Study Protocol
Sponsor:
GlaxoSmithKline Vaccines
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Marketed Product Name	GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra*.
eTrack study number and Abbreviated Title	204687 [EPI FLU-050 VS KR PMS]
Date of protocol	Final: 29 July 2015
Date of protocol amendments/administrative change	Amendment 1 Final: 06 Apr 2016 Amendment 2 (Only for RMP) Final: 31 May 2017 Administrative Change 1 Final: 30 Jul 2018 ***Amendment 3 Final: 08 Mar 2019***
Title	Assessment of safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra* when administered according to the approved Prescribing Information in Korea.
Detailed Title	A prospective, observational, multi-center, drug use investigation to monitor the safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra* when administered according to the approved Prescribing Information in Korea.
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GSK Vaccines' protocol template for observational studies and interventional studies without administration of medicinal products as described in a research protocol based on Protocol Document Standard version 13.2

Protocol *Amendment 3* Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204687 [EPI FLU-050 VS KR PMS]
Date of *protocol amendment*	***Amendment 3 Final: 08 Mar 2019***
Detailed Title	A prospective, observational, multi-center, drug use investigation to monitor the safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra* when administered according to the approved Prescribing Information in Korea.
Sponsor signatory ***(Amendment 3: 08 Mar 2019)***	***Bach-Yen Nguyen*** ***Clinical and Epidemiology Project Lead, Flu and Preparedness Activities*** ***Clinical R & D*** ***U.S. Vaccine Research and Development Center***
Signature	_____
Date	_____

Protocol *Amendment 3* Rationale

Amendment* number:** ***Amendment 3
Rationale/background for changes:
• ***Editorial changes*** • ***Changes as per MFDS Request*** – ***Describe statistical processing method in "10.5.2. Safety Analysis"*** – ***Correct typo errors on Research Subject Inclusion Criteria Table in "4.2. Inclusion Criteria" (ONLY applicable in Korean protocol)*** • ***Clarification of ADR analysis to be consistent with planned AEs and SAEs analysis***

Protocol *Amendment 3* Physician Agreement

I agree:

- To conduct the Drug Use Investigation in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other Drug Use Investigation conduct procedures and/or Drug Use Investigation conduct documents provided by GlaxoSmithKline Vaccines (GSK Vaccines).
- To assume responsibility for the proper conduct of the Drug Use Investigation at this site.
- That I am aware of, and will comply with applicable ethical practices and regulatory requirements.
- To ensure that all persons assisting me with the Drug Use Investigation are adequately informed about *Fluarix Tetra* and Drug Use Investigation-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) (at sites that do not have IRB oversight, before they can implement changes to the protocol, they need prior agreement of the sponsor), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the Drug Use Investigation).
- To co-operate with a representative of GSK Vaccines in the monitoring process of the Drug Use Investigation 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 physician's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Vaccines will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Vaccines 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 Drug Use Investigation and for one year following completion of the Drug Use Investigation.
- Agree that GSK Vaccines may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Vaccines with an updated Curriculum Vitae and other documents required by regulatory agencies for this Drug Use Investigation.

eTrack study number and Abbreviated Title	204687 [EPI FLU-050 VS KR PMS]
Date of *protocol amendment*	***Amendment 3 Final: 08 Mar 2019***
Detailed Title	A prospective, observational, multi-center, drug use investigation to monitor the safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra* when administered according to the approved Prescribing Information in Korea.

Physician name _____

Signature _____

Date _____

SYNOPSIS

Detailed Title	A prospective, observational, multi-center, drug use investigation to monitor the safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, Fluarix Tetra when administered according to the approved Prescribing Information in Korea.
Rationale for the Drug Use Investigation	GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, Fluarix Tetra was registered in Korea in December 2014 indicated for 3 years and above. As per MFDS requirements, this drug use investigation (as a part of PMS) is being conducted to collect safety information on the use of Fluarix Tetra over a 6 years period. In order to meet the MFDS's requirement requesting that at least 600 subjects are followed after Fluarix Tetra administration, according to the approved PI in Korea, around 720 adults and children from three years of age are intended to be enrolled in order to collect safety information within 21 days (Day 0 to Day 20) post vaccination. In addition to the extension of an age indication to include 6 to 35 months of age for Fluarix Tetra, additional drug use investigation for new age group is being conducted to collect safety information on the use of Fluarix Tetra for 4 years according to the MFDS requirement. Almost 720 children aged 6 to 35 months will be enrolled in order to collect safety information within 21 days (Day 0 to Day 20) post vaccination.
Objective	To assess the safety of GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, *Fluarix Tetra*, in terms of frequency and intensity of AEs and SAEs when administered according to the local PI in adults and children from 6 months of age in Korea.
Study design ***(Amendment 3: 08 Mar 2019)***	**Drug use investigation design**: A prospective, observational, non-comparative, multi-center study in Korea. **Vaccination schedule**: Vaccination as per locally approved PI (which is not part of the drug use investigation): to adults and previously vaccinated children aged ≥6 months, a single 0.5 ml dose of *Fluarix Tetra* will be administered. To previously unvaccinated children aged 6 months to <9 years, two doses will be administered with a second 0.5 ml dose at least 4 weeks apart from the first one as per the local PI in Korea. **Safety monitoring**:

- Recording of all AEs during the 21 days (Day 0 to Day 20) using diary cards after *Fluarix Tetra* is administered.
- ***Recording of all ADRs reported during the 21 days (Day 0 to Day 20) follow-up period after administration of Fluarix Tetra***
- Recording of SAEs from the date of vaccination until 21 days (Day 0 to Day 20) after *Fluarix Tetra* is administered during the subject's participation in the study.

Blood Samples: No blood samples will be collected in this drug use investigation.

All subjects who receive at least one dose of the *Fluarix Tetra* and can be evaluated for whether the subject experienced an AE will be included in the **safety population**. For each subject, this drug use investigation will include a single or two visits and a follow-up contact 21 days (Day 0 to Day 20) after each vaccination with *Fluarix Tetra*.

Pregnant subjects who receive *Fluarix Tetra* or subjects who become pregnant within 21 days after vaccination with *Fluarix Tetra* will be followed to determine the outcome of the pregnancy, if possible. At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to GSK, if possible. Generally, follow-up should be no longer than 6 to 8 weeks following the estimated delivery date, if possible.

Duration of the drug use investigation:

- 6 years (for children 36 months and above and adults).

- 4 years (for children from 6 to 35 months of age)

Type of drug use investigation: Self-contained.

Data collection: Standardised hard copy CRF (SAEs, ADRs, Pregnancy information will be collected by using the SAE, ADR, Pregnancy Reporting Form).

Discussion of study design

(Amendment 3: 08 Mar 2019)

All AEs including ***ADRs and*** SAEs reported during the 21 days (Day 0 to Day 20) post-vaccination follow-up period of *Fluarix Tetra* in the drug use investigation will be collected as part of safety data in this drug use investigation. These AEs will be further classified by GSK at the time of statistical analyses as expected/unexpected based on the current PI.

Number of subjects	According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, max 1440 subjects (720 vaccinees ≥ 3 years old and above and 720 vaccinees between 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly
Endpoints	**Occurrence of AEs** during the 21 days (Day 0 to Day 20) follow-up period after vaccination. **Occurrence of SAEs** starting from the date of vaccination in the drug use investigation up to 21 days (Day 0 to Day 20) after vaccination of the subject in the drug use investigation.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CP	Concept Protocol
CRF	Case Report Form
EDD	Estimated Delivery Date
EPI	Expanded Program on Immunization
GEP	Good Epidemiological Practice
GSK	GlaxoSmithKline
IAF	Informed Assent Form
ICF	Informed Consent Form
IM	Intramuscular
IRB	Institutional Review Board
IU	International Units
KIDS	Korean Institute of Drug Safety & Risk Management
LAR	Legally Acceptable Representative
LOC	Local Operating Company
LSC	Local Study Contact
LSLV	Last Subject's Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
PI	Prescribing Information
PMS	Post Marketing Surveillance
PT	Preferred Term

QIV	Quadrivalent Influenza Vaccine
SAE	Serious adverse event
SDV	Source Document Verification
VCSP	Vaccines' Central Safety and Pharmacovigilance

GLOSSARY OF TERMS

Adverse drug reaction:	Adverse drug reaction represents adverse, unintended reactions from normal administration/use of the pharmaceuticals, etc. for which the causal relationship with the particular pharmaceutical cannot be excluded. Of the voluntarily reported adverse events, those with no known causal relationship with the pharmaceutical are deemed to be adverse drug reactions.
Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Drug use investigation (study):	Company sponsored pharmaco-epidemiological studies or surveys carried out in accordance with the terms of the marketing authorization and conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol.
Expected adverse event:	An adverse event that is expected from the subject during the post-vaccination follow-up period as described in the locally approved Prescribing Information.
Subject:	An individual who has been contacted in order to participate or participates in the drug use investigation.
Unexpected adverse event:	Any adverse event reported in addition to those expected during the drug use investigation. Adverse events that are not reflected in the approved Prescribing Information.

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 and/or medications will be written without the superscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Fluarix Tetra	GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra*.

1. INTRODUCTION

1.1. Background

Vaccination is currently the most effective means of controlling the impact of influenza in populations at risk (elderly and children). Influenza viruses circulate in humans virtually every winter in temperate regions of both hemispheres and throughout the year in tropical regions.
Currently, the strategy is to use a trivalent influenza vaccine which contains two A strains (H1N1 and H3N2) and one B strain. Since 1983, two evolutionarily distinct strains of influenza B virus coexist in the human population and since 1988 both strains are circulating in various countries worldwide [Barr, 2006]. In five of the last eight years, more influenza cases were due to the mismatched B virus than to H1N1 virus [CDC, 2010].
Data in literature suggest that children, without appropriate immunologic priming, vaccinated with a vaccine containing the recommended B-strain might not be protected against an infection with the co-circulating strain from the other B-lineage. Indeed, in a study on non-immunized (unprimed) infants, no cross-reactive antibodies were found in the sera [Levandowski, 1991].
As the two evolutionarily distinct strains of influenza B virus co-circulate and as cross-reactivity between those two lineages is low and even almost non-existing in an unprimed population, an additional B-strain antigen in the seasonal vaccine may offer a better protection [Englund, 2006; Levandowski, 1991].
GSK Vaccines has developed a QIV which contains two A-strains and two B-strains. The drug use investigation was designed to evaluate the safety of the QIV in adults and children from 6 months of age in Korea.

