Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
B-1330 Rixensart - Belgium

eTrack study number and Abbreviated Title	207737 (EPI-FLU-056 VS EU)
Date of protocol	Final Version 1: 24 May 2018
Date of protocol amendment	Amendment 1 Final: 11 September 2018
Title	Enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccines
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
Co-ordinating author	PPD 4Clinics Belgium for GSK Biologicals'
Contributing authors	• PPD Epidemiologist • PPD Clinical Epidemiology Project Lead • PPD ***VP Head of Clinical R&D*** • PPD Project Statistician • PPD Lead Statistician • PPD Study Delivery Lead • PPD, Clinical Safety representative • PPD Clinical Safety representative • PPD Regulatory Affairs representative • PPD Oversight Data Manager • PPD Study Data Manager

GSK Biologicals' protocol template for observational studies and interventional studies without administration of medicinal products as described in a research protocol based on the Protocol Document Standard version 15.0

Protocol Sponsor Signatory Approval

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Sponsor signatory	Jacqueline Miller, VP Head of Clinical R&D

Signature _____

Date _____

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Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with 'Good Clinical Practice' (GCP) or other applicable guidelines (such as Good Epidemiology Practice [GEP] and Good Pharmacovigilance Practice [GVP]) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	207737 (EPI-FLU-056 VS EU)
Date of protocol	Final Version 1: 24 May 2018
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Investigator name _____

Signature _____

Date _____

Name, function and title of the Studienleiter _____

Signature _____

Date _____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut, 89
B-1330 Rixensart - Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

Protocol Amendment 1 Rationale

Amendment number: 1
Rationale/background for changes: The protocol has been amended to respond to comments from the concerned Ethical Review Boards. In addition, the interim analysis section has been updated to remove the analysis planned for end October 2018, due to the expectation that the majority of subject recruitment may commence from mid-October 2018, rather than initially planned (01-OCT-2018). The list of abbreviations and the reference list have been revised in alignment with the other changes. Grammatical and typographical errors have been corrected.

SYNOPSIS

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
Objectives	**Primary** • 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 adverse drug reaction (ADR) cards. **Secondary** • 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).
Rationale for the study	The European Medicines Agency (EMA) has released guidance on enhanced safety surveillance for seasonal influenza vaccines in the European Union (EU), replacing the annual evaluation of safety and immunogenicity of seasonal influenza vaccines in small scale clinical trials since 2015. This guidance sets out new standards for surveillance that all Marketing Authorisation Holders (MAHs) of 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 risk. This study is designed to comply with the EMA guidance and aims to assess adverse events of interest (AEIs) experienced within 7 days post vaccination with GSK's quadrivalent seasonal influenza vaccine (*AlphaRix Tetra* in Belgium; *Influsplit Tetra* in Germany, *Fluarix Tetra* in Spain; referred to as *GSK's quadrivalent seasonal influenza vaccine* later in the text). This study may help to inform decisions regarding future influenza vaccine safety surveillance for influenza vaccines in Europe.

Study design

- Type of design: multi-country, multicentre, prospective, passive enhanced safety surveillance (ESS) study
- This is a Targeted Safety Study (TSS)
- 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
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Sampling schedule: Not applicable
- Primary completion Date (PCD): PCD is defined as the date of final collection of data for all primary outcomes
- End of Study (EoS): Last Subject Last Visit
- Duration of the study: The study is anticipated to run from 01 October 2018 to 15 January 2019. 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. The target sample size is approximately 1,000 vaccinated subjects to be reached before 31 December 2018. 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.
  - Epoch 001: Prospective data collection starting at Visit 1 (Day 1) and ending at Visit 2 (Day 8 or when the ADR card is returned by mail) for all subjects who have previously been vaccinated against influenza in preceding seasons or aged ≥9 years at the time of vaccination, or ending at Visit 4 (Day 36 or when the last ADR card is returned by mail) for children aged <9 years who have not previously been vaccinated against influenza in preceding seasons). Subjects will have up to 14 days post vaccination to return their ADR card (at the next study visit or by mail).

Synopsis Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min/Max)	Epochs
Prospective	Approximately 1000	6 months and above	Epoch 001

Discussion of study design

The study is a passive enhanced safety surveillance aiming to collect prospectively AEIs and/or other AEs experienced within 7 days post vaccination with GSK's quadrivalent seasonal influenza vaccine, using customized Adverse Drug Reaction cards. Data will be collected via the healthcare professionals (HCP) who administer the seasonal influenza vaccination.

After written informed consent/informed assent is obtained from the subject/subject's parent(s)/Legally Acceptable Representative (LAR), an ADR card will be distributed to the enrolled subjects/subjects' parent(s)/LAR who will be asked to complete the card and return this to the HCP (or a member of his/her team) either in person at the next scheduled visit or by mail. Upon return, the card information will be entered into a database using eCRF.

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

Number of subjects

Approximately 1000 vaccinees receiving GSK's quadrivalent seasonal influenza vaccine will be enrolled in this study in Belgium, Germany and Spain.

Endpoints

Primary

- 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).

Secondary

- 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).

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AEI	Adverse Event of Interest
CDC	***Centers for Disease Control and Prevention***
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EoS	End of Study
ESS	Enhanced Safety Surveillance
EU	European Union
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
LAR	Legally Acceptable Representative
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary Completion Date
RSE	Relative Standard Error
SAE	Serious Adverse Event
SDR	Source Document Review
SDV	Source Document Verification
SPM	Study Procedures Manual
TSS	Targeted Safety Study
WHO	***World Health Organization***

GLOSSARY OF TERMS

Adverse event (AE):	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorisation, either made at the time of product approval or during the lifecycle of the approved product.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
End of Study (EoS): **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV

Enhanced safety surveillance (ESS) for influenza vaccination:	The main objective of enhanced safety surveillance (ESS) is for influenza vaccination to detect a potential increase in reactogenicity and allergic events that is intrinsic to the product (i.e., not due to a specific batch deviation or local programmatic issue) in near real-time in the earliest vaccinated cohorts. Three options are envisaged for enhanced surveillance as per EMA guidance: 1. Active surveillance; 2. Passive surveillance; 3. Data mining or other use of electronic health record data.
Epoch:	An epoch is a set of consecutive time points or a single time point from a single protocol. Epochs are defined to support a main purpose which either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the time points included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, immunogenicity follow-up, safety follow-up, ESFU, follow-up.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 10.3 for details on criteria for evaluability).
Interventional Human Subject Research:	Studies in which participants are administered medical care, medicinal products and/or medical/scientific procedures as described in a research protocol.
International Organization for Standardization (ISO) week:	The ISO week date system is a system that is part of the ISO 8601 date and time standard issued by the International Organization for Standardization week which specifies numeric representations of date and time. This standard notation helps to avoid confusion in international communication caused by the many different national notations and increases the portability of computer user interfaces.
Legally acceptable representative (LAR): **(The terms legal representative or legally authorized representative are used in some settings)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the trial.

