GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Passive enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccines: a pilot study in Belgium, Germany and Spain during the 2018/19 influenza season
eTrack study number and Abbreviated Title	207737 (EPI-FLU-056 VS EU)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 04-OCT-2018 Amendment 1: 14-Feb-2019
Co-ordinating author:	PPD (Lead Statistician)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)	

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse event
AEI	Adverse Events of Interest
CI	Confidence Interval
CTRS	Clinical Trial Registry Summary
DE	Design effect
eCRF	Electronic Case Report Form
EU	European Union
FSFV	First Subject First Visit
GSK	GlaxoSmithKline
HCP	Healthcare Professional
ICC	Intra-cluster correlation
ISO	International Organization for Standardization
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SR	Study Report
TFL	Tables Figures and Listings
UL	Upper Limit of the confidence interval
VS	Vaccine safety

1. DOCUMENT HISTORY

Date	Description	Protocol Version
04-OCT-2018	first version	Protocol Amendment 1 (11-Sep-2018)
14-FEB-2019	Amendment 1 The SAP has been amended – To include a table summarizing the number of AEs reported per subject after each GSK's quadrivalent seasonal influenza vaccine dose and after both doses – To remove the Exposed Set – To clarify some elimination codes – To clarify that the co-administered vaccinations will be coded using the GSK Drug dictionary and will be tabulated by vaccination class	Protocol Amendment 1 (11-Sep-2018)

2. STUDY DESIGN

- Type of design: multi-country, multicentre, prospective, passive enhanced safety surveillance study.
- This is a Targeted Safety Study.
- Study population: subjects aged 6 months or above in Spain and aged 18 years or above in Belgium and Germany, and receiving GSK's quadrivalent seasonal influenza vaccine according to the local prescribing information.
- Data collection: electronic Case Report Form (eCRF).
- Study recruitment period: the recruitment period is anticipated to run for 3 months from 01 October 2018 to 31 December 2018, except for subjects aged <9 years who have not been previously vaccinated against influenza in preceding seasons, for whom the recruitment period will end on 01 December 2018 to allow sufficient time to collect information on the second dose that is expected to occur at least 4 weeks after the first dose.
- Study duration: the study is anticipated to run from 01 October 2018 to 15 January 2019. The intended duration of the study per subject will be approximately 8 days for all subjects who have previously been vaccinated against influenza in preceding seasons or aged ≥9 years at the time of vaccination, and approximately 36 days for children aged <9 years who have not previously been vaccinated against influenza in preceding seasons.
- Number of subjects: approximately 1000 vaccinees receiving GSK's quadrivalent seasonal influenza vaccine will be enrolled in this study in Belgium, Germany and Spain by 31 December 2018.
- Customized adverse drug reaction (ADR) cards will be used to collect prospectively the adverse events of interest (AEIs) and/or other adverse event (AEs) experienced within 7 days post each vaccination (i.e. the day of vaccination and the following 6 days).

The cards will contain pre-defined AEIs (refer to section 12) to be reported as well as a free text field to report other AEs experienced by the subjects. Subjects will also have the possibility to indicate that no AE occurred within the 7 days' time window.

The subjects/subjects' parent'(s)/ legally acceptable representative will be asked to complete the ADR cards with any AEIs and/or other AEs occurring within 7 days post vaccination and to return the cards to the Healthcare Professional (HCP) at the next study visit or by mail.

- **Risk status for influenza-associated morbidity and mortality:** The risk status (i.e. at risk/not at risk) is to be assessed by the HCP based on his/her judgment and experience. Risk groups usually recommended for seasonal influenza vaccination in the EU include but are not limited to:
  - pregnant women
  - individuals >6 months with chronic heart or lung diseases, metabolic or renal disease, chronic liver disease, chronic neurological conditions or immunodeficiencies
  - residents of long-term care facilities for older persons and the disabled
  - children aged 6–59 months
  - healthcare workers including those who work in facilities that care for the elderly or persons with disabilities

  The risk status (i.e. at increased risk/not at increased risk) will be recorded in the eCRF. However, the risk factors will not be recorded in the eCRF.