1.2. Rationale for the study

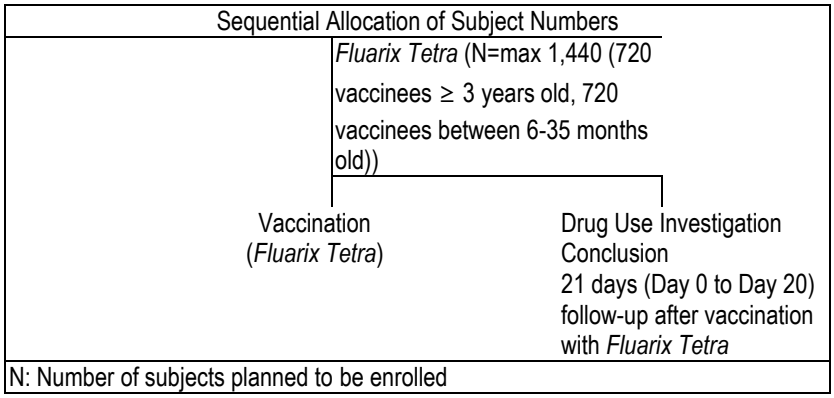
GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, *Fluarix Tetra* was registered in Korea in December 2014. As per MFDS requirements, this drug use investigation (as part of PMS) is being conducted to collect safety information on the use of *Fluarix Tetra* over a 6 years period. In order to meet the MFDS's requirement requesting that at least 600 subjects to be followed after *Fluarix Tetra* administration, according to the approved PI in Korea, around 720 adults and children from three years of age are intended to be enrolled in order to collect safety information within 21 days (Day 0 to Day 20) post vaccination.
In addition to the extension of an age indication to include 6 to 35 months of age for Fluarix Tetra, additional drug use investigation for new age group is being conducted to collect safety information on the use of *Fluarix* Tetra for 4 years according to the MFDS requirement. Almost 720 children aged 6 to 35 months will be enrolled in order to collect safety information within 21 days (Day 0 to Day 20) post vaccination.

2. OBJECTIVE

- To assess the safety of GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, *Fluarix Tetra*, in terms of frequency and intensity of AEs and SAEs when administered according to the local PI in adults and children from six months of age in Korea.

Refer to Section 10.1 for the definition of the endpoints (AE and SAE).

3. STUDY DESIGN OVERVIEW



Drug use investigation conclusion will depend on the 21 days contact of the subject in the drug use investigation. Definition of Conclusion of drug use investigation for a subject: A subject who is available for the concluding follow-up contact 21 days (Day 0 to Day 20) after receiving *Fluarix Tetra* is considered to have completed the drug use investigation.

- Drug use investigation design: A prospective, observational, non-comparative, multi-center study in Korea.
- Vaccination schedule: Vaccination as per locally approved PI (which is not part of the drug use investigation): to adults and previously vaccinated children aged ≥6 months, a single 0.5 ml dose of *Fluarix Tetra* will be administered. To previously unvaccinated children aged 6 months to <9 years, two doses will be administered with a second 0.5 ml dose at least 4 weeks apart from the first one as per the local PI in Korea.

Fluarix Tetra may be administered to pregnant women/lactating women as per PI, if there is a clear need. Pregnancy outcome (whether full-term or premature, information on the status of the mother and child) in vaccinated pregnant subjects will be followed-up at 6-8 weeks after delivery, if possible.

Note:

- Vaccination with *Fluarix Tetra* is not part of the drug use investigation.
- Signature of the subject/subject's parent(s)/LAR(s) on the ICF/IAF signify enrolment of the subject into the drug use investigation. The ICF/IAF is for the collection and handling of safety information and not for the vaccination procedure.

- Administration of vaccines included in the EPI and other licensed vaccines are allowed in this drug use investigation regardless of the time of administration.

- Safety monitoring:
  - Recording of all AEs during the 21 days (Day 0 to Day 20) using diary cards after *Fluarix Tetra* is administered.
  - The participating physician will transcribe the collected information into the CRF in English.
  - ***Recording of all ADRs reported during the 21 days (Day 0 to Day 20) follow-up period after administration of Fluarix Tetra***
  - Recording of SAEs from the date of vaccination until 21 days (Day 0 to Day 20) after *Fluarix Tetra* is administered during the subject's participation in the study.
  - All AEs , ADRs and SAEs starting immediately following administration of *Fluarix Tetra* must be recorded onto the CRF and all ADRs and SAEs must be reported using the ADR reporting form and SAE reporting form, the latter to be sent to GSK according to the required timelines, irrespective of intensity or whether or not they are considered vaccination-related.
  - Parents of children aged 6 months to <12 years wil be contacted to provide details of any AEs experienced by the children 21 days after the children receives the vaccination.
  - Subjects for whom diary card transcription into CRF will be done through phone contact are considered to have completed the drug use investigation.
- Blood Samples: No blood samples will be collected in this drug use investigation.
- All subjects who receive at least one dose of the *Fluarix Tetra* and can be evaluated for whether the subject experienced an AE will be included in the safety population. For each subject, this drug use investigation will include a single or two visits and a follow-up contact 21 days (Day 0 to Day 20) after each vaccination with *Fluarix Tetra*.
- Pregnant subjects who receive *Fluarix Tetra* or subjects who become pregnant within 21 days after vaccination with *Fluarix Tetra* will be followed to determine the outcome of the pregnancy, if possible. At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to GSK, if possible. Generally, follow-up should be no longer than 6 to 8 weeks following the EDD, if possible.
- Duration of the drug use investigation:

  - 6 years (for children 36 months and above and adults).

  - 4 years (for children from 6 to 35 months of age)
- Type of drug use investigation: Self-contained.

- Data collection: Standardised hard copy CRF (SAEs, ADRs, Pregnancy information will be collected by using the SAE, ADR, Pregnancy Reporting Form).

3.1. Discussion of study design

All AEs including SAEs reported during the 21 days (Day 0 to Day 20) post-vaccination follow-up period of *Fluarix Tetra* in the drug use investigation will be collected as part of safety data in this drug use investigation. These AEs will be further classified by GSK at the time of statistical analyses as expected/unexpected based on the current PI.

4. DRUG USE INVESTIGATION COHORT

4.1. Number of subjects/centers

According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, max 1440 subjects (720 vaccinees ≥ 3 years old and above and 720 vaccinees between 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly.

4.1.1. Recruitment at study centers

- This prospective, observational drug use investigation will be conducted at multiple centers (mainly in hospitals and private clinics) in Korea.
- Study population: Subjects aged ≥6 months who receive *Fluarix Tetra* as a part of routine practice at a private clinic or hospital. Only subjects to whom *Fluarix Tetra* is administered in routine clinical practice will be invited to participate in the drug use investigation.
- Eligible subjects will join the drug use investigation after the ICF/IAF has been signed by the subject/subject's parent(s)/LAR(s).
- The drug use investigation is required to be conducted in at least one hospital with IRB oversight in order for the drug use investigation to be conducted in private clinics with no IRB.
- The vaccine will be purchased by the subject/subject's parent(s)/LAR(s).
- The recruitment will be monitored by the study monitor.

4.2. Inclusion criteria for enrolment

All subjects must satisfy the following criteria at drug use investigation entry:

- Male or female subjects who were vaccinated with *Fluarix Tetra* or eligible to receive *Fluarix Tetra* according to the locally approved PI.

  Note: According to current approved PI, the subjects below are included.

Subjects	1st dose	Follow-up contact after 21 days	2nd dose	Follow-up contact after 21 days
Primed	●	●		
Unprimed [1]	●	●	●	●
Unprimed [2]	●	●		
Unprimed with history of *Fluarix Tetra* [3]			●	●

- Primed: adults and previously vaccinated children aged ≥6 months
- Unprimed: previously unvaccinated children aged 6 months to <9 years

[1] Unprimed children who participate in the drug use investigation following the administration of both doses of *Fluarix Tetra*

[2] Unprimed children who participate in the drug use investigation following the administration of the first dose of *Fluarix Tetra*

[3] Unprimed children who participate in the drug use investigation following the administration of the second dose of *Fluarix Tetra*

- 2nd dose would be given at least 4 weeks after the 1st dose.

- Signed informed consent as ICF/IAF obtained from the subject/subject's parent(s)/LAR(s).

4.3. Exclusion criteria for enrolment

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

- Those who are not eligible for vaccination with *Fluarix Tetra* according to the local PI.
  - Hypersensitivity reaction to *Fluarix Tetra*
  - History of hypersensitivity reaction to Influenza vaccine
  - History of Guillain-Barre syndrome or other nervous abnormalities to Influenza vaccine within 6 weeks post-vaccination
- Those who are not eligible for vaccination with *Fluarix Tetra* according to the medical judgement of physician.

5. SELECTION OF STUDY CENTERS AND PHYSICIANS

5.1. Selection of study centers

Study centers will be selected among the hospitals and private clinics where *Fluarix Tetra* is used, which can fully achieve the following conditions:

- Centers that are securing equipment, facilities and manpower capable of fully achieving the purpose of the study

- Centers that are securing physicians who have expertise in the *Fluarix Tetra* and influenza, have received training necessary for performance of the study, or have practical experience
- Centers that can handle subject's personal information to keep them confidential
- Centers that can give support to enable the physician to be familiar with the notification and protocol

5.2. Selection of physicians

Physicians will be selected, who can fully achieve the following conditions:

- Physicians who have expertise in the *Fluarix Tetra* and influenza, have received training necessary for performance of the study, or have practical experience
- Physicians who can be familiar with and follow the notification and protocol

6. CONDUCT OF THE STUDY

6.1. Regulatory and ethical considerations, including the informed consent process

The drug use investigation will be conducted according to the local rules and regulations of the country (MFDS).

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. When submission to the local regulatory authority is required, the timing of the submission relative to IRB submission or approval and whether or not the authority will provide their approval of or favourable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

IRB approval has to be obtained prior to drug use investigation start. If the regulatory authority and/or IRB advise that drug use investigation studies do not need ethical review this must be documented. In any event, submission to an IRB in all institutions where IRB are available must be carried out and documented.

6.2. Subject identification

Subject numbers will be assigned sequentially to subjects who consent/whose parent(s)/LAR(s) consent to allow their children to participate in the drug use investigation, according to the range of subject numbers allocated to each study center.

6.3. General study aspects

6.3.1. Description, dosage/administration of *Fluarix Tetra*

6.3.1.1. Description of *Fluarix Tetra*

Refer to the locally approved PI for information on the formulation and presentation of the *Fluarix Tetra* vaccine to be used in this drug use investigation.

6.3.1.2. Dosage and administration of *Fluarix Tetra*

The vaccine should be administered as an intramuscular injection (0.5 mL).

6.3.2. Contraindications to subsequent vaccination

Refer to the approved product label/package insert.

6.3.3. Warnings and precautions

Refer to the approved product label/package insert.

6.3.4. Concomitant medication/vaccination

All concomitant medications/vaccinations according to local practice are allowed during the drug use investigation and administration of these should be documented in the CRF.

At each drug use investigation visit/contact, the physician should question the subject/ subject's parent(s)/LAR(s) about any medication taken and vaccination received by the subject.

All concomitant medications/vaccinations, with the exception of vitamins and/or dietary supplements, are to be recorded in the CRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

A prophylactic medication is a medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥37.5 °C (99.5 °F) on oral/axillary/ tympanic setting].

Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the CRF concomitant medication section and in the SAE report form, as applicable. Refer to Section 7.1.3 for the definition of a SAE.