Primary completion date (PCD):	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial/ pharmaco-epidemiological study was concluded according to the pre-specified protocol or was terminated.
Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study (TSS):	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines/products will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
AlphaRix Tetra™ (Belgium) Influsplit Tetra™ (Germany) Fluarix Tetra™ (Spain)	Quadrivalent Seasonal Influenza vaccine

1. INTRODUCTION

Influenza is an acute, highly contagious, respiratory disease caused by influenza viruses, mainly spread through respiratory droplets. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and even death.

Influenza is a major public health burden. It is responsible for 50 million disease episodes and 15,000 to 70,000 deaths in the EU/EEA each year, although with considerable variation from season to season [Uhart, 2016] and by methodology used [Nicoll, 2012]. Influenza occurs in annual epidemics that are associated with significant morbidity and mortality and have substantial public health impact, in particular in the elderly and in children younger than one year of age [Zhou, 2012]. In the US, approximately 9.2 to 60.8 million people contract influenza annually, resulting in an average of 140,000 to 710,000 hospitalisations and 12,000 to 56,000 deaths [CDC, 2016a].

Annual influenza vaccination is the most effective measure to reduce the risk of influenza infection and its complications [Foppa, 2015]. During the 2015-2016 influenza season, CDC estimated that the overall influenza vaccination coverage among all people ≥6 months of age was 45.6%. It prevented almost 5 million influenza illnesses, 2.5 million medical visits to health providers, 71,000 hospitalizations, and 3,000 deaths [CDC, 2016b]. However, due to frequent genetic and antigenic changes in influenza viruses, seasonal vaccines are frequently reformulated with updated viral strains based on annual World Health Organization (WHO) recommendations [WHO, 2018]. Therefore, there is a need for constant benefit-risk monitoring of these vaccines.

The European Medicines Agency (EMA) has released guidance on enhanced safety surveillance for seasonal influenza vaccines in the European Union (EU) [EMA, 2014; EMA, 2016], replacing the annual evaluation of safety and immunogenicity of seasonal influenza vaccines in small scale clinical trials since 2015. This guidance sets out new standards for surveillance that all Marketing Authorisation Holders (MAHs) of 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 risk.

This study is designed to comply with the EMA guidance and aims to assess adverse events of interest (AEIs) experienced within 7 days post vaccination with GSK's quadrivalent seasonal influenza vaccine (*AlphaRix Tetra* in Belgium; *Influsplit Tetra* in Germany, *Fluarix Tetra* in Spain; referred to as *GSK's quadrivalent seasonal influenza vaccine* later in the text).

Of note GSK's quadrivalent seasonal influenza vaccine is indicated for active immunisation of adults and children from 6 months of age for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine. The use of GSK's quadrivalent seasonal vaccines should be based on official recommendations. Immunisation should be carried out by intramuscular injection. Annual revaccination with the current vaccine is

recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus might change from year to year. The vaccine is recommended for a single dose except for children aged <9 years, who have not previously been vaccinated against influenza, for whom a second dose should be given after an interval of at least 4 weeks.

This study may help to inform decisions regarding future influenza vaccine safety surveillance for influenza vaccines in Europe.

2. BENEFIT : RISK ASSESSMENT

The EPI-FLU-056 study does not involve administration of an investigational product and does ***not*** imply random allocation of vaccination to enrolled subjects. Subjects will be receiving their vaccination as per routine care prior to enrolment in the study, which is a passive enhanced safety surveillance aiming to collect prospectively AEIs and/or other AEs (see APPENDIX C) experienced within 7 days post vaccination with GSK's quadrivalent seasonal influenza vaccine, using customized Adverse Drug Reaction cards (see APPENDIX A).

Please refer to the current reference safety information and/or prescribing information for the summary of potential risks and benefits of GSK's quadrivalent seasonal influenza vaccine.

Although vaccination itself is not part of the protocol, for general information, the following section outlines the risk assessment and mitigation strategy per the EU risk management plan:

2.1. Risk Assessment

Important Potential Risks	Data/Rationale for Risk	Mitigation Strategy
Anaphylaxis	Anaphylaxis can occur at any age, with the highest age-specific rates observed in the 0-19 year group (70 cases per 100,000 person-years). Anaphylaxis following immunisation is serious but rare; the estimated incidences are in the range of 1-10 per 1 million doses distributed depending on the vaccine distributed [Ruggeberg, 2007].	The investigator/prescribers are advised of possible anaphylaxis following GSK's quadrivalent seasonal influenza vaccine administration by information included in product labels.

Important Potential Risks	Data/Rationale for Risk	Mitigation Strategy
Febrile seizure	In April 2010, there was a reported increase in febrile convulsion following influenza vaccination in young children in Western Australia. Following extensive investigations into this safety issue, epidemiological analyses determined that administration of the 2010 seasonal influenza vaccines, Fluvax® and Fluvax Junior® (manufactured by Bio CSL), was associated with an increased risk of febrile convulsions, however, the risk has not been confirmed for other influenza vaccines, including GSK's quadrivalent seasonal influenza vaccine.	As with other vaccines, vaccination with GSK's quadrivalent seasonal influenza vaccine should be postponed in subjects suffering from an acute febrile illness; fever is also listed as an adverse reaction.
Guillain-Barré syndrome (GBS)	A few cases of GBS have been reported to GSK. Most published studies investigating GBS suggest incidence estimates between 0.84 and 1.91 per 100,000 persons per year. To date, a total of 29 published studies investigating GBS have been carried out in ten European countries. The majority of studies (21/29) provided an incidence estimate that fell between 1.0 and 2.0 per 100,000 persons per year. [McGrogan, 2009].	None: GBS is listed as rare adverse reaction in the label. There is no known prevention for GBS.
Bell's palsy	The annual incidence of Bell's palsy is 15 to 30 per 100,000 people. The peak incidence occurs between the second and fourth decades (15 to 45 years). 10% of patients experience one or more recurrences [Greco, 2012]. Bell's palsy has been reported in people who had intranasal influenza vaccine. A link between Bell's palsy and seasonal influenza vaccine that are given by intramuscular injection has not been established.	None