- **Type of study:** self-contained.

3. OBJECTIVES

3.1. Primary Objective

- To estimate, in each country and overall, the cumulative percentages of subjects reporting AEIs and/or other AEs within 7 days following vaccination with GSK's quadrivalent seasonal influenza vaccine using ADR cards.

3.2. Secondary Objectives

- To estimate, in each country and overall, the weekly percentages of subjects reporting AEIs and/or other AEs within 7 days following vaccination with GSK's quadrivalent seasonal influenza vaccine using ADR cards, overall, by age strata (6 months to 17 years; 18 to 65 years; >65 years), and risk status (at risk/not at risk).
- To estimate, in each country and overall, the cumulative percentages of subjects reporting AEIs and/or other AEs within 7 days following vaccination with GSK's quadrivalent seasonal influenza vaccine using ADR cards, by age strata (6 months to 17 years; 18 to 65 years; >65 years), and risk status (at risk/not at risk).

4. ENDPOINTS

4.1. Primary endpoint

- Occurrence of AEIs and/or other AEs within 7 days post each GSK's quadrivalent seasonal influenza vaccination (i.e., the day of vaccination and the following 6 days) reported using ADR cards, according to MedDRA classification, by cumulative weeks (expected ISO weeks 40 to 52).

4.2. Secondary endpoints

- Occurrence of AEIs and/or other AEs within 7 days post each GSK's quadrivalent seasonal influenza vaccination (i.e., the day of vaccination and the following 6 days) reported using ADR cards, according to MedDRA classification, each week (expected ISO weeks 40 to 52).
- Occurrence of AEIs and/or other AEs within 7 days post each GSK's quadrivalent seasonal influenza vaccination (i.e., the day of vaccination and the following 6 days) reported using ADR cards, according to MedDRA classification, by cumulative weeks (expected ISO weeks 40 to 52).

5. ANALYSIS SETS

5.1. Definition

The following analysis sets are defined:

Analysis Set	Description
Enrolled	All subjects with informed consent signed
Enrolled without code 900	All subjects from the Enrolled Set without elimination code 900 *Note that this analysis Set will be applied only if a code 900 will be attributed*
Safety	All subjects from the Enrolled Set who were vaccinated with GSK's quadrivalent seasonal influenza vaccine and who received the ADR card
Solicited Safety	All subjects from the Safety Set who returned the ADR card and who documented the presence or absence of AE(s)

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each analysis set.

The elimination codes will be provided to each dose of GSK's quadrivalent seasonal influenza vaccine dose independently.

A subject will be excluded from the Safety Set under the following conditions:

Elimination Code	Condition under which the code is used	Visit
900	Invalid informed consent or unverifiable data	(Doses 1 and 2)
1500	Subjects not planned to receive 2 doses of GSK's quadrivalent seasonal influenza vaccine	Visit 3 (Dose 2)
1510	Subjects not vaccinated with GSK's quadrivalent seasonal influenza vaccine	Visit 1 (Dose 1) and Visit 3 (Dose 2)*
1520	Subjects didn't receive the ADR card	Visit 1 (Dose 1)§ and Visit 3(Dose 2)§

*Elimination code to be provided only in subjects planned to receive 2 doses of GSK's quadrivalent seasonal influenza vaccine
§Elimination code to be provided only in subjects vaccinated with GSK's quadrivalent seasonal influenza vaccine

A subject will be excluded from the Solicited Safety Set under the following conditions:

Elimination Code	Condition under which the code is used	Visit
900	Invalid informed consent or unverifiable data	(Doses 1 and 2)
1500	Subjects not planned to receive 2 doses of GSK's quadrivalent seasonal influenza vaccine	Visit 3 (Dose 2)
1510	Subjects not vaccinated with GSK's quadrivalent seasonal influenza vaccine	Visit 1 (Dose 1) and Visit 3 (Dose 2)*
1520	Subjects didn't receive the ADR card	Visit 1 (Dose 1)§ and Visit 3 (Dose 2)§
1530	Subjects didn't return the ADR card or returned the ADR card without documentation of the presence or absence of AE(s)	Visit 1 (Dose 1)# and Visit 3 (Dose 2) #

*Elimination code to be provided only in subjects planned to receive 2 doses of GSK's quadrivalent seasonal influenza vaccine
§Elimination code to be provided only in subjects vaccinated with GSK's quadrivalent seasonal influenza vaccine
#Elimination code to be provided only in subjects who received the ADR card

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported:

- Failure to meet inclusion/exclusion criteria other than the one leading to elimination from analysis sets
- Subjects have visits out of protocol allowed window interval between study visits

6. STATISTICAL ANALYSES

SAS 9.3 or higher will be used for the statistical analyses.