6.3.4.1. Time window for recording concomitant medication/vaccination in the CRF

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at any time during the period starting with the administration of *Fluarix Tetra* and ending 21 days (Day 0 to Day 20) after vaccination must be recorded in the CRF.

Any vaccine not foreseen in the drug use investigation protocol administered in the period beginning 21 days (Day -20 to Day 0) preceding the dose of *Fluarix Tetra* and ending 21 days (Day 0 to Day 20) after the dose of *Fluarix Tetra* must be recorded in the CRF.

Any investigational medication or vaccine administered throughout the drug use investigation (i.e. from 21 days before the first dose of the vaccine and 21 days after administration of the dose of the vaccine) must be recorded in the CRF.

6.4. Outline of study procedures

Table 1 presents the list of drug use investigation procedures.

Table 1 List of study procedures

Type of contact	Enrolment **	Follow-up contact 21 days after vaccination **
Informed consent [1]	●	
Check inclusion/exclusion criteria	●	
Demographic data	●	
Medical history	●	
Vaccination history *	●	
Physical examination	●	
Pre-vaccination body temperature	●	
Record vaccination information	●	
Distribution of diary cards	○	
Record AEs within 21 days (Day 0 to Day 20) post-vaccination, by physician	●	●
Return of diary cards [a]		○
Diary card transcription by physician		●
Record concomitant medication/vaccination	●	●
Reporting of ADRs	●	●
Reporting of SAEs	●	●
Drug use investigation conclusion		●

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

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

[1] Informed consent for participation into the drug use investigation can be taken after vaccination. The vaccination procedure is not part of the drug use investigation.

* Vaccination history is influenza vaccine history within the three previous seasons.
[a] The subject/subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the physician or phone or mail, to report any AEs/ADRs/SAEs during the 21 days (Day 0 to Day 20) using diary cards after *Fluarix Tetra* is administered.
** Subjects who are pregnant and receive *Fluarix Tetra* or subjects who become pregnant within 21 days after receiving *Fluarix Tetra* should report to/notify GSK, if possible. Pregnancy outcome in vaccinated pregnant subjects will be followed-up at 6-8 weeks after delivery, if possible.

6.5. Detailed description of study procedures

6.5.1. Procedures prior to study participation

6.5.1.1. Informed consent

The ICF/IAF for this drug use investigation is for the collection and handling of personal and safety information after vaccination with *Fluarix Tetra*. Diary cards will be used to collect safety information and for SDV. The ICF/IAF for this drug use investigation will not include consent for vaccination as vaccination is at the discretion of the subject/subject's parent(s)/LAR(s) and the physician. Informed consent may be taken after the vaccination. Parent(s)/LAR(s) who agree to have their eligible children participate in this drug use investigation will return the diary card to physician and accept a telephone interview from physicians for collection of safety information. Information collected will be treated confidentially and for the purpose of reporting SAE(s) to KIDS, and for public disclosure, if required.

Before performing any other study procedure, the signed informed consent as ICF/IAF of the subject/subject's parent(s)/LAR(s) must be obtained.

6.5.2. Procedures related to vaccination and outside the drug use investigation

6.5.2.1. Contraindications, warnings, and precautions to vaccination

Contraindications, warnings, and precautions to vaccination are to be checked at the beginning of each vaccination visit (see Sections 6.3.2 and 6.3.3).

6.5.2.2. Pre-vaccination body temperature

The body (oral, axillary or tympanic) temperature of all subjects needs to be measured prior to *Fluarix Tetra* administration. The preferred route for recording temperature in this drug use investigation will be oral/axillary/tympanic depending on the age of enrolled vaccinees. . If the subject has fever [fever is defined as temperature ≥37.5 °C (99.5 °F) on oral, axillary or tympanic setting on the day of vaccination, the vaccination visit will be rescheduled.

6.5.2.3. Vaccination

- After completing the prerequisite procedures prior to vaccination, *Fluarix Tetra* will be administered according to the PI (refer to Section 6.3.1.2 for description of the vaccine administration procedure). If the physician or delegate determines that the

subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

- The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of *Fluarix Tetra*.

6.5.3. Procedures during the study

6.5.3.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

6.5.3.2. Demographic data

Record demographic data such as age, height, weight, gender, and ethnicity in the subject's CRF.

6.5.3.3. Medical history

Perform a history-directed medical examination and record any significant pre-existing conditions or signs and/or symptoms present judged by physicians in a subject prior to the start of the drug use investigation in the CRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this drug use investigation or by referral to an appropriate health care provider.

6.5.3.4. Vaccination history

Influenza vaccine history within the three previous seasons must be recorded in the CRF. And collect information regarding all vaccines not foreseen in the protocol administered to the subject 21 days (Day -20 to Day 0) prior to vaccination with *Fluarix Tetra*.

6.5.3.5. Physical examination

Perform a physical examination of the subject. Collected information needs to be recorded in the CRF.

6.5.3.6. Reproductive history (Only for Pregnant Subjects)

Once the physician becomes aware of a pregnancy, the reproductive history of the pregnant subject will be collected and recorded in the CRF.

6.5.3.7. Record concomitant medication/vaccination

Concomitant medication/vaccination must be recorded in the CRF (see Section 6.3.4).

6.5.3.8. Distribution, return, and transcription of diary cards

The physician will provide the diary card to the subject/subject's parent(s)/LAR(s) to record e.g. medication taken until the next visit/contact. The subject/subject's

parent(s)/LAR(s) will be instructed to return the completed diary card to the physician at the next visit/contact.

- Collection and verification of the completed diary card will take place during discussion with the subject/subject's parent(s)/LAR(s) at the subsequent visit/contact. Any unreturned diary cards will be sought from the subjects through telephone call(s) or any other convenient procedure. The physician will transcribe the collected information into the CRF in English.
- Collection of pregnancy outcome information from pregnant subjects who received *Fluarix Tetra*, at 6-8 weeks after the EDD, if possible.

6.5.3.9. Record AEs, ADRs and SAEs

- The subject/subjects' parent(s)/LAR(s) will be instructed to contact the physician immediately should the subjects manifest any signs or symptoms they perceive as serious.
- Refer to Section 7.2 for procedures for the physician to record AEs, ADRs and SAEs and to Section 7.3 for guidelines on how to report these ***ADRs/SAEs*** to GSK Vaccines.
- After vaccination, diary cards will be provided to the subjects to record body (oral/ axillary/tympanic) temperature and any AEs (i.e. on the day of vaccination and during the next 20 days) occurring after vaccination. The subject/subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the physician on their next drug use investigation visit or provide details during the phone or by postal mail.

6.5.3.10. Procedures during follow-up visits/contacts for AEs/ ADRs /SAEs

Note that some of the procedures to be performed during the follow-up visits/contacts (record AEs) are described in Section ***6.5.3.6*** up to Section 6.5.3.9.

- Collection and verification of completed diary card during discussion with the subject/subject's parent(s)/LAR(s) at the subsequent visit/contact. Any unreturned diary cards will be sought from the subjects through telephone call(s) or any other convenient procedure. The physician will transcribe the collected information into the CRF in English.
- Checking for pregnancy within 21 days after *Fluarix Tetra* vaccination, if possible.

6.5.3.11. Study conclusion

The physician will review safety data collected to ensure accuracy and completeness and will complete the drug use investigation conclusion page in the CRF.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The physician or site staff is/are responsible during the drug use investigation for the detection and documentation of events meeting the criteria and definition of an AE***, ADR and*** a SAE as provided in this protocol.

Each subject/subject's parent(s)/LAR(s) will be instructed to contact the physician immediately should the subject manifests any signs or symptoms they perceive as serious.

7.1. Safety definitions

7.1.1. 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.

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.

Examples of included AE:

- Significant or unexpected worsening or exacerbation of the condition.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after *Fluarix Tetra* administration even though they may have been present prior to the start of the drug use investigation.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.

Examples of AE (DO NOT include):

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the drug use investigation that do not worsen.

NB. AEs to be recorded as expected AEs are described in Section **Error! Reference source not found.**. All other AEs will be recorded as unexpected AEs.

Example of events to be recorded in the medical history section of the CRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the drug use investigation (i.e. prior to the first study vaccination).

7.1.2. Definition of adverse drug reaction

Adverse drug reaction (ADR) represents adverse, unintended reactions from normal administration/use of the pharmaceuticals, etc. for which the causal relationship with the particular pharmaceutical cannot be excluded. Of the voluntarily reported adverse events, those with no known causal relationship with the pharmaceutical are deemed to be adverse drug reactions.

7.1.3. Definition of a serious adverse event

A SAE is any AE that:

a. Results in death.

b. Is life-threatening.

   NB: 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 existing hospitalisation.

   NB: 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 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/diagnosed prior to informed consent signature) that did not worsen from baseline is not considered an SAE.

d. Results in disability/incapacity, or

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

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.

7.1.4. *Pregnancy*

Any eligible pregnant female for whom the participating physician has decided to administer *Fluarix Tetra* vaccine may be enrolled in the drug use investigation after the subject has signed the ICF/IAF. If the participating physician becomes aware of a pregnancy during the course of the 21 days follow-up of his/her female subjects, he/she has to notify GSK using the Pregnancy Notification form within 2 weeks, if possible.

All pregnant subjects in the drug use investigation will be followed up to 6-8 weeks after delivery for outcome of pregnancy, if possible.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE, as described in Section 7.1.1 and 7.1.3, and will be followed, if possible, as described in Section 7.4.1.

7.1.5. *Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events*

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the physician to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in section 7.1.1, or of an SAE, as defined in Section 7.1.3. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the drug use investigation or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the physician as more severe than expected for the subject's condition, or that are present or detected at the start of the drug use investigation and do not worsen, will not be reported as AEs or SAEs.

The physician will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.2. Detecting and recording adverse events, adverse drug reactions, serious adverse events, and pregnancies

7.2.1. Time period for detecting and recording adverse events, adverse drug reactions serious adverse events, and pregnancies

All AEs, ADRs and SAEs starting immediately following administration of *Fluarix Tetra* must be recorded onto the CRF and all ADRs and SAEs must be reported using the ADR reporting form and SAE reporting form, the latter to be sent to GSK according to the

required timelines, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the receipt of *Fluarix Tetra* in the drug use investigation and will end 21 days following administration of *Fluarix Tetra* for each subject. See Section 7.3 for instructions on recording and reporting SAEs.

An overview of the protocol-required reporting periods for AEs, ADRs , SAEs and pregnancies is given in

Table 2.

Table 2 Reporting periods for adverse events, adverse drug reaction, serious adverse events, and pregnancies

Drug use investigation activity	Vaccination	21 days (Day 0 to Day 20) post-vaccination
Reporting of AEs (expected & unexpected)	●	●
Reporting of ADRs	●	●
Reporting of SAEs	●	●
Reporting of pregnancies *	●	●

* Subjects who are pregnant and receive *Fluarix Tetra* or subjects who become pregnant within 21 days after receiving *Fluarix Tetra* in the drug use investigation, the pregnancy outcome (whether full-term or premature, information on the status of the mother and child) of these subjects will be followed-up for 6-8 weeks after delivery, if possible.