Important Potential Risks	Data/Rationale for Risk	Mitigation Strategy
Narcolepsy	Several epidemiological studies have reported an increased risk of narcolepsy in subjects who received GSK's pandemic vaccine, Pandemrix™ H1N1. Although H1N1pdm09 strain has been included in Flu D-QIV, there is no clinical evidence of increased risk of narcolepsy for GSK seasonal vaccines, including Flu D-QIV.	None
Injection site haemorrhage in individuals with thrombocytopenia or any other coagulation disorder	Injection site haemorrhage may occur at the injection site in populations at increased risk of haemorrhage, such as those with thrombocytopenia or acquired/hereditary coagulation disorders.	The investigator/prescribers are advised of possible injection site haemorrhage in individuals with thrombocytopenia or any coagulation disorder following GSK's quadrivalent seasonal influenza vaccine administration by information included in product labels

There are no inherent risks noted for subjects as a direct result of participating in this study.

2.2. Benefit Assessment

By receiving GSK's quadrivalent seasonal influenza vaccine as part of their standard medical care, the subject may have the benefit of being protected against seasonal influenza.

2.3. Overall Benefit:Risk Assessment

The decision to receive GSK quadrivalent seasonal influenza vaccine is made between the healthcare professional (HCP) and the subject, weighing the potential benefits and risks as part of standard medical care.

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 adverse drug reaction (ADR) cards.

Refer to Section 10.1.1 for the definition of the primary endpoints.

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).

Refer to Section 10.1.2 for the definition of the secondary endpoints.

4. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 7), are essential and required for study conduct.

- Type of design: multi-country, multicentre, prospective, passive enhanced safety surveillance (ESS) study
- This is a Targeted Safety Study (TSS)
- 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
- Biological samples: Not applicable
- Sampling schedule: Not applicable
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Primary completion Date (PCD): PCD is defined as the date of final collection of data for all primary outcomes

  Refer to glossary of terms for the definition of PCD.
- End of Study (EoS): Last Subject Last Visit

  Refer to glossary of terms for the definition of EoS.
- Duration of the study: The study is anticipated to run from 01 October 2018 to 15 January 2019. 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. The target sample size is approximately 1,000 vaccinated subjects to be reached before 31 December 2018. 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.

– Epoch 001: Prospective data collection starting at Visit 1 (Day 1) and ending at Visit 2 (Day 8 or when the ADR card is returned by mail) for all subjects who have previously been vaccinated against influenza in preceding seasons or aged ≥9 years at the time of vaccination, or ending at Visit 4 (Day 36 or when the last ADR card is returned by mail) for children aged <9 years who have not previously been vaccinated against influenza in preceding seasons). Subjects will have up to 14 days post vaccination to return their ADR card (at the next study visit or by mail).

Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min/Max)	Epochs
Prospective	Approximately 1000	6 months and above	Epoch 001

4.1. Discussion of Study Design

The study is a passive enhanced safety surveillance aiming to collect prospectively AEIs and/or other AEs (see APPENDIX C) experienced within 7 days post vaccination with GSK's quadrivalent seasonal influenza vaccine, using customized Adverse Drug Reaction cards (see APPENDIX A). Data will be collected via the HCP or study medical staff who administer the seasonal influenza vaccination or who provide the ***informed*** consent form and the ADR cards.

After written informed consent/informed assent is obtained from the subject/subject's parent(s)/Legally Acceptable Representative (LAR), an ADR card will be distributed to the enrolled subjects/subjects' parent(s)/LAR who will be asked to complete the card and return this to the HCP (or a member of his/her team) either in person at the next scheduled visit or by mail. Upon return, the card information will be entered into a database using eCRF.

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

5. STUDY POPULATION

5.1. Number of Subjects/Centres

Approximately 1000 vaccinees receiving GSK's quadrivalent seasonal influenza vaccine will be enrolled in this study in Belgium, Germany and Spain.

The number of study subjects (n = 1000) is expected to enable detection of very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100) AEIs and/or other AEs.

Refer to Section 10.2 for the additional details of the criteria used in the estimation of sample size.

5.2. Inclusion Criteria for Enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity and regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The objective of the study is to cover all age ranges as per GSK's quadrivalent vaccine indication. However, due to feasibility constraints, Belgium and Germany will only recruit subjects 18 years of age and above (German participating sites will target essentially older adults [subjects aged from 50 years onwards]). Spain will target subjects between 6 months and 65 years of age at the time of the vaccination.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., complete the ADR card, return for the next scheduled visit or return the ADR card by mail within a timely manner).
- A male or female subject vaccinated with GSK's quadrivalent seasonal influenza vaccine (one or two dose schedule) according to the routine medical practices between 01 October 2018 and 31 December 2018.
- Subjects aged 6 months or above at the time of the vaccination ***according to the countries' specificities***.
- Written informed consent/informed assent obtained from the subjects/subjects' parent(s)/Legally Acceptable Representative(s) (LARs).

5.3. Exclusion Criteria for Enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity and regulatory acceptability of the study. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criterion should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care

  Please refer to the glossary of terms for the definition of child in care.

6. CONDUCT OF THE STUDY

6.1. Regulatory and Ethical Considerations, including the Informed Consent Process

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), Good Epidemiology Practice (GEP), Good Pharmacovigilance Practice (GVP), or other applicable guidelines, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study prior to a site initiating the study in that country or will document that neither a favourable opinion nor an approval to conduct the study is needed.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject/ subject's parent(s)/LAR(s) informed consent and subject informed assent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK Biologicals will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/thumb printed informed consent must be obtained from each subject and/or each subject's parent(s)/LAR(s) or the impartial witness and subject informed assent, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the applicable ICH GCP or other applicable guidelines and GSK Biologicals required elements. While it is strongly recommended that this model ICF be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, a subject who can only be enrolled in the study with the consent of his/her parent(s) or LAR (e.g., minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her parent or LAR. It should be assessed whether an assent is required depending on the age of the study population and the local requirements.

GSK Biologicals strongly recommends that if the subject reaches the age of consent during the study they will be asked to provide consent at the next study visit (if applicable). This procedure should be applied according to local laws and regulations.