All analyses will be descriptive and will be presented by country and overall.

Note that standard data derivation rule and stat methods are described in section 11 and will not be repeated below.

If an elimination code 900 will be attributed, then all the analyses planned to be done on the Enrolled Set will actually be done on the Enrolled without code 900 Set, except Templates 3 and 4 from EPI-FLU-056 VS EUR (207737) TFL Final Analysis.

6.1. Demographics/baseline characteristics and study visits attendance

The number of subjects enrolled into the study will be tabulated by center.

The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal.

The number of subjects included in each analysis Set will be tabulated overall and by ISO week (expected ISO weeks 40 to 52). Refer to section 13 for details of the ISO weeks.

Demographic characteristics (age at vaccination (Dose 1) in months if less than 1 year and in years if greater or above than 1 year, gender, geographic ancestry) and risk status for influenza-associated morbidity and mortality will be summarized using descriptive statistics for each analysis set:

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

Minimum and maximum visit dates and deviations from specifications for age and intervals between study visits will be tabulated for the Enrolled Set.

Visits attendance will be tabulated for the Safety Set and for the Solicited Safety Set.

Summary of time interval between Visit 1 or 3 and date of ADR card returned will be tabulated for the Solicited Safety Set.

6.2. Vaccine exposure

The analyses will be done on the Enrolled Set.

The number of subjects administered with one and two doses of GSK's quadrivalent seasonal influenza vaccine will be tabulated.

The number of subjects vaccinated with GSK's quadrivalent seasonal influenza vaccine will be graphically displayed by ISO week.

The number and percentage of subjects vaccinated with GSK's quadrivalent seasonal influenza vaccine by ISO week will be tabulated by risk status for influenza-associated morbidity and mortality, by age category and by vaccine batch number.

Completeness of GSK's quadrivalent seasonal influenza vaccine data in eCRF (vaccine administration date and vaccine batch number) will be tabulated.

Co-administered vaccination on the same day as the GSK's quadrivalent seasonal influenza will be coded using the GSK Drug dictionary. The number and percentage of subjects who received co-administered vaccination on the same day as the GSK's quadrivalent seasonal influenza will be tabulated by co-administered vaccination class.

6.3. Analysis of safety

6.3.1. ADR compliance

The percentage of subjects who received the ADR card will be tabulated by centre on the Enrolled Set.

The percentage of subjects who returned the ADR card and those who returned the ADR card with documentation of the presence or absence of AEs will be tabulated by centre on the Safety Set.

Completeness of onset dates (day, month and year) for AEs reported within 7 days post-vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards will be tabulated for the Solicited Safety Set.

6.3.2. Analysis of Primary Objective

The analysis of AEIs and/or other AEs reported using ADR cards will be descriptive and will be performed on the Safety Set.

The safety Set was selected as the primary analysis as this is a post marketing study and intends to reflect the pharmacovigilance activities.

For each vaccine dose*, the cumulative percentage of subjects reporting AEIs and/or other AEs within 7 days post-vaccination period (i.e., the day of vaccination and the following 6 days) using ADR cards from study start up to each study week (expected ISO weeks 40 to 52) will be estimated by MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) as follows:

- The denominator will be the number of subjects from the Safety Set who were vaccinated with GSK's quadrivalent seasonal influenza vaccine at any point from study start (i.e., 01 October 2018) up to the end of the week of interest, in a given country or for all countries.
- The numerator will be the number of subjects from the denominator who reported the AE on the ADR card within 7 days following vaccination.

