I14.	XM07J	
General non-specific symptoms			
Irritability	225A.	225A.	
Drowsiness	1B67.	XM06R	
Fatigue	168..	1682.	
Neurological			
Bell's palsy	F310.	F310.	
Peripheral tremor	1B22.	XE0rn	
Guillain-Barre Syndrome (GBS)	F3700	F3700	
Seizure/ Febrile convulsions	1B64. 1B6B.	XaDbE XM03I	
Headache	1B1G.	XM0CV	
Musculoskeletal			
Muscle aches/ myalgia	N2410	X75rs	
Arthropathy	N037.	X701f	
Local Symptoms			
Local erythema	SP3y4 SP3y5 SP3y6 SP3y7	X75ty	

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

14. ANNEX 3 ADVERSE DRUG REACTIONS SOLICITED IN THE CARD

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

15. ANNEX 4 ISO WEEKS

Table below presents the International Organization for Standardization (ISO) weeks 35 to 48 considered in the analysis (from 01SEP2017 to 30NOV2017):

Week	Week Starting - Ending
35	01/09/2017 - 03/09/2017
36	04/09/2017 - 10/09/2017
37	11/09/2017 - 17/09/2017
38	18/09/2017 - 24/09/2017
39	25/09/2017 - 01/10/2017
40	02/10/2017 - 08/10/2017
41	09/10/2017 - 15/10/2017
42	16/10/2017 - 22/10/2017
43	23/10/2017 - 29/10/2017
44	30/10/2017 - 05/11/2017
45	06/11/2017 - 12/11/2017
46	13/11/2017 - 19/11/2017
47	20/11/2017 - 26/11/2017
48	27/11/2017 - 30/11/2017