The investigator has the final responsibility for the final presentation of the ICF and IAF, respecting the mandatory requirements of local regulations. The ICF and IAF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

7. DETAILED STUDY PROCEDURES

7.1. Subject Identification

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

7.2. General Study Aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

7.3. Outline of the Study Procedures

Table 2 List of study procedures

Epoch	Prospective data collection			
Visit number	**Visit 1**	**Visit 2**	**Visit 3 #**	**Visit 4 #**
Time points	**Day 1**	**Day 8**	**Day 29**	**Day 36**
Type of contact	Study visit	Study visit or mailing*	Study visit	Study visit or mailing*
Country	Belgium, Germany, and Spain	Belgium, Germany, and Spain	Spain	Spain
Informed consent	●			
Check inclusion criteria	●			
Check exclusion criteria	●			
Collect demographic data	●			
Collect "at risk" status as per HCP assessment	●			
Record the vaccination data for GSK's quadrivalent seasonal influenza vaccine	●		●	
Check and record co-administered vaccination	●		●	
Distribute ADR cards	O		O	
Train subject/subject's parent (or LAR) to complete ADR cards	O		O	
Subject/subject's parent (or LAR) records post-vaccination AEIs and/or other AEs occurring within 7 days post vaccination	●	●	●	●
Subject/subject's parent (or LAR) returns ADR cards *		O		O
Investigator or delegate transcribes data from ADR cards into the eCRF		●		●
Record of vaccine-related SAEs occurring within 7 days post vaccination	●	●	●	●
Study conclusion		●##		●

ADR card: adverse drug reaction card; AE: adverse event; AEI: adverse event of interest; eCRF: electronic case report form; HCP: healthcare professional; LAR: legally acceptable representative; SAE: serious adverse event

● is used to indicate a study procedure that requires documentation in the individual eCRF

○ is used to indicate a study procedure that does not require documentation in the individual eCRF

Only applicable for children aged <9 years who have not previously been vaccinated against influenza in preceding seasons and to whom a second dose should be given after an interval of at least 4 weeks and within the study period (see Table 3), and if the second dose of influenza vaccine is GSK's quadrivalent seasonal influenza vaccine.

Not applicable for children aged <9 years if they follow the recommendations of a 2-dose schedule with 4 weeks interval.

* Subject/subject's parent (or LAR) returns ADR cards either in person during a study visit or by mail, to the HCP (or a member of his/her team)

Whenever possible, the investigator should arrange study visits within the optimal intervals and no later than the allowed intervals (Table 3).

Table 3 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Visit 1 (Day 1) → Visit 2 (Day 8)	7 days	7 days – 14 days
Visit 1 (Day 1) → Visit 3 # (Day 29)	28 days	28 days – 42 days
Visit 3 # (Day 29) → Visit 4 # (Day 36)	7 days	7 days – 14 days

Only applicable for children aged <9 years who have not previously been vaccinated against influenza in preceding seasons and to whom a second dose should be given after an interval of at least 4 weeks and within the study period, and if the second dose of influenza vaccine is GSK's quadrivalent seasonal influenza vaccine.

7.4. Detailed Description of Study Procedures

7.4.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject/subject's parent(s)/LAR(s) must be obtained before study participation. The signed informed assent of a subject below the age of consent (i.e., minor) should be obtained in addition to the signed informed consent by his/her parent(s)/LAR(s) according to local rules and regulations. Refer to Section 6.1 for the requirements on how to obtain informed consent and assent, as appropriate.

7.4.2. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 5.2 and 5.3 before enrolment.

7.4.3. Collect demographic data

Record demographic data (including month and year of birth, gender and race) in the subject's eCRF.

7.4.4. Collect "at risk status"

Record the "risk status" (i.e., at risk/not at risk) for influenza-associated morbidity and mortality as per HCP assessment in the subject's eCRF.

The risk status should be defined 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

7.4.5. Record vaccination data for GSK's quadrivalent seasonal influenza vaccine

Record in the subject's eCRF information on seasonal influenza vaccine, such as the date of administration and the batch number.

7.4.6. Check and record co-administered vaccination

Co-administered vaccination administered on the same day as the subject's GSK's quadrivalent seasonal influenza vaccine must be recorded in the eCRF.

7.4.7. ADR cards

Customized ADR cards will be used to collect the AEIs and/or other AEs within 7 days post each vaccination (i.e., the day of vaccination and the following 6 days). After written informed consent/informed assent is obtained from the subject/the subject' parent(s)/LAR, the ADR cards will be provided to the subjects/subjects' parent'(s)/LAR on the day of vaccination. The subjects/subjects' parent'(s)/LAR 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 HCP at the next study visit or by mail. The investigator or delegate will transcribe the collected information into the eCRF database.

Note: ADR cards can be filled in by a minor subject under the supervision of the subject's parent(s)/LAR(s) provided that the minor has the competence to assess and report the information to be provided on the ADR cards. The ultimate accountability for the completion of the ADR cards remains with the subject's parent(s)/LAR(s). The investigator should discuss this accountability with the subject's parent(s)/LAR(s).

7.4.8. Study conclusion

The investigator will:

- Review all the data collected to ensure accuracy and completeness.
- Complete the Study Conclusion screen in the eCRF.

7.5. Biological Sample Handling and Analysis

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE of specific interest or an SAE as provided in this protocol.

Each subject/subject's parent(s)/ LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious/of concern or indicating a change in their health status.

8.1. Safety Definitions

8.1.1. Definition of an adverse event

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

8.1.2. Definition of a serious adverse event

An SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of an existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting.

   Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an SAE.

d. Results in disability/incapacity,

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

or

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Adverse events of specific interest

AEs that comprise the primary interest of the study are designated as AEIs. Please refer to APPENDIX C for the pre-defined list of AEIs.

8.2. Reporting of SAEs and Other Events

It will be clearly communicated to participating HCPs that the study does not replace reporting of AEs/SAEs that should occur as part of routine practice as specified by local regulations. It is not the intention of the surveillance to influence or change the usual local reporting processes. HCPs should continue to report any AEs/SAEs they would typically report using the mechanisms routinely used in their healthcare practice. Therefore, although the data collected for this study is primarily safety-related data, reporting mechanisms of AEs to regulatory authorities should not be altered and are to continue according to local standards.