* Note that a second dose of GSK's quadrivalent seasonal influenza vaccine is planned to be administered only to children aged <9 years who have not previously been vaccinated against influenza in preceding seasons.

95% CI accounting for clustering effect of centers will be computed on all estimated percentages. The method for estimating the CIs is described in section 11

The design effects and the intra-cluster correlation coefficients will also be estimated, as described in section 11 for the cumulative percentage of subjects reporting AEs by MedDRA Primary SOC and PT within 7 days post-each vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (expected ISO weeks 40-52).

6.3.3. Analysis of Secondary Objectives

The analysis of AEIs and/or other AEs reported using ADR cards will be descriptive and will be performed on the Safety Set.

For each vaccine dose*, the weekly percentage of subjects reporting AEIs and/or other AEs within 7 days post-vaccination period (i.e., the day of vaccination and the following 6 days) using ADR cards will be estimated by MedDRA Primary SOC and PT as follows:

- The denominator will be the number of subjects from the Safety Set who were vaccinated with GSK's quadrivalent seasonal influenza vaccine during the week of interest (expected ISO weeks 40 to 52), in a given country or for all countries.
- The numerator will be the number of subjects from the denominator who reported the AE on the ADR card within 7 days following vaccination.

In addition, for each vaccine dose*, the weekly and cumulative percentages of subjects reporting AEIs and/or other AEs within 7 days post-vaccination period using ADR cards, according to MedDRA Primary SOC classification, will be estimated by age strata (6 months to 17 years; 18 to 65 years; >65 years) and risk status (at risk/not at risk).

* Note that a second dose of GSK's quadrivalent seasonal influenza vaccine is planned to be administered only to children aged <9 years who have not previously been vaccinated against influenza in preceding seasons.

95% CI accounting for clustering effect of centers will be computed on all estimated percentages. The method for estimating the CIs is described in section 11.

6.3.4. Other Analyses

6.3.4.1. Serious adverse events deemed to be related to GSK's quadrivalent seasonal influenza vaccine according to HCP

The cumulative percentage of subjects reporting SAEs deemed to be related to GSK's quadrivalent seasonal influenza vaccine according to HCP within 7 days post each vaccination (i.e. the day of vaccination and the following 6 days), over the whole study period (expected ISO weeks 40-52), will be estimated by MedDRA Primary SOC and PT on the Enrolled Set.

SAEs deemed to be related to GSK's quadrivalent seasonal influenza vaccine according to HCP occurring within 7 days post vaccination (i.e. the day of vaccination and the following 6 days) will be described in detail.

6.3.4.2. Sensitivity analyses

6.3.4.2.1. Analysis on the Solicited Safety Set

The cumulative percentage of subjects reporting AEIs and/or other AEs within 7 days post each vaccination period (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (expected ISO weeks 40-52), will be estimated by MedDRA Primary SOC and PT on the Solicited Safety Set.

6.3.4.2.2. CI not accounting for clustering effect of centers

To assess the impact of cluster data on the estimated 95%CIs, the 95%CIs will also be computed using the Clopper-Pearson exact CI method not taking into account the clustering effect for the following analysis:

- Cumulative percentage of subjects reporting AEs within 7 days post each vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (expected ISO weeks 40-52) by MedDRA Primary SOC and PT on the Safety Set.

6.3.4.3. Number of AEs per subject

The number of AEs reported within 7 days post- vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards per subject, over the whole study period (ISO weeks 42-52) will be tabulated on the Safety Set.

6.3.4.4. Analysis by center

The cumulative percentage of subjects reporting AEs by MedDRA Primary SOC and PT within 7 days post each vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (expected ISO weeks 40-52) will be estimated by center on the Safety Set.

6.3.4.5. Analysis after any vaccination in Spain

The cumulative percentage of subjects reporting AEs by MedDRA Primary SOC and PT within 7 days post any vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (ISO weeks 42-52) will be estimated in Spain on the Safety Set.