Note: Post-vaccination AEs will be collected and reported only for *Fluarix Tetra* received under the drug use investigation procedure (after signing the ICF/IAF).

All AEs***/ADRs/SAEs*** reported within 21 days (Day 0 to Day 20) of administration of *Fluarix Tetra* within the drug use investigation need to be recorded in the CRF. These AEs/***ADRs/***SAEs will be classified as expected/unexpected at the time of statistical analyses (refer to GLOSSARY OF TERMS for definitions of expected/unexpected AEs).

Note: Assessment of causality and outcome will be performed by the physician according to the following classification. Causality will be assessed as: Certain; Probable/Likely; Possible; Not-Related; Conditional/ Unclassified; Unassessable/Unclassifiable. Outcome will be assessed as recovered; not recovered; recovering; resolved with sequelae; fatal; unknown.

7.2.2. Evaluation of adverse events, adverse drug reactions and serious adverse events

7.2.2.1. Active questioning to detect adverse events, adverse drug reactions and serious adverse events

The physician needs to collect information on any AE in the subject. At the time of analysis, an assessment on whether the AE is expected (contained in the local PI) or unexpected (not contained in the local PI) will be done by GSK.

As a consistent method of collecting safety information, the subject/subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Have you acted differently or felt different/has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?'*

When an AE/SAE occurs, it is the responsibility of the physician to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The physician will then record all relevant information regarding an AE***/ADR***/SAE on the CRF, ADR Report Form or SAE Report Form as applicable. It is not acceptable for the physician to send photocopies of the subject's medical records to GSK Vaccines instead of the appropriate completed AE/SAE pages on the CRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Vaccines. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Vaccines.

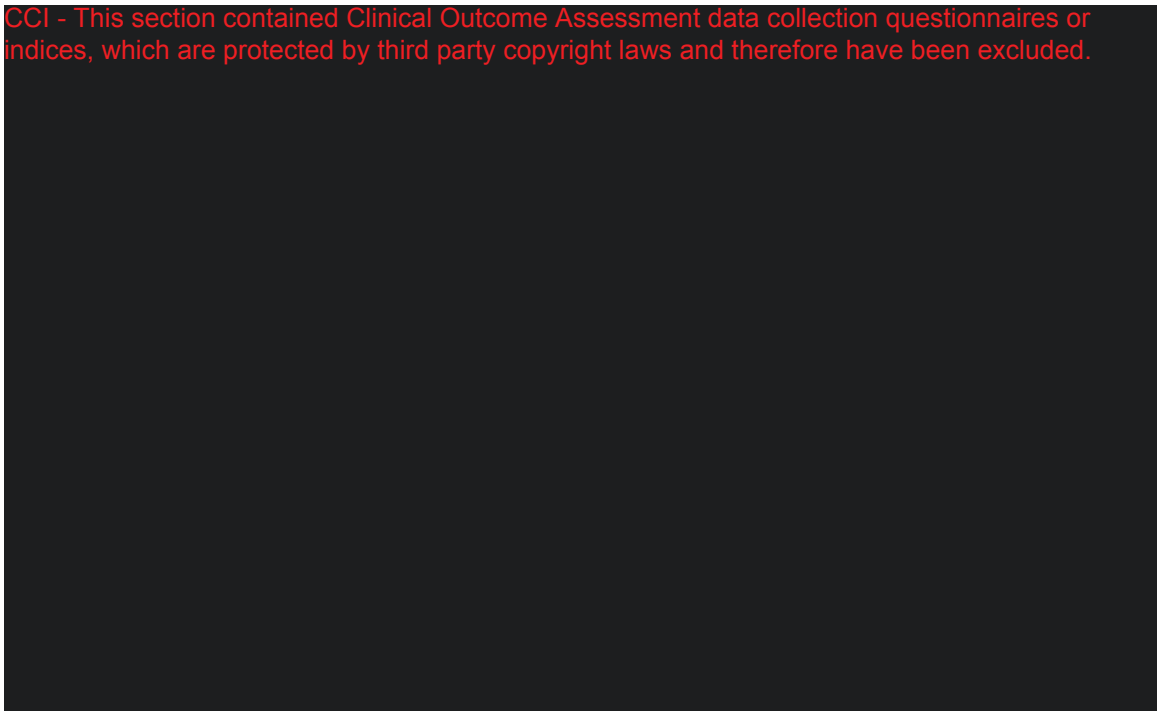
The physician will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE***/ADR***/SAE and not the individual signs/symptoms.

7.2.2.2. Assessment of intensity

Intensity of the following AEs will be assessed as described:

The physician will assess the maximum intensity that occurred over the duration of the event for all other AEs, including ***ADR and*** SAEs reported during the drug use investigation. The assessment will be based on the physician's clinical judgement.

The intensity of each AE***, ADR*** and SAE recorded in the CRF***, ADR Report form*** or SAE Report Form, as applicable, should be assigned to one of the following categories:



An AE that is assessed as Grade 3 (CCI should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 7.1.3.

7.2.2.3. Assessment of causality

The physician is obligated to assess the relationship between *Fluatrix Tetra* and the occurrence of each AE/SAE. The physician will use clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to *Fluarix Tetra* will be considered and investigated. The physician will also consult the local PI for marketed products in the determination of his/her assessment of AEs.

There may be situations when a SAE has occurred and the physician has minimal information to include in the initial report to GSK Vaccines. However, it is very important that the physician always makes an assessment of causality for every event prior to submission of the SAE to GSK Vaccines. The physician may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The physician should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

Causality of AEs should be assessed by the physician using the following question:

Is there a reasonable possibility that the AE may have been caused by *Fluarix Tetra*?

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined 'serious' (see Section 7.1.3), additional examinations/tests will be performed by the physician in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify)

NOTE: The use of the term "drug" here refers to *Fluarix Tetra*.

The relationship of the drug to an AE will be determined by the physician based on the following definitions:

1. Certain:
   - The relationship of the administration and use of the drug is reasonable and it is not able to be explained by other medication, chemical substances or concomitant disease, it shows clinically reasonable response on withdrawal of the drug, the decisive case in the pharmacological or phenomenological aspect on re-challenge of the drugs if needed.

2. Probable/Likely:
   - The temporal sequence of the administration and use of the drug is appropriate and it does not seem that it is accompanied by other medications, chemical substances or concomitant disease, in the case that shows clinically appropriate response on withdrawal of the drug (no information for re-challenge).

3. Possible:
   - The temporal sequence of the administration and use of the drug is appropriate but it is also able to be explained by other medications, chemical substances or concomitant disease, and information related to withdrawal of the drug is insufficient or vague.

4. Not-Related:

- The AE is not related to the drug if there is evidence that clearly indicates an alternative explanation. If the subject has not received the drug, the timing of the exposure to the drug and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

5. Conditional/Unclassified:

   - In the case that more information is needed for a proper evaluation or additional information is under review.

6. Unassessable/Unclassifiable:

   - In the case that could not be judged due to insufficient or conflicting information and no way to complement or validate.

7.2.2.4. Assessment of the outcomes

Outcome of any non-serious AE occurring within 21 days post-vaccination or any SAE reported during the entire drug use investigation will be assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).
- Unknown.

7.2.2.5. Medically attended visits

For each AE the subject experiences, subject/subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the CRF.

7.3. Reporting of serious adverse events, adverse drug reactions and pregnancies

7.3.1. Prompt reporting of serious adverse events and other events to GSK Vaccines

SAEs will be reported promptly to GSK as described in Table 3 once the physician determines that the event meets the protocol definition of an SAE.

ADRs will be reported promptly to GSK as described in Table 3, if possible, once the physician becomes aware of an ADR.

Pregnancies will be reported promptly to GSK as described in Table 3 once the physician becomes aware of a pregnancy in the time period defined in Section 7.2.1, if possible. The subject will be followed to determine the outcome of the pregnancy, if possible.

At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to GSK, if possible. Generally, follow-up should be no longer than 6 to 8 weeks following the EDD, if possible.

Table 3 Time frames for submitting SAEs and other event reports related to GSK Vaccines

Type of Event	Initial Report		Follow-up of Relevant Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours *	SAE Report Form	24 hours *	SAE Report Form
All ADRs	5 days **	ADR Report Form	5 days **	ADR Report Form
Pregnancies	2 weeks *	Pregnancy Report Form	2 weeks *	Pregnancy Report Form

* Time frame is allowed after receipt or awareness of the information.

** Recommended Time frame for ADR reporting for the investigators after the awareness of the information.

7.3.2. Contact information for reporting serious adverse events and other events to GSK Vaccines

Contact for Reporting SAEs, ADRs and Pregnancies	
Please see the Local PMS Contact Information for contact details.	
Back-up Contact for Reporting SAEs, ADRs and Pregnancies	
GSK Vaccines Clinical Safety & Pharmacovigilance	Fax: +32 2 656 51 16 or +32 2 656 80 09 email: safety-vac.WW@gsk.com
GSK Korea	Fax: 02-775-8758 or 02-749-4438
DreamCIS	Fax: 02-2010-4592
24/24 hours and 7/7 days availability	

7.3.3. Completion and transmission of SAE to GSK Vaccines

Once an physician becomes aware that an SAE has occurred in a drug use investigation subject, he/she will report the information to GSK within 24 hours. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the physician (or designee), and forwarded to .GSK within the designated time frames. If the physician does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional relevant information is received and forwarded to GSK within 24 hours.

The physician will always provide an assessment of causality at the time of the initial report. The causality assessment may change depending on the availability of additional/follow-up information.

Facsimile (Fax) or E-mail transmission of the SAE Report Form is the preferred method to transmit this information to the Contact for Reporting SAEs, ADRs and Pregnancies. In rare circumstances and due to failure of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification

via the telephone does not replace the need for the physician to complete and sign the SAE Report Form within 24 hours.

In the event of a death determined by the physician to be related to vaccination, sending of the fax must be accompanied by telephone call to the Contact for Reporting SAEs, ADRs and Pregnancies.

7.3.4. Completion and transmission of ADR report to GSK Vaccines

Once the physician is aware of an adverse drug reaction that the subject experienced, he/she should report to GSK.

The physician (or his/her designee) should record as all detailed information obtained about the adverse drug reaction as possible in the section for ADR Report Form completely and send to GSK. If the physician does not have all information about the adverse drug reaction, he/she does not wait for additional information before completing the form and notifies to GSK. When obtaining additional information, the report form should be updated.

The physician sends ADR Report Form to the Contact for Reporting SAEs, ADRs and Pregnancies that collects an adverse drug reaction by fax or e-mail.

7.3.5. Completion and transmission of pregnancy reports to GSK Vaccines

Once the physician becomes aware that a subject is pregnant, the physician (or designee) must complete a Pregnancy Report Form and fax or e-mail it to the Contact for Reporting SAEs, ADRs and Pregnancies (refer to the Sponsor Information Sheet) within 2 weeks, if possible.