If the participating HCP becomes aware of an SAE experienced by a study participant occurring within 7 days post vaccination that is deemed to be related to GSK's quadrivalent seasonal influenza vaccine according to the judgement of the HCP, the SAE should be reported to GSK within 24 hours of becoming of aware using the eCRF. This will be linked to the central safety database (Argus) with a study ID link mechanism therefore it is not necessary to report separately to central safety (GSK Biologicals Clinical Safety & Pharmacovigilance, e-mail: PPD using the GSK reporting forms) unless there are issues with access to the eCRF preventing the electronic reporting of the SAE within the required timeframe. If GSK deems additional information is necessary, request ***for*** additional information will be sent to the HCP.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject Completion

A subject who returns for the concluding visit foreseen in the protocol or has returned the completed ADR card is considered to have completed the study.

9.2. Subject Withdrawal

A subject who does not return for the concluding visit foreseen in the protocol or has not returned the completed ADR card will be considered a withdrawal from the study. If the subject informs the Investigator of the reason for withdrawal from the study, the reason for this will be entered into the electronic Case Report Form as detailed below:

- ***Seasonal influenza vaccine-related Serious Adverse Event***
- ***Protocol Violation (to be specified)***
- ***Consent withdrawal, not due to an adverse event (to be specified if the information is available)***
- ***Not willing/not able to participate in the visit***
- ***Migrated/moved from the study area***
- ***Lost to follow-up***
- ***Sponsor study termination***
- ***Other (please specify)***

10. STATISTICAL METHODS

10.1. Endpoints

10.1.1. 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).

10.1.2. 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).

10.2. Determination of Sample Size

Approximately 1000 subjects will be enrolled in this study.

Table 4 shows the probability to observe at least one AE, the exact 95% Confidence Intervals (CIs) for the percentage of vaccinated subjects with the AE and Relative Standard Error (RSE) for a range of scenarios in term of number of vaccinated subjects and true percentage of vaccinated subjects with the AE:

- With an overall sample size of 1000 vaccinated subjects (whole study period, all countries) and a true percentage of vaccinated subjects with the AE ranging from 1% to 10%, the corresponding probability to observe at least one vaccinated subject with the AE is >99% and the RSE ranges from 9.5% to 31.5%.
- With an overall sample size of 75 vaccinated subjects (by week, all countries) and a true percentage of vaccinated subjects with the AE ranging from 1% to 10%, the corresponding probability to observe at least one vaccinated subject with the AE ranges from 52.9% to >99% and the RSE ranges from 34.6% to 114.9%.

Table 5 shows the evolution by week of the cumulative probability to observe at least one AE, the exact 95% CI for the cumulative percentage of vaccinated subjects with the AE and RSE in the course of the study for an overall sample size of 1000 (all countries) and 333 (by country) vaccinated subjects and a true percentage of vaccinated subjects with the AE of 1%.

Table 4 Probability to observe at least one AE, exact 95% Confidence Intervals and Relative Standard Error according to number of vaccinated subjects and true percentage of vaccinated subjects with the AE

Number of vaccinated subjects	True percentage of vaccinated subjects with the AE (%)	Probability§ to observe ≥1 vaccinated subject with the AE (%)	Number of vaccinated subjects with the AE	Exact 95% CI* on the percentage of vaccinated subjects with the AE		Associated relative standard error (%)
				Lower Limit	Upper limit	
1500 (whole study period, all countries)	10	>99	150	8.53	11.63	7.7
	8	>99	120	6.68	9.49	8.8
	6	>99	90	4.85	7.32	10.2
	4	>99	60	3.07	5.12	12.6
	2	>99	30	1.35	2.84	18.1
	1	>99	15	0.56	1.64	25.7
	0.5	>99	7.5	0.21	1.00	36.4
	0.1	77.7	1.5	0.01	0.43	81.6
1000 (whole study period, all countries)	10	>99	100	8.21	12.03	9.5
	8	>99	80	6.39	9.86	10.7
	6	>99	60	4.61	7.66	12.5
	4	>99	40	2.87	5.41	15.5
	2	>99	20	1.23	3.07	22.1
	1	>99	10	0.48	1.83	31.5
	0.5	>99	5	0.16	1.16	44.6
	0.1	63.2	1	0.00	0.56	99.9
75 (per week, all countries)	10	>99	7.5	4.27	19.12	34.6
	8	>99	6	2.99	16.60	39.2
	6	99.0	4.5	1.83	13.99	45.7
	4	95.3	3	0.83	11.25	56.6
	2	78.0	1.5	0.14	8.28	80.8
	1	52.9	0.75	0.01	6.65	114.9
500 (whole study period, by country)	10	>99	50	7.51	12.97	13.4
	8	>99	40	5.78	10.73	15.2
	6	>99	30	4.08	8.45	17.7
	4	>99	20	2.46	6.11	21.9
	2	>99	10	0.96	3.65	31.3
	1	>99	5	0.33	2.32	44.5
	0.5	91.8	2.5	0.08	1.59	63.1
	0.1	39.4	0.5	0.00	0.93	141.4
333 (whole study period, by country)	10	>99	33.3	7.00	13.74	16.4
	8	>99	26.6	5.32	11.45	18.6
	6	>99	20	3.70	9.12	21.7
	4	>99	13.3	2.17	6.70	26.8
	2	>99	6.7	0.79	4.15	38.4
	1	96.5	3.3	0.23	2.76	54.5
	0.5	81.2	1.7	0.04	1.99	77.3
	0.1	28.3	0.3	0.00	1.30	173.2
25 (per week, by country)	10	92.8	2.5	1.70	28.67	60.0
	8	87.6	2	0.98	26.03	67.8
	6	78.7	1.5	0.44	23.27	79.2
	4	64.0	1	0.10	20.35	98.0

Number of vaccinated subjects	True percentage of vaccinated subjects with the AE (%)	Probability§ to observe ≥1 vaccinated subject with the AE (%)	Number of vaccinated subjects with the AE	Exact 95% CI* on the percentage of vaccinated subjects with the AE		Associated relative standard error (%)
				Lower Limit	Upper limit	
	2	39.7	0.5	0.00	17.21	140.0
	1	22.2	0.25	0.00	15.52	199.0

§ Binomial distribution
* [Clopper, 1934]

Table 5 Cumulative probability to observe at least one AE, exact 95% Confidence Intervals and Relative Standard Error by week for a true percentage of subjects with the AE of 1%

Number of vaccinated subjects	ISO weeks	Cumulative number of vaccinated subjects	Cumulative probability§ to observe ≥1 vaccinated subject with the AE (%)	Cumulative number of vaccinated subjects with the AE	Average percentage of vaccinated subjects with the AE (%)	Exact 95% CI* on the cumulative percentage of vaccinated subjects with the AE		Associated relative standard error (%)
						Lower Limit	Upper limit	
1000 (whole study period, all countries)	40-40	75	52.9	0	1.00	0.00	4.80	114.9
	40-41	150	77.9	1	1.00	0.02	3.66	81.2
	40-42	225	89.6	2	1.00	0.11	3.17	66.3
	40-43	300	95.1	3	1.00	0.21	2.89	57.4
	40-44	375	97.7	3	1.00	0.17	2.32	51.4
	40-45	450	98.9	4	1.00	0.24	2.26	46.9
	40-46	525	>99	5	1.00	0.31	2.21	43.4
	40-47	600	>99	6	1.00	0.37	2.16	40.6
	40-48	675	>99	6	1.00	0.33	1.92	38.3
	40-49	750	>99	7	1.00	0.38	1.91	36.3
	40-50	825	>99	8	1.00	0.42	1.90	34.6
	40-51	900	>99	9	1.00	0.46	1.89	33.2
	40-52	1000	>99	10	1.00	0.48	1.83	31.5
333 (whole study period, by country)	40-40	25	22.2	0	1.00	0.00	13.72	199.0
	40-41	50	39.5	0	1.00	0.00	7.11	140.7
	40-42	75	52.9	0	1.00	0.00	4.80	114.9
	40-43	100	63.4	1	1.00	0.03	5.45	99.5
	40-44	125	71.5	1	1.00	0.02	4.38	89.0
	40-45	150	77.9	1	1.00	0.02	3.66	81.2
	40-46	175	82.8	1	1.00	0.01	3.14	75.2
	40-47	200	86.6	2	1.00	0.12	3.57	70.4
	40-48	225	89.6	2	1.00	0.11	3.18	66.3
	40-49	250	91.9	2	1.00	0.10	2.86	62.9
	40-50	275	93.7	2	1.00	0.09	2.61	60.0
	40-51	300	95.1	3	1.00	0.21	2.89	57.4
	40-52	333	96.5	3	1.00	0.19	2.61	54.5

§ Binomial distribution
* [Clopper, 1934]

10.3. Sets for Analyses

10.3.1. Enrolled Set

The Enrolled Set will include all subjects with informed consent signed.

10.3.2. Exposed Set

The Exposed Set will include all enrolled subjects who are vaccinated with GSK's quadrivalent seasonal influenza vaccine.

10.3.3. Safety Set

The Safety Set will include all subjects from the Exposed Set who received the ADR card.

10.3.4. Solicited Safety Set

The Solicited Safety Set will include all subjects from the Safety Set who returned the ADR card.

10.4. Derived and Transformed Data

Demography:

- For a given subject and a given demographic variable, missing measurements will not be imputed.
- Age at the vaccination will be computed as the difference between the vaccination date and the date of birth. The age will be expressed in years.

Safety:

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

10.5. Analysis of Demographics

The number of subjects included in each analysis set will be tabulated by ISO week (expected ISO weeks 40 to 52), overall and by country.

Demographic characteristics (age at study vaccination in years, gender, race) and risk status will be summarised overall and by country using descriptive statistics for each analysis set:

- Frequency tables 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.

10.6. Analysis of Primary Objective

The primary 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 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 (ISO weeks 40 to 52) will be estimated by MedDRA Preferred Term, overall and by country, as follows:

- The denominator will be the number of subjects ***from the Safety Set*** 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 will be computed on all estimated percentages. The method for estimating the CIs will be described in the statistical analysis plan.

10.7. Analysis of Secondary Objectives

The primary 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 Preferred Term, overall and by country, as follows:

- The denominator will be the number of subjects ***from the Safety Set*** vaccinated with GSK's quadrivalent seasonal influenza vaccine during the week of interest (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 System Organ Class classification, will be estimated in each country and overall, 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 will be computed on all estimated percentages. The method for estimating the CIs will be described in the statistical analysis plan.

10.8. Other Analyses

The GSK's quadrivalent seasonal influenza vaccine batch numbers administered during the study vaccination period will be tabulated by ISO week, overall and by country, on the Exposed Set.

The percentage of subjects who returned the ADR card will be tabulated by centre, country and overall on the Safety Set.

As a sensitivity analysis, the analysis of AEIs and/or other AEs reported using ADR cards will also be performed on the Solicited Safety Set.

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

The percentage of subjects who received co-administered vaccination on the same day as their GSK's quadrivalent seasonal influenza vaccine will be tabulated by GSK's quadrivalent seasonal influenza vaccine dose, overall and by country.

10.9. Interpretation of Analyses

All analyses will be descriptive.

10.10. Conduct of Analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.10.1. Sequence of analyses

Three interim analyses and a final analysis will be performed.

- The ***first*** interim analysis will be performed by mid-November 2018
- The ***second*** interim analysis will be performed by end-November 2018
- The ***third*** interim analysis will be performed by mid-December 2018
- The final analysis will be performed when all data up to the end of the study will be available and cleaned

10.10.2. 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 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 study vaccination in years, gender, race) will be summarised using descriptive statistics.
- 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 Preferred Term, with 95% CI.

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

No study report will be written for the interim analyses.

11. ADMINISTRATIVE MATTERS

To comply with ICH Guideline for GCP or other applicable guidelines (such as GEP and GVP) administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, ownership and publications must be met.

Anticipated study milestones are presented below. Any changes to those initial milestones will be reported in the study report:

Milestone	*Planned date*	*Actual date**	*Comments*
Approval by Ethics Committees	*28 September 2018*	*24 August 2018*	*Approval of the protocol*
First subject enrolled	*01 October 2018*	*N/A*	*First visit anticipated*
Last subject enrolled	*15 January 2019*	*N/A*	*Last visit anticipated*
Database Freeze	*22 March 2019*	*N/A*	*None*
Completion of Statistical Analysis	*19 April 2019*	*N/A*	*None*
Final Report of Main Study Results	*06 June 2019*	*N/A*	*None*

to be completed at the date of the final study report

11.1. Case Report Form/Electronic Case Report Form Instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

Once the database is archived and the clinical study report is complete and approved by all parties, each participating investigator will be provided with a CD-ROM of the final version of the data generated at his/her investigational site.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV)/Source Document Review (SDR) per Risk Based Monitoring Plan. By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g., audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to ***30*** years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality Assurance

To ensure compliance with GCP, GEP, GVP, or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of Information on Publicly Available Registers and Publication Policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations.

11.6. Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK Biologicals site or other mutually-agreed location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

12. COUNTRY SPECIFIC REQUIREMENTS

There are no country-specific requirements for Belgium or Spain and one for Germany related to gender distribution.

Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP ORDER)

The EPI-FLU-056 study does not involve administration of an investigational product. GSK's quadrivalent seasonal influenza vaccine is approved for active immunization of persons aged 6 months and older for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine and will be administered according to routine medical practice prior to subject's enrolment in the study. As per inclusion criteria, both females and males are eligible to be part of the study with no specific restrictions associated with gender. The objective of the study is to assess AEIs or other AEs experienced within 7 days post vaccination regardless of gender.

There is no intent to analyse the safety of GSK's quadrivalent seasonal influenza vaccine by gender which implies that the potential relationship between the gender distribution and the safety outcomes will not be under scrutiny in this enhanced safety surveillance.

13. REFERENCES

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Foppa B, Po-Yung C, Reynolds S. et al. Deaths averted by influenza vaccination in the U.S. during the seasons2005/06 through 2013/14. Vaccine. 2015; 33(26): 3003-9.

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Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations Associated With Influenza and Respiratory Syncytial Virus in the United States, 1993–2008. Clin Infect Dis. 2012; 54: 1427–36.

APPENDIX A ADR Card

GlaxoSmithKline

Version 6 – 24 May 2018

CONFIDENTIAL Subject Number: | | | | | - | | | |

Enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccine

This surveillance is designed to capture adverse events following immunisation.
Please report if you get any adverse event experienced following your influenza (flu) vaccination.

1. About you / About the person vaccinated

Date of Birth __ / ____ (mm/yyyy) ☐ **Male** ☐ **Female**

2. When/where the flu vaccine was administered?

What date were you vaccinated / was the vaccine given? ___ /____ /2018

Who administered the vaccine? a Healthcare Professional: ☐ **Yes** ☐ **No**

If no, please say who administered the vaccine : _____

3. Please report any symptoms/conditions in the 7 days after the flu vaccine (i.e., the day of vaccination and the following 6 days)

Please look at the list of possible adverse events following vaccination on the next page.

Please tick the box and indicate the start date for any adverse event you/the person vaccinated experienced.

Please return the card in the envelope provided to your healthcare professional or study medical staff.
Please return by post or in person.

Thank you for your help

4. If there were no symptoms experienced in the 7 days after vaccination (i.e., the day of vaccination and the following 6 days), tick and return

☐ **I have NOT/the person vaccinated has NOT experienced any adverse event following vaccination:**

Please return the card in the envelope provided to your healthcare professional or study medical staff.
Please return by post or in person.

Thank you for your help

Formal study name:
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
GSK study abbreviation:
EPI-FLU 056 VS EU

Contact:
XXXXX

CONFIDENTIAL Subject Number: ☐☐☐☐-☐☐☐☐

Enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccine

Symptoms or reactions you experienced in the 7 days (i.e., the day of vaccination and the following 6 days) after your influenza vaccination	Please tick if you experienced the symptom	Start date of the symptom dd/mm/yyyy
Irritated or red eyes	☐	__/___/___
Runny nose	☐	__/___/___
Blocked nose	☐	__/___/___
Nose bleed	☐	__/___/___
Common cold	☐	__/___/___
Cough	☐	__/___/___
Sore throat	☐	__/___/___
Hoarse voice	☐	__/___/___
Wheezing	☐	__/___/___
Loss of appetite	☐	__/___/___
Nausea – feeling sick to your stomach	☐	__/___/___
Vomiting – being sick to your stomach	☐	__/___/___
Diarrhoea	☐	__/___/___
Fever (temperature >38°C)	☐	__/___/___
Allergic reaction (rash, itchy skin and/or eyes, runny nose)	☐	__/___/___
Severe allergic reaction (Rash, difficulty breathing, dizziness, fast heart rate, swelling of lips/tongue)	☐	__/___/___
Swelling of the face	☐	__/___/___
Rash in a restricted part of the body	☐	__/___/___
Rash all over body	☐	__/___/___
Feeling irritable	☐	__/___/___
Feeling tired	☐	__/___/___
Headache	☐	__/___/___
Shivering or feeling shaky	☐	__/___/___
Seizure / fits	☐	__/___/___
Muscle aches	☐	__/___/___
Joint pain	☐	__/___/___
Redness around injection site	☐	__/___/___
Swelling around injection site	☐	__/___/___
Pain at the injection site	☐	__/___/___
Other 1. _____ 2. _____ 3. _____	☐ ☐ ☐	__/___/___ __/___/___ __/___/___

APPENDIX B 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

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R & D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	207737 (EPI-FLU-056 VS EU)
Amendment number:	Amendment 1
Amendment date:	11 September 2018
Co-ordinating author:	PPD 4Clinics Belgium for GSK Biologicals'
Rationale/background for changes: The protocol has been amended to respond to comments from the concerned Ethical Review Boards. In addition, the interim analysis section has been updated to remove the analysis planned for end October 2018, due to the expectation that the majority of subject recruitment may commence from mid-October 2018, rather than initially planned (01-OCT-2018). The list of abbreviations and the reference list have been revised in alignment with the other changes. Grammatical and typographical errors have been corrected.	

Amended text has been included in *bold italics* in the body of the protocol. The amended text (in *bold italics*) and the deleted text (in ~~strikethrough~~) are provided below:

Contributing authors

- PPD Epidemiologist
- PPD Clinical Epidemiology Project Lead
- PPD ***VP Head of Clinical R&D***
- PPD Project Statistician
- PPD Lead Statistician
- PPD h, Study Delivery Lead
- PPD Clinical Safety representative
- PPD Clinical Safety representative
- PPD Regulatory Affairs representative
- PPD Oversight Data Manager
- ~~PPD Study Data Manager~~
- PPD Study Data Manager

LIST OF ABBREVIATIONS

CDC	*Centers for Disease Control and Prevention*
WHO	*World Health Organization*

1. INTRODUCTION

Influenza is an acute, highly contagious, respiratory disease caused by influenza viruses, mainly spread through respiratory droplets. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and even death.

Influenza is a major public health burden. It is responsible for 50 million disease episodes and 15,000 to 70,000 deaths in the EU/EEA each year, although with considerable variation from season to season [Uhart, 2016] and by methodology used [Nicoll, 2012]. Influenza occurs in annual epidemics that are associated with significant morbidity and mortality and have substantial public health impact, in particular in the elderly and in children younger than one year of age [Zhou, 2012]. In the US, approximately 9.2 to 60.8 million people contract influenza annually, resulting in an average of 140,000 to 710,000 hospitalisations and 12,000 to 56,000 deaths [CDC, 2016a].

Annual influenza vaccination is the most effective measure to reduce the risk of influenza infection and its complications [Foppa, 2015]. During the 2015-2016 influenza season, CDC estimated that the overall influenza vaccination coverage among all people ≥6 months of age was 45.6%. It prevented almost 5 million influenza illnesses, 2.5 million medical visits to health providers, 71,000 hospitalizations, and 3,000 deaths [CDC, 2016b]. However, due to frequent genetic and antigenic changes in influenza viruses, seasonal vaccines are frequently reformulated with updated viral strains based on annual World Health Organization (WHO) recommendations [WHO, 2018]. Therefore, there is a need for constant benefit-risk monitoring of these vaccines.

[…]

Of note GSK's quadrivalent seasonal influenza vaccine is indicated for active immunisation of adults and children from 6 months of age for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine. The use of GSK's quadrivalent seasonal vaccines should be based on official recommendations. Immunisation should be carried out by intramuscular injection. Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus might change from year to year. The vaccine is recommended for a single dose except for children aged <9 years, who have not previously been vaccinated against influenza, for whom a second dose should be given after an interval of at least 4 weeks.

2. Benefit : Risk Assessment

The EPI-FLU-056 study does not involve administration of an investigational product and does ***not*** imply random allocation of vaccination to enrolled subjects.

4.1 Discussion of Study Design

Data will be collected via the HCP or study medical staff who administer the seasonal influenza vaccination or who provide the ~~inform~~ ***informed*** consent form and the ADR cards.

5.2 Inclusion Critera for Enrolment

The objective of the study is to cover all age ranges as per GSK's quadrivalent vaccine indication. However, due to feasibility constraints, Belgium and Germany will only recruit subjects 18 years of age and above (German participating sites will target essentially older adults [subjects aged from 50 years onwards]). Spain will target subjects between 6 months and 65 years of age at the time of the vaccination.

All subjects must satisfy ALL the following criteria at study entry:

[…]

- Subjects aged 6 months or above at the time of the vaccination ***according to the countries' specificities***

8.2 Reporting of SAEs and Other Events

If GSK deems additional information is necessary, request ~~of~~ ***for*** additional information will be sent to the HCP.

9.2 Subject Withdrawal

A subject who does not return for the concluding visit foreseen in the protocol or has not returned the completed ADR card will be considered a withdrawal from the study. If the subject informs the Investigator of the reason for withdrawal from the study, the reason for this will be entered into the electronic Case Report Form as detailed below:

- ***Seasonal influenza vaccine-related Serious Adverse Event***
- ***Protocol Violation (to be specified)***
- ***Consent withdrawal, not due to an adverse event (to be specified if the information is available)***
- ***Not willing/not able to participate in the visit***
- ***Migrated/moved from the study area***
- ***Lost to follow-up***
- ***Sponsor study termination***
- ***Other (please specify)***

10.6 Analysis of Primary Objective

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 (ISO weeks 40 to 52) will be estimated by MedDRA Preferred Term, overall and by country, as follows:

- The denominator will be the number of subjects ***from the Safety Set*** 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.

10.7 Analysis of Secondary Objectives

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 Preferred Term, overall and by country, as follows:

- The denominator will be the number of subjects ***from the Safety Set*** vaccinated with GSK's quadrivalent seasonal influenza vaccine during the week of interest (ISO weeks 40 to 52), in a given country or for all countries.

10.10.1 Sequence of analyses

~~Four~~ ***Three*** interim analyses and a final analysis will be performed.

- ~~The first interim analysis will be performed by end-October 2018.~~
- The ~~second~~ ***first*** interim analysis will be performed by mid-November 2018
- The ~~third~~ **second** interim analysis will be performed by end-November 2018
- The ~~fourth~~ ***third*** interim analysis will be performed by mid-December 2018
- The final analysis will be performed when all data up to the end of the study will be available and cleaned

11. ADMINISTRATIVE MATTERS

Anticipated study milestones are presented below. Any changes to those initial milestones will be reported in the study report:

Milestone	*Planned date*	*Actual date**	*Comments*
Approval by Ethics Committees	*28 September 2018*	*24 August 2018*	*Approval of the protocol*
First subject enrolled	*01 October 2018*	*N/A*	*First visit anticipated*
Last subject enrolled	*15 January 2019*	*N/A*	*Last visit anticipated*
Database Freeze	*22 March 2019*	*N/A*	*None*
Completion of Statistical Analysis	*19 April 2019*	*N/A*	*None*
Final Report of Main Study Results	*06 June 2019*	*N/A*	*None*

to be completed at the date of the final study report

11.3. Record Retention

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to ~~15~~ ***30*** years.

13. REFERENCES

Centers for Disease Control and Prevention (CDC). Estimated influenza illnesses, medical visits, hospitalizations, and deaths averted by influenza vaccination in the United States. 2016a. Available at: https://wwwcdcgov/flu/about/disease/2015-16htm.

Centers for Disease Control and Prevention (CDC). Laboratory-Confirmed Influenza Hospitalizations. 2016b. Available at: gis.cdc.gov/GRASP/Fluview/FluHospRates.html.

Nicoll A, Ciancio BC, Lopez Chavarrias V, et al. Influenza-related deaths--available methods for estimating numbers and detecting patterns for seasonal and pandemic influenza in Europe. Euro Surveill. 2012 May 3;17(18).

Foppa B, Po-Yung C, Reynolds S. et al. Deaths averted by influenza vaccination in the U.S. during the seasons2005/06 through 2013/14. Vaccine. 2015; 33(26): 3003-9.

Uhart M, Bricout H, Clay E, et al. Public health and economic impact of seasonal influenza vaccination with quadrivalent influenza vaccines compared to trivalent influenza vaccines in Europe. Hum Vaccin Immunother. 2016; 12:2259–68.

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Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations Associated With Influenza and Respiratory Syncytial Virus in the United States, 1993–2008. Clin Infect Dis. 2012; 54: 1427–36.

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207737 (EPI-FLU-056 VS EU)
Date of protocol	Final Version 1: 24 May 2018
Date of protocol amendment	Amendment 1 Final: 11 September 2018
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
Sponsor signatory	Jacqueline Miller, VP Head of Clinical R&D

Signature PPD

Date 12 Sep 2018

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