7. ANALYSIS INTERPRETATION

All analyses are descriptive.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Three planned interim analyses and a final analysis after study end will be performed.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)* requiring expedited communication to upper management (Yes/No)	Reference for TFL
First interim analysis	E1_02	Safety monitoring	No	No	EPI-FLU-056 VS EUR (207737) TFL Interim Analyses
Second interim analysis	E1_03	Safety monitoring	No	No	EPI-FLU-056 VS EUR (207737) TFL Interim Analyses
Third interim analysis	E1_04	Safety monitoring	No	No	EPI-FLU-056 VS EUR (207737) TFL Interim Analyses
Final analysis	E1_01	SR, CTRS	No	Yes	Refer to EPI-FLU-056 VS EUR (207737) TFL Final Analysis

The planned dates for database snapshot and statistical report completed, with the ISO weeks covered in the analyses, are provided in below table for each planned interim analysis.

Description	Analysis ID	Planned date for database snapshot	Planned date for statistical report completed	ISO weeks covered in the statistical analysis
First interim analysis	E1_02	12NOV2018	16NOV2018	Weeks 40*-43 (01OCT2018 to 28OCT2018)
Second interim analysis	E1_03	26NOV2018	30NOV2018	Weeks 40*-45 (01OCT2018 to 11NOV2018)
Third interim analysis	E1_04	10DEC2018	14DEC2018	Weeks 40*-47 (01OCT2018 to 25NOV2018)

*The first ISO week covered in the statistical analyses will depend on the first subject first visit (FSFV). If FSFV is 15OCT2018 then the first ISO week covered in the analysis will be ISO week 42.

In addition, a fourth unplanned interim analysis was performed mid-January to monitor the safety after the second dose of GSK's quadrivalent seasonal influenza vaccine (refer to EPI-FLU-056 VS EUR (207737) Additional Analysis Request E01_05 - Interim analysis 4).

8.2. Statistical considerations for interim analyses

The interim analyses will be generated to evaluate the trend of reporting of AEs (i.e. safety monitoring) and will be performed on data which are cleaned as much as possible.

The following analyses will be performed for each interim analysis, overall and by country:

- The number of subjects enrolled into the study will be tabulated by center.
- The number and percentage of subjects vaccinated with GSK's quadrivalent seasonal influenza vaccine during each ISO week will be tabulated overall, by age strata and risk status.
- Demographic characteristics (age at vaccination (Dose 1) in months if less than 1 year and in years if greater or above than 1 year, gender, geographic ancestry) will be summarised using descriptive statistics.
- The number and percentage of subjects who received and who returned the ADR card will be tabulated by centre.
- The weekly percentage of subjects reporting AEIs and/or other AEs within 7 days post-vaccination period (i.e. the day of vaccination and the following 6 days) using ADR cards will be estimated by MedDRA Primary SOC and PT with 95% CI.
- SAEs deemed to be related to GSK's quadrivalent seasonal influenza vaccine occurring within 7 days post vaccination (i.e. the day of vaccination and the following 6 days) will be described.

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

9. CHANGES FROM PLANNED ANALYSES

The definition of the Solicited Safety Set was updated to exclude subjects who did not document the presence or absence of AE(s) on the returned ADR card and the Enrolled without code 900 Set was added.

The following analyses not planned in the protocol will be performed:

- The cumulative percentage of subjects reporting AEs by MedDRA Primary SOC and PT within 7 days post each vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (expected ISO weeks 40-52) will be estimated by center on the Safety Set.

- The cumulative percentage of subjects reporting AEs by MedDRA Primary SOC and PT within 7 days post any vaccination (i.e. the day of vaccination and the following 6 days) using ADR cards, over the whole study period (ISO weeks 42-52) will be estimated in Spain on the Safety Set.