The Pregnancy Report Form will always be completed as thoroughly as possible with all available details and then dated and signed by the physician (or designee), if possible. Even if the physician does not have all information regarding the pregnancy, the form should still be completed and forwarded to GSK within 2 weeks, if possible. Once additional relevant information is received, the form will be updated and forwarded to GSK within 2 weeks, if possible.

In absence/dysfunction of facsimile equipment, the Contact for Reporting SAEs, ADRs and Pregnancies should be notified by telephone within 2 weeks, if possible. As soon as the facsimile equipment is working again, the physician (or designee) must fax the Pregnancy Report Form to the Contact for Reporting SAEs, ADRs and Pregnancies (refer to the Sponsor Information Sheet) within 2 weeks, if possible.

7.3.6. Regulatory reporting requirements for serious adverse events

The physician will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 0. GSK Vaccines has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the

safety of a product surveillance. Prompt notification of SAEs by the physician to the Contact for Reporting SAEs, ADRs and Pregnancies is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

7.4. Follow-up of adverse events, serious adverse events, and pregnancies

7.4.1. Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the physician is required to proactively follow each subject and provide further information to GSK Vaccines on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the drug use investigation.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 21 days after vaccination.

Physicians will follow-up subjects:

- With SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- Or in the case of other non-serious AEs, until or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed-up until they have returned to normal or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the study monitor.

GSK Vaccines may request that the physician perform or arrange for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The physician is obliged to assist. If a subject dies during participation in the drug use investigation or during a recognised follow-up period, GSK Vaccines will be provided with a copy of any available post-mortem findings, including histopathology.

7.4.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy, if possible. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK, if possible. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the EDD, if possible.

7.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the physician and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's CRF.

8. EFFICACY ASSESSMENT

Efficacy of a vaccine is assessed by the reduction in the occurrence of the disease targeted by the vaccine in people immunized with the vaccine comparing to those not vaccinated. A drug use investigation will be implemented within the routine clinical setting to collect unspecified safety and efficacy data of the drug through the study period. It will be difficult for the physicians to request the subject after vaccination to revisit for assessment and/or laboratory testing not deemed necessary in normal clinical practice due to the physical, logistic, and economic burden to the subject. Therefore, the efficacy assessment of *Fluarix Tetra* would likely be omitted in this drug use investigation.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who is available for the concluding follow-up contact 21 days after receiving *Fluarix Tetra* is considered to have completed the drug use investigation.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Physicians will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (see Section 7.3).

Withdrawals will not be replaced.

From an analysis perspective, a 'withdrawal' from the drug use investigation refers to any subject who was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the drug use investigation when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Physicians will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the CRF. The physician will document whether the decision to withdraw a subject from the study was made by the

subject/subject's parent(s)/LAR(s) or by the physician, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-SAE
- Protocol violation (specify)
- Consent withdrawal, not due to an AE
- Moved from the study area
- Lost to follow-up
- Death
- Other (specify)

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Endpoints

- Occurrence of expected and unexpected AEs during the 21 days (Day 0 to Day 20) follow-up period after vaccination.
- Occurrence of SAEs starting from the date of vaccination in the drug use investigation up to 21 days (Day 0 to Day 20) after vaccination of the subject in the drug use investigation.

10.2. Sample size consideration

According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, max 1440 subjects (720 vaccinees ≥ 3 years old and above and 720 vaccinees between 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly.

Table 4 presents the exact two-sided 95% CI for a sample size of 600 subjects for each group [2)].

Table 4 Exact two-sided 95% CI for the percentage of subjects reporting at least one symptom with a sample size of 600 subjects

Observed rate expressed as a percentage (number of subjects reporting at least one symptom *)	Exact two-sided 95% CI for this observed rate for a sample size of 600 subjects	
	Lower limit (LL)	Upper limit (UL)
1%	0.4	2.2
2%	1.0	3.5
3%	1.8	4.7
4%	2.6	5.9
5%	3.4	7.1

Observed rate expressed as a percentage (number of subjects reporting at least one symptom *)	Exact two-sided 95% CI for this observed rate for a sample size of 600 subjects	
	Lower limit (LL)	Upper limit (UL)
10%	7.7	12.7
15%	12.2	18.1
20%	16.9	23.4

* The symptom could be any one of expected AE, unexpected AE, or SAE.

10.3. Drug use investigation cohort to be evaluated

10.3.1. Total vaccinated cohort

The total vaccinated cohort will include all subjects who receive *Fluarix Tetra* and participated in the drug use investigation:

- When subjects are vaccinated out of label and physicians already gathered the information, this information will be added in the PMS report separately.

10.3.2. Total Safety cohort

The total Safety cohort will include all subjects who receive Fluarix Tetra, participated in the drug use investigation and provide post vaccination safety data.

10.4. 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 report.

10.4.1. Sequence of analyses

Analysis will be performed bi-annually for the first two years and annually for the remaining follow-up years for each study group (3 years old and above, and 6-35 months old children). (based on pre defined cut-off date for enrolment). A comprehensive analysis, pooling all years will be performed at the end of the drug use investigation. The analysis, including individual data listings, will be based on the cohort for vaccinated subjects for whom the drug use investigation conclusion page has been received at GSK before the pre-defined cut-off date. All periodic and final statistical analysis reports will be sent to the GSK VCSP and to MFDS.

The result of the drug use investigation will be included in the PMS periodic reports. Bi-annual PMS reports will be written for the first two years and PMS annual reports will be written for the remaining years. A comprehensive PMS report will be written at the end of the drug use investigation. All analyses described will be performed on cleaned data for each bi-annual/annual report.

10.4.2. Statistical considerations for interim analyses

As this is a descriptive drug use investigation there will be no statistical adjustments required for the each bi-annual/annual analysis. The results of these analyses will not have an impact on the future drug use investigation conduct.

10.5. Statistical methods

10.5.1. Analysis of demographics/baseline characteristics

Descriptive demographic characteristics (age, height, weight, gender, and ethnicity) of the study cohort will be tabulated.

In the descriptive summary, mean, standard deviation, median, minimum, and maximum will be computed for continuous variables such as age. Frequencies and percentages will be calculated for categorical variables such as gender.

The pre-existing medical history, vaccination history within the three previous seasons (yes/no), ***concomitant medication/vaccination at least once during the 21 days (Day 0 to Day 20) follow up period*** and record years will also be presented.

The distribution of subjects vaccinated among the drug use investigation centers by years will be tabulated.

10.5.2. Analysis of safety

A safety analysis based on the total safety cohort will include all subjects who were vaccinated as per Korean PI and have completed 21-days follow-up after at least one dose, regardless of the number of dose.

10.5.2.1. Within group assessment

The AEs/***ADRs/***SAEs will be analysed in the drug use investigation report according to the expectedness and unexpectedness criteria (Refer to GLOSSARY OF TERMS for the definitions of expected AEs and unexpected AEs).

The number and percentage, with exact 95% CI, of any AEs, ADRs ***and SAEs*** occurring within 21 days (Day 0 to Day 20) will be tabulated for the number of subjects receiving *Fluarix Tetra*.

The verbatim reports of signs and symptoms will be matched and coded according to the appropriate WHOART PT. The drug use investigation physician will review and confirm the appropriate WHOART PT by responding to data queries if any discrepancies are reported while coding. The percentage of subjects with AEs, ADRs, and ***SAEs*** occurring within 21 days (Day 0 to Day 20) with its exact 95% CI will be tabulated by PT.

The outcome of pregnancy (reported in the pregnancy report form) for subjects who were pregnant at the time of vaccination and those who become pregnant within 21 days after vaccination will be presented, if possible.

SAEs reported during the drug use investigation period [each subject receiving the vaccine up to 21 days (Day 0 to Day 20) after vaccination and for pregnant subjects until 6-8 weeks after delivery] will be described in detail, if possible.

The incidence proportion of AEs as overall and by age group and gender will be measured with the exact 95% CI. An exploratory comparison between these groups will be performed using Chi-square exact test with the statistical significance level 0.05.

11. ADMINISTRATIVE MATTERS

To comply with acceptable ethical principles, local regulatory requirements, and administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, and public disclosure must be fulfilled. Blinding of subjects initials when safety data is used for analysis and for GSK LOC provides the subject's No. on the PMS report before submission to MFDS. (GSK does not forward personally identifiable information and MFDS requires reporting of drug use investigation subject's No. in the PMS report).

11.1. Case Report Form

CRFs (and subject diary cards, if applicable), will be supplied by GSK Vaccines for recording all data.

Unless specifically required by MFDS, 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 data cleaning procedures.

While completed CRFs are reviewed by a GSK Vaccines' designated study monitor at the study site, omissions or inconsistencies detected by subsequent in-house CRF review may necessitate clarification or correction of data or omissions or inconsistencies with documentation and approval by the physician or appropriately qualified designee. In all cases the physician remains accountable for the study data collected.

Any questions or comments related to the CRF should be directed to the assigned study monitor.

The physician will keep a paper copy of each CRF and any data query forms of the final version of the data generated at the site.

11.2. Monitoring by GSK Vaccines

Monitoring visits by a GSK Vaccines' designated study monitor are for the purpose of confirming that GSK Vaccines' sponsored study are being conducted in accordance with the acceptable ethical principles and the regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), verifying that the site staff and facilities continue to be adequate to conduct the study).

The physician 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 a CRF review and a SDV. By SDV we understand verifying CRF by comparing them with the source data that will be made available by the physician for this purpose.

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

In accordance with applicable regulations, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements. When reviewing data collection procedures, the discussion will also include identification, agreement, and documentation of data items for which the CRF entries will serve as the source document.

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 and any amendments, any other study agreements, acceptable ethical principles, applicable local regulatory requirements, and all applicable regulatory requirements.

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

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

11.3. Archiving of data at study sites

Following closure of the study, the physician must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection), and whenever feasible, to allow any subsequent review of data 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 for studies with an eCRF); however, caution needs to be exercised before such action is taken. The physician must assure 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 physician must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the physician/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the physician/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 that site for the study, any institutional requirements or applicable laws or regulations; otherwise, the minimum retention period will default to 3 years.

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

11.4. Audits

To ensure compliance with acceptable ethical principles 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 physician 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 public registers

Study information from this protocol will be posted on www.clinicaltrials.gov before enrolment of subjects begins.

11.6. Ownership, confidentiality, and publication

11.6.1. Ownership

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

11.6.2. Confidentiality

Documented evidence that a potential physician is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the

physician and other site staff. This information and data will not be used by the physician or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the physician or site staff; (ii) information which it is necessary to disclose in confidence to an IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

11.6.3. Publication

For multi-centers studies, the first publication or disclosure of study results shall be a complete, joint multi-centers publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a 'Publication'), the physician shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 working days, or at least 15 working days for abstracts/posters/presentations). Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

11.6.4. Provision of study results to physicians, posting to the clinical trials registers, and publication

Where required by applicable regulatory requirements, an physician signatory will be identified for the approval of the study report. The physician 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 site or other mutually-agreeable location.