An unplanned interim analysis was performed mid-January to monitor the safety after the second dose of GSK's quadrivalent seasonal influenza vaccine.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

Refer to the document entitled:

- EPI-FLU-056 VS EUR (207737) TFL Final Analysis
- EPI-FLU-056 VS EUR (207737) TFL Interim Analyses

The following group name will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
1	GSK's quadrivalent seasonal influenza vaccine	None

The following sub-group names will be used in the TFLs:

Sub-group	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Country	1	Belgium	None
	2	Germany	None
	3	Spain	None
	4	Overall	None
Age category*	1	6 months to 17 years	None
	2	18-65 years	None
	3	>65 years	None
Risk status for influenza-associated morbidity and mortality	1	At risk	None
	2	Not at risk	None

*At dose 1 of GSK's quadrivalent seasonal influenza vaccine

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The recruitment will be performed by center and this may create a clustering effect (i.e. higher homogeneity of the outcome within a cluster and/or higher heterogeneity of outcomes between clusters as compared with what is expected from a simple random sampling).

Subjects medically followed by the same physician 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 center 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.

Similarities (or homogeneity) between subjects in centers 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 of centers will be estimated using the extended Clopper-Pearson exact CI 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].

If the proportion is 0% or 100%, or if all subjects used to compute the proportion are coming from the same center, then the two-sided 95% CI will be estimated using the classical method described in Clopper-Pearson exact CI (denoted as Clopper-Pearson exact CI not extended for cluster data in the TFLs) [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

The design effect (DE), assessing the impact of clustered data on the variance of the estimated rates (thus on the the precision of the estimated rates), 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
m is the average number of subjects per center in the sub-group

If the proportion is 0% or 100%, or if all subjects used to compute the proportion are from the same center, then ICC and DE will not be estimated.

The exact two-sided 95% CI for a proportion within a group not accounting for clustering effect will be calculated using the classical 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].

11.2. Data derivation

11.2.1. Date derivation

SAS date derived from a character date: in case day is missing, 15 will be used. This will be applied for the date of birth (day not recorded in eCRF). In case day & month are missing, 30June is used.

However, if the start date of the AE is incomplete or missing, the following imputation will be used (the examples are given assuming 16OCT2018 as date of vaccine administration).

- Day missing:
  - Month of onset = month of administration: day of vaccine administration will be used (e.g. OCT2018 → 16OCT2018)
  - Month of onset > month of vaccine administration: first day of the month will be used (e.g. NOV2018 → 01NOV2018)
  - Month of onset < month of vaccine administration: AE not included in the statistical analysis
  - Month or year missing: month/year of vaccine administration will be used (e.g. 18 → 18OCT2018)
  - Day, month and year missing: date of vaccine administration will be used (e.g. blank → 16OCT2018)

Interval: interval between 2 dates is expressed in days. It is the number of days between the 2 dates. Therefore, interval is 0 day if the 2 dates are the same.

11.2.2. Demography

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

Age at the vaccination will be computed as the difference between the vaccination date (dose 1 of GSK quadrivalent seasonal influenza vaccine) and the date of birth. The age will be expressed in months (if less than 1 year) or in years (if greater or above than 1 year).

11.2.3. Withdrawn from the study

A subject who returns for the concluding visit* foreseen in the protocol or has returned the completed ADR card (i.e. presence or absence of AE(s) documented on the ADR card) is considered to have completed the study.

**Visit 2 for subjects planned to be administered with 1 dose of GSK's quadrivalent seasonal influenza vaccine, Visit 4 for subjects planned to be administered with 2 doses of GSK's quadrivalent seasonal influenza vaccine.*

11.2.4. Safety

The presence or absence of AEs on the returned ADR card will be considered as documented if the response to the eCRF question ' Were any Adverse Drug Reactions reported on this ADR card?' is Yes or No.

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

Onset day for an event (e.g. AE): the onset day is the number of days between the last vaccination and the onset/start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case of incomplete dates.

11.3. Data presentation

The following decimal description will be used for the analyses:

Display Table	Parameters	Number of decimal digits
Demographic characteristics, vaccine exposure	%	1
	Mean, Q1, Q3, median age	1
	Standard deviation	1
Safety	%, LL & UL of CI	2
	Design effect	3
	Intra-cluster correlation	3

Q1 = 25th percentile, Q3 = 75th percentile

12. ANNEX 2 CODE LIST OF PRE-SPECIFIED AEIS

Project title: Passive enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccines: a pilot study in Belgium, Germany and Spain during the 2018/19 influenza season

Preferred code list

If a patient presents with adverse events within 7 days following vaccination (i.e., the day of vaccination and the following 6 days), please code (ideally as a symptom) any of the following events into their computerised record

Pre-defined Adverse Events of Interest	MedDRA PT Terms	ICD-10 Codes	Notes
Respiratory/Miscellaneous			
Conjunctivitis	Conjunctivitis (10010741)	H10.9	Irritated or red eyes
Rhinorrhoea	Rhinorrhoea (10039101)	J34.89	Runny nose
Nasal congestion	Nasal congestion (10028735)	R09.81	Blocked nose
Epistaxis	Epistaxis (10015090)	R04.0	Nose bleed
Coryza	Rhinitis (10039083)	J00	Common cold
Cough	Cough (10011224)	R05	Cough
Oropharyngeal pain	Oropharyngeal pain (10068319)	J02.9	Sore throat
Hoarseness	Dysphonia (10013952)	R49.0	Hoarse voice
Wheezing	Wheezing (10047924)	R06.2	Wheezing
Gastrointestinal			
Decreased appetite	Decreased appetite (10061428)	R63.0	Loss of appetite
Nausea	Nausea (10028813)	R11.0	Feeling sick
Vomiting	Vomiting (10047700)	R11.10	Being sick
Diarrhoea	Diarrhoea (10012735)	R19.7	Diarrhea
Fever/pyrexia			
Fever	Pyrexia (10037660)	R50.9	Temperature >38°C
Sensitivity/anaphylaxis			
Hypersensitivity reaction	Hypersensitivity (10020751)	T78.4	Allergic reaction
Anaphylactic reaction	Anaphylactic reaction (10002198)	T78.2	Severe allergic reaction
Facial oedema	Face oedema (10016029)	R60.0	Swelling of the face
Rash			
Rash	Rash (10037844)	L27.1	Rash in a restricted part of the body
Generalised rash	Rash generalised (10037858)	L27.0	Rash all over body

Pre-defined AEIs	MedDRA PT Terms	ICD-10 Codes	Notes
General non-specific symptoms			
Irritability	Irritability (10022998)	R68.12 (Fussy baby) R45.4 (Irritability and anger)	Feeling irritable
Fatigue	Fatigue (10016256)		Feeling tired
Headache	Headache (10019211)	R51	Headache
Neurological			
Bell's palsy	Facial paralysis (10016062)	G51.0	
Peripheral tremor	Chills (10008531)	R68.83	Shivering/ chills
Guillain-Barré Syndrome (GBS)	Guillain-Barre syndrome (10018767)	G61.0	
Seizure/ Febrile convulsions	Febrile convulsion (10016284)	R56.0	Seizure/ fits
Musculoskeletal			
Muscle aches/ myalgia	Myalgia (10028411)	M79.1	Muscle aches
Arthropathy	Arthropathy (10003285)	M25.9, M19.9	Joint pain
Local Symptoms			
Local erythema	Injection site erythema (10022061)	T50.B95	Redness around the injection site
Local swelling	Injection site swelling (10053425)	T50.B95	Swelling around the injection site
Local pain	Injection site pain (10022086)	T50.B95	Pain at the injection site
If a patient hands back the ADR card with their symptoms – please code these and include the code xxxxx			

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

Principal Investigator: XXXX

13. ANNEX 3 ISO WEEKS

Table below presents the International Organization for Standardization (ISO) weeks 40 to 52 covered in the statistical analyses:

Week	Week Starting (Monday) - Ending (Sunday)
40	01OCT2018 to 07OCT2018
41	08OCT2018 to 14OCT2018
42	15OCT2018 to 21OCT2018
43	22OCT2018 to 28OCT2018
44	29OCT2018 to 04NOV2018
45	05NOV2018 to 11NOV2018
46	12NOV2018 to 18NOV2018
47	19NOV2018 to 25NOV2018
48	26NOV2018 to 02DEC2018
49	03DEC2018 to 09DEC2018
50	10DEC2018 to 16DEC2018
51	17DEC2018 to 23DEC2018
52	24DEC2018 to 30DEC2018 ***For the stat analysis, 31DEC2018 will be included in the ISO week 52***