The results summary will be posted to the GSK Clinical Study Register no later than 12 months after the LSLV or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable

13. REFERENCES

1) 시판 후 약물감시 업무 가이드라인
https://www.drugsafe.or.kr/iwt/ds/ko/bbs/EgovBbs.do?bbsId=BBSMSTR_000000000041&nttId=536
2) Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413.
3) Barr IG, Komadina N, Durrant C, Sjogren H, Hurt AL, Shaw RP. Circulation and antigenic drift in human influenza B-viruses in SE Asia and Oceania since 2000 et al. *Commun Dis Intell.* 2006;30:350-357.
4) Beyer WEP, Palache AM., Baljet M et al. Antibody induction by influenza vaccines in elderly: a review of the literature. *Vaccine.* 1989;7:385-394.
5) Brydak L, Machala M. Humoral immune response to influenza vaccination in patients from high risk groups. *Drugs*. 2000;60:35-53.
6) CDC. http://www.cdc.gov/flu/weekly/fluactivity.htm
7) Englund JA, Walter EB, Gbadebo A, Monto AS, Zhu Y, Neuzil KM. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics.* 2006;118:e579-e585.
8) Hannoun C, Megas F, and Piercy J. “Immunogenicity and protective efficacy of influenza vaccination”. *Virus Res.* 2004;103:133-138.
9) Heckler R, Baillot A, Engelmann H, Neumeier E, Windorfer A. Cross-protection against homologous drift variants of influenza A and B after vaccination with split vaccine. *Intervirology.* 2007;50:58-62.
10) Levandowski RA, Regnery HL, Staton E, Burgess BG, Williams MS, Groothuis IR. Antibody responses to influenza B viruses in immunologically unprimed children. *Pediatrics.* 1991;88:1031-1036.

APPENDIX A AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 3**	
eTrack study number and Abbreviated Title(s)	204687 [EPI FLU-050 VS KR PMS]
Amendment number:	Amendment 3
Amendment date:	08 Mar 2019
Co-ordinating authors:	PPD, Medical Writing Project Leader, DreamCIS
Rationale/background for changes: • Editorial changes • Changes as per MFDS Request – Describe statistical processing method in "10.5.2. Safety Analysis" – Correct typo errors on Research Subject Inclusion Criteria Table in "4.2. Inclusion Criteria" (ONLY applicable in Korean protocol) • Clarification of ADR analysis to consistent with AEs and SAEs analysis	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Cover Page

Co-ordinating author

(~~Administrative Change 1: 30 Jul 2018~~ *Amendment 3: 08 Mar 2019*)

PPD ***, Medical Writing Project Leader, DreamCIS***

Contributing authors **(~~Administrative Change 1: 30 Jul 2018~~ *Amendment 3: 08 Mar 2019*)**	PPD, Regional Epidemiology Manager, AP. PPD, Statistician. PPD, Safety Physician/PPD PPD, and PPD, Safety Scientist PPD, Global Epidemiologist. PPD, Study Delivery Lead, Vaccines. PPD, Oversight Data Manager, Vaccines. PPD, Named Safety Contact PPD, Local Medical Leads, Vaccines, Korea PPD ***, Korea*** PPD, Vaccines, Korea. PPD, Local Delivery Lead, Vaccines, Korea.

GSK Vaccines' protocol template for observational studies and interventional studies without administration of medicinal products as described in a research protocol based on Protocol Document Standard version 13.2

Protocol ~~Administrative Change 1~~ *Amendment 3* Sponsor Signatory Approval

Date of *protocol amendment*	~~Administrative Change 1 Final: 30 Jul 2018~~ ***Amendment 3 Final: 08 Mar 2019***
Detailed Title	A prospective, observational, multi-center, drug use investigation to monitor the safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix Tetra* when administered according to the approved Prescribing Information in Korea.
Sponsor signatory ***(Amendment 3: 08 Mar 2019)***	~~Sanjoy Datta~~ ~~VP Vaccine Medical & Clinical Intercontinental~~ ***Bach-Yen Nguyen*** ***Clinical and Epidemiology Project Lead, Flu and Preparedness Activities*** ***Clinical R & D*** ***U.S. Vaccine Research and Development Center***

Protocol ~~Administrative Change~~ *Amendment 3* Rationale

Amendment **number:** ~~Administrative Change 1~~ ***Amendment 3***
Rationale/background for changes:
~~• Administrative changes (change of contact details of safety reporting (e-mail address), corrections to names of study personnel, correction of typographical error)~~ • ***Editorial changes*** • ***Changes as per MFDS Request*** — ***Describe statistical processing method in "10.5.2. Safety Analysis"*** — ***Correct typo errors on Research Subject Inclusion Criteria Table in "4.2. Inclusion Criteria" (ONLY applicable in Korean protocol)*** • ***Clarification of ADR analysis to be consistent with planned AEs and SAEs analysis***

Protocol ~~Administrative Change 1~~ *Amendment 3* Physician Agreement

SYNOPSIS

Study design

(Amendment 3: 08 Mar 2019)

Drug use investigation design: A prospective, observational, non-comparative, multi-center study in Korea.

Vaccination schedule: Vaccination as per locally approved PI (which is not part of the drug use investigation): to adults and previously vaccinated children aged ≥6 months, a single 0.5 ml dose of *Fluarix Tetra* will be administered. To previously unvaccinated children aged 6 months to <9 years, two doses will be administered with a second 0.5 ml dose at least 4 weeks apart from the first one as per the local PI in Korea.

Safety monitoring:

- Recording of all AEs during the 21 days (Day 0 to Day 20) using diary cards after *Fluarix Tetra* is administered.

- ***Recording of all ADRs reported during the 21 days (Day 0 to Day 20) follow-up period after administration of Fluarix Tetra***

- Recording of SAEs from the date of vaccination until 21 days (Day 0 to Day 20) after *Fluarix Tetra* is administered during the subject's participation in the study.

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Duration of the drug use investigation:

- 6 years (for children 36 months and above and adults).

- 4 years (for children from 6 to 35 months of age)

Type of drug use investigation: Self-contained.

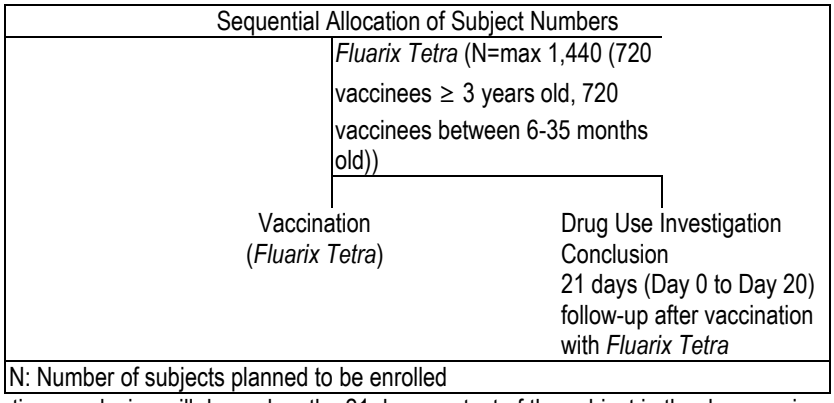
Data collection: Standardised hard copy CRF (SAEs, ADRs, Pregnancy information will be collected by using the SAE, ADR, Pregnancy Reporting Form).

Discussion of study design

(Amendment 3: 08 Mar 2019)

All AEs including ***ADRs and*** SAEs reported during the 21 days (Day 0 to Day 20) post-vaccination follow-up period of *Fluarix Tetra* in the drug use investigation will be collected as part of safety data in this drug use investigation. These AEs will be further classified by GSK at the time of statistical analyses as expected/unexpected based on the current PI.

3. STUDY DESIGN OVERVIEW



Drug use investigation conclusion will depend on the 21 days contact of the subject in the drug use investigation. Definition of Conclusion of drug use investigation for a subject: A subject who is available for the concluding follow-up contact 21 days (Day 0 to Day 20) after receiving *Fluarix Tetra* is considered to have completed the drug use investigation.

……

- Safety monitoring:
  - Recording of all AEs during the 21 days (Day 0 to Day 20) using diary cards after *Fluarix Tetra* is administered.
  - The participating physician will transcribe the collected information into the CRF in English.
  - ***Recording of all ADRs reported during the 21 days (Day 0 to Day 20) follow-up period after administration of Fluarix Tetra***
  - Recording of SAEs from the date of vaccination until 21 days (Day 0 to Day 20) after *Fluarix Tetra* is administered during the subject's participation in the study.
  - All AEs , ADRs and SAEs starting immediately following administration of *Fluarix Tetra* must be recorded onto the CRF and all ADRs and SAEs must be reported using the ADR reporting form and SAE reporting form, the latter to be sent to GSK according to the required timelines, irrespective of intensity or whether or not they are considered vaccination-related.
  - Parents of children aged 6 months to <12 years wil be contacted to provide details of any AEs experienced by the children 21 days after the children receives the vaccination.
  - Subjects for whom diary card transcription into CRF will be done through phone contact are considered to have completed the drug use investigation.

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- Duration of the drug use investigation:

  - 6 years (for children 36 months and above and adults).

  - 4 years (for children from 6 to 35 months of age)
- Type of drug use investigation: Self-contained.
- Data collection: Standardised hard copy CRF (SAEs, ADRs, Pregnancy information will be collected by using the SAE, ADR, Pregnancy Reporting Form).

6.3.4.1. Time window for recording concomitant medication/vaccination in the CRF

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at any time during the period starting with the administration of *Fluarix Tetra* and ending 21 days (Day 0 to Day 20) after ***vaccination*** must be recorded in the CRF.

Any vaccine not foreseen in the drug use investigation protocol administered in the period beginning 21 days (Day -20 to Day 0) preceding the dose of *Fluarix Tetra* and ending 21 days (Day 0 to Day 20) after the dose of *Fluarix Tetra* must be recorded in the CRF.

Any investigational medication or vaccine administered throughout the drug use investigation (i.e. from 21 days before the first dose of the vaccine and 21 days after administration of the dose of the vaccine) must be recorded in the CRF.

6.5.3.9. Record AEs, ADRs and SAEs

- The subject/subjects' parent(s)/LAR(s) will be instructed to contact the physician immediately should the subjects manifest any signs or symptoms they perceive as serious.
- Refer to Section 7.2 for procedures for the physician to record AEs, ADRs and SAEs and to Section 7.3 for guidelines on how to report these ~~AEs /~~ADRs/SAEs to GSK Vaccines.
- After vaccination, diary cards will be provided to the subjects to record body (oral/ axillary/tympanic) temperature and any AEs (i.e. on the day of vaccination and during the next 20 days) occurring after vaccination. The subject/subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the physician on their next drug use investigation visit or provide details during the phone or by postal mail.

6.5.3.10. Procedures during follow-up visits/contacts for AEs/ ADRs /SAEs

Note that some of the procedures to be performed during the follow-up visits/contacts (record AEs) ~~and~~ are described in Section ~~6.3.4~~ ***6.5.3.6*** up to Section 6.5.3.9.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The physician or site staff is/are responsible during the drug use investigation for the detection and documentation of events meeting the criteria and definition of an AE ~~or~~**,** ***ADR and*** a SAE as provided in this protocol.

Each subject/subject's parent(s)/LAR(s) will be instructed to contact the physician immediately should the subject manifest any signs or symptoms they perceive as serious.

7.1.4. ~~Adverse events~~ Pregnancy

~~All AEs reported during the 21 days (Day 0 to Day 20) follow-up period after administration of the vaccine dose will be recorded using diary card provided to the subject/subject's parent(s)/LAR(s). The AEs/SAEs will be analysed in the drug use investigation report according to the expectedness and unexpectedness criteria as defined in the locally approved PI (also refer to GLOSSARY OF TERMS).~~

Any eligible pregnant female for whom the participating physician has decided to administer *Fluarix Tetra* vaccine may be enrolled in the drug use investigation after the subject has signed the ICF/IAF. If the participating physician becomes aware of a pregnancy during the course of the 21 days follow-up of his/her female subjects, he/she has to notify GSK using the Pregnancy Notification form within 2 weeks, if possible.

All pregnant subjects in the drug use investigation will be followed up ~~at~~***to*** 6-8 weeks after delivery for outcome of pregnancy, if possible.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE, as described in Section 7.1.1 and 7.1.3, and will be followed, if possible, as described in Section 7.4.1.

~~7.1.6~~. 7.1.5 Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

7.2.1. Time period for detecting and recording adverse events, adverse drug reactions serious adverse events, and pregnancies

All AEs, ADRs and SAEs starting immediately following administration of *Fluarix Tetra* must be recorded onto the CRF and all ADRs and SAEs must be reported using the ADR reporting form and SAE reporting form, the latter to be sent to GSK according to the required timelines, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the receipt of ~~*Fluairx*~~***Fluarix*** *Tetra* in the drug use investigation and will end 21 days following administration of *Fluarix Tetra* for each subject. See Section 7.3 for instructions on recording and reporting SAEs.

.....

Note: Post-vaccination AEs will be collected and reported only for *Fluarix Tetra* received under the drug use investigation procedure (after signing the ICF/IAF).

~~Type~~	~~All AEs~~
~~Period of 'all AEs' follow up~~	~~21 days (Day 0 to Day 20) post vaccination~~
~~Method of follow up~~	~~Diary cards/Telephone contact/Mail~~
~~Method for reporting ADRs/SAEs~~	~~Paper ADR and SAE Forms~~
~~Period of follow up for SAEs~~	~~Throughout the drug use investigation period, beginning the day of vaccination (Day 0) and ending 21 days (Day 0 to Day 20) following each vaccination dose as per the drug use investigation.~~

All AEs***/ADRs/SAEs*** reported within 21 days (Day 0 to Day 20) of administration of *Fluarix Tetra* within the drug use investigation ~~and all SAEs reported from the date of vaccination up to 21 days (Day 0 to Day 20) after administration of *Fluarix Tetra* within the study~~ need to be recorded in the CRF. These AEs/***ADRs/***SAEs will be classified as expected/unexpected at the time of statistical analyses (refer to GLOSSARY OF TERMS for definitions of expected/unexpected AEs).

Note: Assessment of causality and outcome will be performed by the physician according to the following classification. Causality will be assessed as: Certain; Probable/Likely; Possible; Not-Related; Conditional/ Unclassified; Unassessable/Unclassifiable. Outcome will be assessed as recovered; not recovered; recovering; resolved with sequelae; fatal; unknown.

7.2.2.1. Active questioning to detect adverse events, adverse drug reactions and serious adverse events

The physician needs to collect information on any AE in the subject. At the time of analysis, an assessment on whether the AE is expected (contained in the local PI) or unexpected (not contained in the local PI) will be done by GSK.

As a consistent method of collecting safety information, the subject/subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Have you acted differently or felt different/has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?'*

When an AE/SAE occurs, it is the responsibility of the physician to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The physician will then record all relevant information regarding an AE***/ADR***/SAE on the CRF, ADR Report Form or SAE Report Form as applicable. It is not acceptable for the physician to send photocopies of the subject's medical records to GSK Vaccines instead of the appropriate completed AE/SAE pages on the CRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Vaccines. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Vaccines.

The physician will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE***/ADR***/SAE and not the individual signs/symptoms.

7.2.2.2. Assessment of intensity

Intensity of the following AEs will be assessed as described:

The physician will assess the maximum intensity that occurred over the duration of the event for all other AEs, including ***ADR and*** SAEs reported during the drug use investigation. The assessment will be based on the physician's clinical judgement.

The intensity of each AE***, ADR*** and SAE recorded in the CRF, ***ADR Report form*** or SAE Report Form, as applicable, should be assigned to one of the following categories:

10.5.1. Analysis of demographics/baseline characteristics

Descriptive demographic characteristics (age, height, weight, gender, and ethnicity) of the study cohort will be tabulated.

In the descriptive summary, mean, standard deviation, median, minimum, and maximum will be computed for continuous variables such as age. Frequencies and percentages will be calculated for categorical variables such as gender.

The pre-existing medical history, vaccination history within the three previous seasons (yes/no), ***concomitant medication/vaccination at least once during the 21 days (Day 0 to Day 20) follow up period*** and record years will also be presented.

The distribution of subjects vaccinated among the drug use investigation centers by years will be tabulated.

10.5.2.1. Within group assessment

The AEs***/ADRs***/SAEs will be analysed in the drug use investigation report according to the expectedness and unexpectedness criteria (Refer to GLOSSARY OF TERMS for the definitions of expected AEs and unexpected AEs).

The number and percentage, with exact 95% CI, of any AEs~~ and ADRs~~***, ADRs and SAEs*** occurring within 21 days (Day 0 to Day 20) will be tabulated for the number of subjects receiving Fluarix Tetra.

The verbatim reports of signs and symptoms will be matched and coded according to the appropriate WHOART PT. The drug use investigation physician will review and confirm the appropriate WHOART PT by responding to data queries if any discrepancies are reported while coding. The percentage of subjects with AEs, ADRs, and ~~AEs rated as grade 3~~ ***SAEs*** occurring within 21 days (Day 0 to Day 20) with its exact 95% CI will be tabulated by PT.

~~The number and percentage of subjects who received concomitant medication/ vaccination at least once during the 21 days (Day 0 to Day 20) follow-up period will be tabulated, with exact 95% CI. The number and percentage of doses for which the subjects received concomitant medication/vaccination at least once during the 21 days (Day 0 to Day 20)~~

~~follow-up period will be tabulated over the entire drug use investigation period, with exact 95% CI. Similar tabulations will be done for the number of subjects by types of medication/vaccination during the entire drug use investigation period.~~

The outcome of pregnancy (reported in the pregnancy report form) for subjects who were pregnant at the time of vaccination and those who become pregnant within 21 days after vaccination will be presented, if possible.

SAEs reported during the drug use investigation period [each subject receiving the vaccine up to 21 days (Day 0 to Day 20) after vaccination and for pregnant subjects until 6-8 weeks after delivery] will be described in detail, if possible.

The incidence proportion of AEs as overall and by age group and gender will be measured with the exact 95% CI. An exploratory comparison between these groups will be performed using Chi-square exact test with the statistical significance level 0.05.

11.6.3. Publication

For ~~multi center~~***multi-centers*** studies, the first publication or disclosure of study results shall be a complete, joint ~~multi center~~***multi-centers*** publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 2 (Only for RMP)**	
eTrack study number and Abbreviated Title(s)	204687 [EPI FLU-050 VS KR PMS]
Amendment number:	Amendment 2
Amendment date:	31 May 2017
Co-ordinating authors:	PPD, Scientific Writer, Medical Writing Team Manager, Dream CIS
Rationale/background for changes: - In addition to the extension of an age indication to include 6 to 35 months of age for Fluarix Tetra, protocol amended for RMP submission. - Minor changes for correct information and typo error.	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

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SYNOPSIS

Rationale for the Drug Use Investigation	GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, *Fluarix Tetra* was registered in Korea in December 2014 **indicated for 3 years and above.** **In addition to the extension of an age indication to include 6 to 35 months of age for Fluarix Tetra, additional drug use investigation for new age group is being conducted to collect safety information on the use of Fluarix Tetra for 4 years according to the MFDS requirement. Almost 720 children aged 6 to 35 months will be enrolled in order to collect safety information within 21 days (Day 0 to Day 20) post vaccination.**
Study design	**Drug use investigation design**: A prospective, observational, non-comparative, multi-center study in Korea. **Vaccination schedule**: Vaccination as per locally approved PI (which is not part of the drug use investigation): to adults and previously vaccinated children aged ≥ ~~3~~**6 months**, a single 0.5 ml dose of *Fluarix Tetra* will be administered. To previously unvaccinated children aged ~~3~~ **6 months** to <9 years, two doses will be administered with a second 0.5 ml dose at least 4 weeks apart from the first one as per the local PI in Korea. **Duration of the drug use investigation**: **- 6 years (for children 36 months and above and adults).** **- 4 years (for children from 6 to 35 months of age)**
Number of subjects	According to MFDS requirement, at least 600 evaluable subjects should be recruited for **each** drug use investigation. Therefore, about ~~720~~ **1440** subjects **(720 for 3 years and above vaccinees and 720 vaccinees 6-35 months old)** will

be enrolled through the drug use investigation period in anticipation of a dropout rate of 20% but depending on the status of actual enrolment, the plan can be adjusted.

1. INTRODUCTION

1.1 Background

GSK Vaccines has developed a QIV which contains two A-strains and two B-strains. The drug use investigation was designed to evaluate the safety of the QIV in adults and children from ~~three years~~ **6 months** of age in Korea

1.2 Rationale for the study

In addition to the extension of an age indication to include 6 to 35 months of age for Fluarix Tetra, additional drug use investigation for new age group is being conducted to collect safety information on the use of Fluarix Tetra for 4 years according to the MFDS requirement. Almost 720 children aged 6 to 35 months will be enrolled in order to collect safety information within 21 days (Day 0 to Day 20) post vaccination.

2. OBJECTIVE

- To assess the safety of GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, Fluarix Tetra, in terms of frequency and intensity of AEs and SAEs when administered according to the local PI in adults and children from ~~three years~~ s**ix months** of age in Korea.

3. STUDY DESGIN OVERVIEW

Sequential Allocation of Subject Numbers	
Fluarix Tetra (N= ~~720~~ **1,440**)	
Vaccination (*Fluarix Tetra*)	Drug Use Investigation Conclusion 21 days (Day 0 to Day 20) follow-up after vaccination with *Fluarix Tetra*
N: Number of subjects planned to be enrolled	

- Vaccination schedule: Vaccination as per locally approved PI (which is not part of the drug use investigation): to adults and previously vaccinated children aged ≥~~3~~**6 months**, a single 0.5 ml dose of *Fluarix Tetra* will be administered. To previously unvaccinated children aged ~~3~~**6 months** to <9 years, two doses will be administered

with a second 0.5 ml dose at least 4 weeks apart from the first one as per the local PI in Korea.

- Safety monitoring::
  - ~~In previously unvaccinated children aged 36 months to <9 years~~,Parents of Children aged **6 months to < 12 years** will be contacted to provide details of any AEs experienced by the children 21 days after the children receives the vaccination.

  - ~~Children~~ **Subjects** for whom diary card transcription into CRF will be done through phone contact are considered to have completed the drug use investigation.
- Duration of the drug use investigation: 6 years.
  - 6 years (for children 36 months and above and adults).

  - 4 years (for children from 6 to 35 months of age)

4. DRUG USE INVESTIGATION COHORT

4.1 Number of subjects/centers

~~As per the MFDS requirements, safety information from a total of at least 600 evaluable subjects is needed for this drug use investigation. In consideration of a dropout rate of 20%,~~
~~about 720 subjects in total will be enrolled over a period of 6 consecutive years.~~

According to MFDS requirement, at least 600 evaluated subjects should be recruited for each drug use investigation. Therefore, about 1440 subjects (720 for 3 years old and above and 720 between 6-35 months old) will be enrolled through the drug use investigation period in anticipation of a dropout rate of 20% but depending on the status of actual enrolment, the plan can be adjusted.

4.1.1 Recruitment at study centers

This prospective, observational drug use investigation will be conducted at multiple centers (mainly in hospitals and private clinics) in Korea ~~for a period of 6 consecutive years.~~

- Study population: Subjects aged ≥~~3~~**6 months** who receive *Fluarix Tetra* as a part of routine practice at a private clinic or hospital. Only subjects to whom *Fluarix Tetra* ~~will be prescribed~~ **is administered** in routine clinical practice will be invited to participate in the drug use investigation.
- ~~Target enrolment: Around 720 subjects in total will be enrolled over a period of 6 consecutive years to meet the requirement of 600 evaluable subjects.~~

6.5.2.2. Pre-vaccination body temperature

The body (oral, axillary or tympanic) temperature of all subjects needs to be measured prior to *Fluarix Tetra* administration. The preferred route for recording temperature in this drug use investigation will be oral/axillary/tympanic **depending on the age of enrolled vaccinees.** . If the subject has fever [fever is defined as temperature ≥37.5 °C (99.5 °F) on oral, axillary or tympanic setting on the day of vaccination, the vaccination visit will be rescheduled.

7.1.1 Definition of an adverse event

Examples of included ~~an~~AE ~~include~~ :

Examples of included ~~an~~AE (Do Not include) :

7.2.1. Time period for detecting and recording adverse events, adverse drug reactions serious adverse events, and pregnancies

- An overview of the protocol-required reporting periods for AEs, ADRs ,SAEs **and pregnancies** is given in

  Table 2.

  ~~Table 2 presents the reporting periods for AEs, ADRs ,SAEs, and pregnancies.~~

7.3.2 Contact information for reporting serious adverse events and other events to GSK Vaccines

Contact for Reporting SAEs	
Please see the Sponsor Information Sheet for contact details.	
Back-up Contact for Reporting SAEs	
GSK Vaccines Clinical Safety & Pharmacovigilance	Fax: +32 2 656 51 16 or +32 2 656 80 09 **email: safety-vac.ww@gskbio.com**
GSK Korea	Fax: 02-775-8758 or 02-749-4438
DreamCIS	Fax: 02-2010-4592
24/24 hours and 7/7 days availability	

10.2. Sample size consideration

According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, about 1440 subjects (720 vaccinees ≥ 3 years old and above and 720 vaccinees between 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled

participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly
~~According to MFDS requirement, at least 600 evaluable subjects should be recruited for the drug use investigation. Therefore, about 720 subjects will be enrolled through the drug use investigation period in anticipation of a dropout rate of 20%. Depending on the status of actual enrolment, the plan can be adjusted.~~

Table 4 presents the exact two-sided 95% CI for a sample size of 600 subjects **for each group** [2)].

10.4.1. Sequence of analyses

Analysis will be performed bi-annually for the first two years and annually for the remaining follow-up years **for each study group (3 years old and above, and 6-35 months old children).** (based on pre defined cut-off date for enrolment). A comprehensive analysis, pooling all years will be performed at the end of the drug use investigation. The analysis, including individual data listings, will be based on the cohort for vaccinated subjects for whom the drug use investigation conclusion page has been received at GSK before the pre-defined cut-off date. All periodic and final statistical analysis reports will be sent to the GSK VCSP and to MFDS.

11.1 Case Report Form

While completed CRFs are reviewed by a GSK Vaccines' **designated** study monitor at the study site, omissions or inconsistencies detected by subsequent in-house CRF review may necessitate clarification or correction of data or omissions or inconsistencies with documentation and approval by the physician or appropriately qualified designee. In all cases the physician remains accountable for the study data collected.

11.2 Monitoring by GSK Vaccines

Monitoring visits by a GSK **Vaccines' designated** study monitor are for the purpose of confirming that GSK Vaccines' sponsored study are being conducted in accordance with the acceptable ethical principles and the regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), verifying that the site staff and facilities continue to be adequate to conduct the study).

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title(s)	204687 [EPI FLU-050 VS KR PMS]
Amendment/Administrative change number:	Administrative Change 1
Amendment/Administrative change date:	30 Jul 2018
Co-ordinating authors:	PPD , Medical Writing Project Leader, DreamCIS
Rationale/background for changes: - Administrative changes ((change of contact details of safety reporting (e-mail address), corrections to names of study personnel, correction of typographical error)	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

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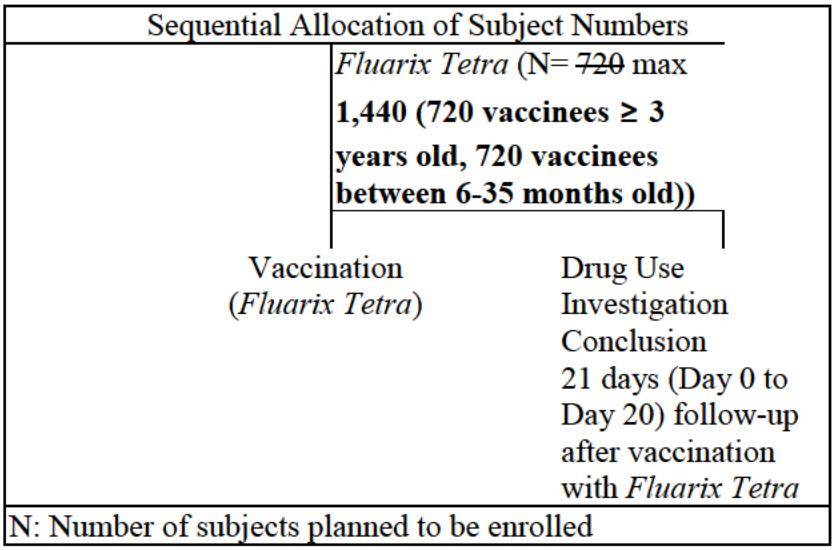
SYNOPSIS

Number of subjects	According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, ~~about~~ **max**~~720~~ 1440 subjects (720 for 3 years and above vaccinees and 720 vaccinees 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly

3. STUDY DESGIN OVERVIEW



4. DRUG USE INVESTIGATION COHORT

4.1 Number of subjects/centers

According to MFDS requirement, at least 600 evaluated subjects should be recruited for each drug use investigation. Therefore, ~~about~~**max** 1440 subjects (720 for 3 years old and above and 720 between 6-35 months old) will be enrolled through the drug use investigation period in anticipation of a dropout rate of 20% but depending on the status of actual enrolment, the plan can be adjusted.

7.3.2 Contact information for reporting serious adverse events and other events to GSK Vaccines

Contact for Reporting SAEs, ADRs and Pregnancies	
Please see the Local PMS Contact Information for contact details.	
Back-up Contact for Reporting SAEs, ADRs and Pregnancies	
GSK Vaccines Clinical Safety & Pharmacovigilance	Fax: +32 2 656 51 16 or +32 2 656 80 09 **email: safety-vac.ww@~~gskbio.com~~gsk.com**
GSK Korea	Fax: 02-775-8758 or 02-749-4438
DreamCIS	Fax: 02-2010-4592
24/24 hours and 7/7 days availability	

7.3.3 Completion and transmission of SAE to GSK Vaccines

Facsimile (Fax) **or E-mail** transmission of the SAE Report Form is the preferred method to transmit this information to ~~the Contact for Reporting SAEs~~ the Contact for Reporting SAEs, ADRs and Pregnancies. In rare circumstances and due to failure of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone does not replace the need for the physician to complete and sign the SAE Report Form within 24 hours.

In the event of a death determined by the physician to be related to vaccination, sending of the fax must be accompanied by telephone call to ~~the Contact for Reporting SAEs~~ the Contact for Reporting SAEs, ADRs and Pregnancies.

7.3.4 Completion and transmission of SAE to GSK Vaccines

The physician sends ADR Report Form to ~~the GSK staff (or designee)~~ the Contact for Reporting SAEs, ADRs and Pregnancies that collects an adverse drug reaction by fax or e-mail. ~~Below are the fax number, telephone number and address of the GSK staff (or designee) collecting an adverse drug reaction.~~

7.3.5 Completion and transmission of pregnancy reports to GSK Vaccines

Once the physician becomes aware that a subject is pregnant, the physician (or designee) must complete a Pregnancy Report Form and fax **or e-mail** it to ~~the Contact for Reporting SAEs~~ the Contact for Reporting SAEs, ADRs and Pregnancies (refer to the Sponsor Information Sheet) within 2 weeks, if possible.

The Pregnancy Report Form will always be completed as thoroughly as possible with all available details and then dated and signed by the physician (or designee), if possible. Even if the physician does not have all information regarding the pregnancy, the form should still be completed and forwarded to GSK within 2 weeks, if possible. Once additional relevant information is received, the form will be updated and forwarded to GSK within 2 weeks, if possible.

In absence/dysfunction of facsimile equipment, ~~the Contact for Reporting SAEs~~ the Contact for Reporting SAEs, ADRs and Pregnancies should be notified by telephone within 2 weeks, if possible. As soon as the facsimile equipment is working again, the physician (or designee) must fax the Pregnancy Report Form to ~~the Contact for Reporting SAEs~~ the Contact for Reporting SAEs, ADRs and Pregnancies (refer to the Sponsor Information Sheet) within 2 weeks, if possible.

7.3.6 Regulatory reporting requirements for serious adverse events

The physician will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 0. GSK Vaccines has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product surveillance. Prompt notification of SAEs by the physician to ~~the Contact for Reporting SAEs~~ the Contact for Reporting SAEs, ADRs and Pregnancies is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

10.2. Sample size consideration

According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, ~~about~~**max** 1440 subjects (720 vaccinees ≥ 3 years old and above and 720 vaccinees between 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly