CONFIDENTIAL

Study Protocol

Sponsor:

GlaxoSmithKline Biologicals SA

9th Floor LS Yongsan Tower building,
92 Hangangdaero, Yongsan-gu,
Seoul, 04386, Korea

Marketed Product Name	GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV) vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant
eTrack study number and Abbreviated Title	208710 (EPI-HPV-077 VS KR PMS)
Date of protocol	Final: 07 November 2017 Amendment 1 Final: 14 May 2018
Title	Post-marketing surveillance of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix* when administered according to the approved Prescribing Information in Korea.
Detailed Title	A prospective, observational, multi-centre, post-marketing surveillance (PMS) to monitor the safety of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix* when administered to 9-25 years old subjects according to the approved Prescribing Information in Korea.
Co-ordinating author	PPD Vaccine Medical Director Korea
Contributing authors (Amended: 14 May 2018)	• PPD ***and*** PPD, Clinical and Epidemiology R&D Project Leads • PPD, Study Delivery Lead • PPD, Safety Physician • PPD, Lead Scientific Writer • PPD ***and*** PPD, Oversight Data Managers • PPD, Statistician • PPD, Regional VP Medical/Clinical GSK Vaccines • PPD, Regional Epidemiologist • PPD ***and*** PPD, Local Medical Leads • PPD ***and*** PPD***, Country Clinical Operations Heads*** • PPD ***Vaccines Medical Director*** • PPD, Named Safety Contact • PPD, Local Delivery Lead

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

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	208710 (EPI-HPV-077 VS KR PMS)
Date of protocol	Amendment 1 Final: 14 May 2018
Detailed Title	A prospective, observational, multi-centre, post-marketing surveillance (PMS) to monitor the safety of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix* when administered to 9-25 years old subjects according to the approved Prescribing Information in Korea
Sponsor signatory (Amended: 14 May 2018)	***Dorota Borys***, Director, Clinical and Epidemiology R&D Project Lead, HPV and Hepatitis vaccines, RDC Belgium, GlaxoSmithKline Biologicals, SA.
Signature	_____
Date	_____

Protocol Amendment 1 Rationale

Amendment number: Amendment 1
Rationale/background for changes: The protocol has been amended to address Ministry of Food and Drug Safety (MFDS) request for adding detailed description of enrolment plan, departments that will participate, method of PMS, collection of information regarding medical history, physical examination, and concomitant medication. In addition, collection of potential immune medicated diseases (pIMD) has been removed as it has not been considered mandatory for PMS, combined with results from other research studies to learn more about the vaccine and related diseases has been added in confidentiality section by referring to current Informed consents form (ICF), changed MFDS reporting method of personally identifiable information and added GSK reporting method of AEs/SAEs has been changed as it has been considered current PMS procedures, clarified vaccination schedule has been changed as it has been based on current prescribing information, and schedule period (such as Day 1 to Day 30) has been changed according to current writing process.

Protocol Amendment 1 Physician Agreement

I agree:

- To conduct the PMS in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with the terms of the PMS agreement and with any other PMS conduct procedures and/or PMS conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the PMS at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) or 'Good Epidemiological Practice' (GEP) or other applicable guidelines and all applicable regulatory requirements.
- To ensure that all persons assisting me with the PMS are adequately informed about the GSK Biologicals PMS vaccine(s)/Product(s) and other PMS-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no samples (including serum samples) are retained onsite or elsewhere without the approval of GSK *Biological*s and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other *biological a*ssays on the samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the PMS 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 Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

eTrack study number and Abbreviated Title	208710 (EPI-HPV-077 VS KR PMS)
Date of protocol	Amendment 1 Final: 14 May 2018
Detailed Title	A prospective, observational, multi-centre, post-marketing surveillance (PMS) to monitor the safety of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix* when administered to 9-25 years old subjects according to the approved Prescribing Information in Korea
Physician name	_____
Signature	_____
Date	_____

Sponsor Information

Sponsor

GlaxoSmithKline Biologicals
9th Floor, LS Yong-san Tower, 92 Hangangdae-ro, Yongsan-gu, Seoul, 04386, Korea

Sponsor Medical Expert for the PMS

Refer to the local PMS contact information document.

Sponsor PMS Monitor

Refer to the local PMS contact information document.

Sponsor PMS Contact for Reporting of a Serious Adverse Event (SAE)

GSK Biologicals Central Back-up PMS Contact for Reporting SAEs: refer to protocol 8.4.1.

PMS Contact for Reporting SAEs: refer to the local study contact information document.

SYNOPSIS

Detailed Title	A prospective, observational, multi-centre, post-marketing surveillance (PMS) to monitor the safety of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix* when administered to 9-25 years old subjects according to the approved Prescribing Information in Korea
Indication (Amended: 14 May 2018)	*Cervarix* is a vaccine indicated for active immunisation against HPV infection in males and females 9-25 years old as 3 doses, 0***, 1 and*** 6 ***months*** schedule. Children and adolescents 9-14 years old can be vaccinated with 2 doses, 0 ***and 6-12 months*** schedule.
Objective	To assess the safety of GSK Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix*, in terms of frequency and intensity of AEs and SAEs when administered according to the local Prescribing Information.
Rationale for the PMS	In Korea, GSK Biologicals' human papillomavirus (HPV)-16/18 vaccine, *Cervarix* was approved in July 2008. As per Ministry of Food and Drug Safety (MFDS) (Korea) requirements, this post-marketing surveillance (PMS) is being conducted to collect safety information on the use of *Cervarix*, in at least 600 Korean subjects within 30 days after the vaccination when administered according to the approved PI in Korea in a real health care setting over a 4 year period.
PMS design (Amended: 14 May 2018)	• PMS design: A prospective, observational, non-comparative, multi-centre PMS in Korea. • Study population: 9-25 years old males and females. • Vaccination schedule: Three doses of *Cervarix* will be administered as per the local Prescribing Information in Korea. Subjects aged 9-14 years old can be vaccinated with two dose schedule. The recommended schedule is as follows: • Vaccination: The 9-25 years old subjects should be administered *Cervarix* with 3 doses ***(0.5mL each)***, 0, 1, and 6 months schedule. The 9-14 years old subjects can be vaccinated with 2 doses, 0 and 6***-12*** months schedule. ***In the 2-doses schedule, if the second dose is administered before 5 months after the first dose, the third dose vaccination is required. In the 3 doses schedule, if the vaccination schedule requires flexibility, the second dose can be administered***

between 1 and 2.5 months and the third dose can be administered between 5 and 12 months after the first dose.

Note: The subject/subject's parent's/ Legally acceptable representative's (LAR) signature in the ICF/IAF signifies enrolment of the subject into the PMS. The ICF/IAF is for the collection and handling of safety information and **not** for the vaccination procedure.

- Safety monitoring:
  - Recording of all AEs during the 30 day period ***(Day 1 to Day 30)*** using diary cards after each dose of *Cervarix* is administered.
  - Recording of SAEs reported throughout the PMS period up to 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* is administered during the subject's participation in the PMS.
- Blood Samples: No blood samples will be collected in this PMS.
- Primary completion Date: last visit of Epoch 1

  Refer to GLOSSARY OF TERMS for the definition of PCD.
- End of Study (EoS): Last subject's last visit. (Follow up after the last dose)

  Refer to GLOSSARY OF TERMS for the definition of EoS.
- Duration of the PMS: The intended duration of this study is approximately 4 years.
  - Epoch 001: Prospective data collection starting at vaccination dose 1 and ending at follow up after ***last dose***.

  The below table presents the study group and the epoch foreseen in the PMS study.

Synopsis table 1 Study group and epoch foreseen in the study

Study group	Number of subjects	Age (Min/Max)	Epoch 001
HPV Group	Approx 600	9/25 years	X

- Pregnant subjects: Pregnant subjects who receive *Cervarix* inadvertently or subjects who become pregnant within 30 days after any vaccination dose will be followed up to determine the pregnancy outcome.

	Pregnancy outcome including the status of the mother and child will be forwarded to GSK. Generally, follow-up should be no longer than 6 to 8 weeks following the estimated delivery date, if possible. • Type of PMS: Self-contained. • Data collection: Standardised hard copy Case Report Form (CRF). SAEs, ADRs and pregnancy information will be collected by using the SAE, ADR and Pregnancy Reporting Form.
Discussion of PMS design (Amended: 14 May 2018)	• All adverse events reported during the 30-day post-vaccination follow-up period and all SAEs reported up to 30 days ***(Day 1 to Day 30)*** after the last dose administered during the PMS will be collected as part of safety data in this PMS. These adverse events will be further classified by GSK at the time of statistical analyses as expected/unexpected based on the current Prescribing Information.
Number of subjects	• As per the MFDS (Korea) requirements, safety information from a total of at least 600 evaluable subjects is needed for this PMS. Therefore, a total of at least 600 evaluable subjects will be enrolled over a period of 4 consecutive years.
Endpoints (Amended: 14 May 2018)	• Occurrence of AEs during the 30-day ***(Day 1 to Day 30)*** follow-up period after each vaccine dose. • Occurrence of any SAE reported throughout the PMS period up to 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* administered during subject's participation in the PMS.

TABLE OF CONTENTS

PAGE

SPONSOR INFORMATION 6

SYNOPSIS 7

LIST OF ABBREVIATIONS 15

GLOSSARY OF TERMS 16

TRADEMARKS 20

1. INTRODUCTION 21
   - 1.1. Background 21
   - 1.2. Rationale for the PMS 21

2. OBJECTIVE (AMENDED: 14 MAY 2018) 22

3. PMS DESIGN OVERVIEW (AMENDED: 14 MAY 2018) 22
   - 3.1. Discussion of PMS design (Amended: 14 May 2018) 23

4. STUDY POPULATION 24
   - 4.1. Number of subjects/centres (Amended: 14 May 2018) 24
     - 4.1.1. Recruitment of PMS centres 24
   - 4.2. Inclusion criteria for enrolment 25
   - 4.3. Exclusion criteria for enrolment 25

5. CONDUCT OF THE PMS 25
   - 5.1. Regulatory and ethical considerations, including the informed consent process 25

6. DETAILED PMS PROCEDURES 27
   - 6.1. Subject identification 27
   - 6.2. General PMS aspects 27
   - 6.3. Outline of PMS procedures (Amended: 14 May 2018) 27
   - 6.4. Detailed description of PMS procedures (Amended: 14 May 2018) 28
     - 6.4.1. Check inclusion and exclusion criteria 28
     - 6.4.2. Informed consent 29
     - 6.4.3. Collect demographic data 29
     - 6.4.4. Record medical history 29
     - 6.4.5. Physical examination 29
     - 6.4.6. *Medication/*Vaccination History 29
     - 6.4.7. Check and record medication/vaccination 29
     - 6.4.8. Check contraindications, warnings and precautions to vaccination 30
     - 6.4.9. Assess body temperature as pre-vaccination 30
       - 6.4.9.1. Vaccination 30
     - 6.4.10. Distribution, return and transcription of diary cards 30
     - 6.4.11. Recording of AEs, ADRs and SAEs 31
     - 6.4.12. Procedures during follow-up visits/contacts 31

6.4.13. PMS conclusion 31

7. DESCRIPTION OF *CERVARIX* 31
7.1. Dosage and administration of *Cervarix* 31
7.2. Contraindications to subsequent vaccination 31
7.3. Warnings and precautions 31
7.4. Concomitant medication/vaccination (Amended: 14 May 2018) 32
7.4.1. Recording of concomitant medications/products and concomitant vaccination 32
7.4.2. Time window for recording concomitant medication/vaccination in the CRF 32

8. SAFETY 33
8.1. Safety definitions 33
8.1.1. Definition of an adverse event 33
8.1.2. Definition of adverse drug reaction 34
8.1.3. Definition of a serious adverse event 34
8.2. Events or outcomes not qualifying as AEs or SAEs (Amended: 14 May 2018) 35
8.2.1. Pregnancy 35
8.2.2. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events 36
8.3. Detecting and recording AEs, ADRs and SAEs (Amended: 14 May 2018) 36
8.3.1. Time period for detecting and recording AEs, ADRs and SAEs 36
8.3.2. Evaluation of AEs, ADRs and SAEs 38
8.3.2.1. Active questioning to detect AEs, ADRs and SAEs 38
8.3.2.2. Assessment of severity 38
8.3.2.3. Assessment of causality 39
8.3.2.4. Assessment of the outcomes 41
8.3.2.5. Medically attended visits 41
8.4. Reporting of SAEs, Pregnancies and other events *related to Cervarix* (Amended: 14 May 2018) 41
8.4.1. Prompt reporting of SAEs related to PMS participation/ related to *Cervarix*, pregnancies and other events to GSK 41
8.4.2. PMS Contact for Reporting SAEs*, ADRs* and pregnancies: Please refer to local PMS contact information 42
8.4.3. Regulatory reporting requirements for SAEs 42
8.4.4. Completion and transmission of SAE reports to GSK Biologicals 43
8.4.5. Completion and transmission of non-serious AEs related to *Cervarix* reports to GSK 43
8.4.6. Completion and transmission of pregnancy reports to GSK Biologicals 44
8.5. Follow-up of AEs and SAEs (Amended: 14 May 2018) 44
8.5.1. Follow-up of pregnancies 45
8.6. Treatment of AEs 45

9. EFFICACY ASSESSMENT 45

10. SUBJECT COMPLETION AND WITHDRAWAL 45
10.1. Subject completion 45
10.2. Subject withdrawal (Amended: 14 May 2018) 45
10.2.1. Subject withdrawal from PMS 46

11. STATISTICAL METHODS 46
11.1. Endpoints (Amended: 14 May 2018) 46
11.2. Determination of sample size 47
11.3. Study cohorts to be evaluated 47
11.3.1. Total Vaccinated cohort 47
11.3.2. Total Safety cohort 47
11.4. Conduct of analyses 47
11.4.1. Sequence of analyses 48
11.4.2. Statistical considerations for interim analyses 48
11.5. Statistical methods (Amended: 14 May 2018) 48
11.5.1. Analysis of demographics/baseline characteristics 48
11.5.2. Analysis of safety 48
11.5.2.1. Within group assessment 49

12. ADMINISTRATIVE MATTERS (AMENDED: 14 MAY 2018) 49
12.1. Case Report Form 49
12.2. Monitoring by GSK Biologicals 50
12.3. Archiving of data at PMS sites 51
12.4. Audits 52
12.5. Posting of information on public registers 52
12.6. Ownership, confidentiality and publication (Amended: 14 May 2018) 52
12.6.1. Ownership 52
12.6.2. Confidentiality 52
12.6.3. Publication 53
12.6.4. Provision of PMS results to physicians, posting to the clinical trials registers and publication 53

13. COUNTRY SPECIFIC REQUIREMENTS 54

14. REFERENCES 55

LIST OF TABLES

PAGE

Table 1 Study group and epoch foreseen in the study 23

Table 2 *Expected enrolment plan of subject* 24

Table 3 *List of PMS procedures* 28

Table 4 Reporting periods for AEs, ADRs and SAEs 37

Table 5 Time frames for submitting SAEs and other events reports to GSK Biologicals 42

Table 6 Exact two-sided 95% CI for the percentage of subjects reporting at least one symptom with a sample size of 600 subjects 47

LIST OF APPENDICES

PAGE

APPENDIX A AMENDMENTS ADMINISTRATIVE CHANGES TO THE PROTOCOL 56

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CP	Concept Protocol
CRF	Case Report Form
EoS	End of Study
EPI	Expanded Program on Immunization
GEP	Good Epidemiological Practice
GSK	GlaxoSmithKline
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LSOP	Local Standard Operating Procedure
MFDS	Ministry of Food and Drug Safety
PCD	Primary Completion Date
PI	Prescribing Information
PII	Personally Identifiable Information
PMS	Post-Marketing Surveillance
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SPM	Study Procedure Manual
VCSP	GSK Biologicals' Central Safety and Pharmacovigilance

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- Combined estrogen and progesterone oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive oestrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the PMS, and this male is the sole partner for that subject,

The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.

- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.,
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle**.**

Adverse drug reaction: An adverse drug reaction is any adverse event whose causality to the drug cannot be ruled out and is assessed as "certain" or "probably/likely" or "possible" or "conditional/unclassified" or "unassessible /unclassifiable".

Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the PMS based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS): **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a set of consecutive time points or a single time point from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the time points included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical/epidemiology trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.

Expected adverse event:	The presence/occurrence/intensity of an AE that is expected from the subjects during the post-vaccination follow-up period as described in the locally approved Prescribing Information
Legally acceptable representative **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the PMS.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Post-marketing surveillance:	Routine country-specific post vaccine/drug approval surveillance PMS mandated by regulatory authorities that applies an observational approach for the collection of safety information from subjects in a normal healthcare setting.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study endpoints.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: ‘A written description of a change(s) to or formal clarification of a protocol.’ GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, PMS design, or scientific integrity of the PMS.

Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the PMS.
Self-contained study:	Study with objectives not linked to the data of another study.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the PMS.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the PMS.
Surveillance:	Surveillance is defined as the ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Unexpected adverse event:	Any AE that is not described in the approved Prescribing Information. Unexpected AEs are therefore not expected to occur during the post-vaccination follow-up period.

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademarks of the GSK group of companies	Generic description
Cervarix	GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV) vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant

1. INTRODUCTION

1.1. Background

Anal cancer is rare in the general population with an average worldwide incidence of 1 per 100,000, but is reported to be increasing in more developed regions. Globally, there are an estimated 27,000 new cases every year [de Martel C, 2012]. Women have higher incidences of anal cancer than men. Incidence is particularly high among populations of men who have sex with men (MSM), women with history of cervical or vulvar cancer, and immunosuppressed populations, including those who are HIV-infected and patients with a history of organ transplantation.

In South Korea, the incidence of anal cancer by sex is 0.4 ASR (Age-standardized rates per 100,000 men per year) for men and 0.3 ASR (Age-standardized rates per 100,000 women per year) for women [WHO/ICO HPV information center].

Data on the role of Human papillomavirus (HPV) in anogenital cancers other than the cervix is limited, but there is an increasing body of evidence strongly linking HPV DNA with cancers of the anus, vulva, vagina, and penis. Although these cancers are much less frequent compared to cervical cancer, their association with HPV make them potentially preventable and subject to similar preventative strategies as those for cervical cancer. [WHO/ICO HPV information center].

HPV related anal cancer is predominantly associated with infection with HPV types 16 and 18 [Chaturvedi, 2010], that are included in *Cervarix*. This infers the possibility of using similar preventive strategies for both cancer types.

Based on two studies comparing the immunogenicity of *Cervarix* and *Gardasil* in females (HPV-010 and HPV-071) with two other studies (HPV-011 and HPV-040) providing immunogenicity and safety data for *Cervarix* vaccination in males, the indication of *Cervarix* was updated to include anal cancer caused by HPV types 16, 18 for both women and men by Ministry of Food and Drug Safety (MFDS) (Korea).

1.2. Rationale for the PMS

In Korea, GSK Biologicals' HPV vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant (*Cervarix*) was approved in July 2008. The indication was updated to include anal cancer caused by HPV types 16, 18 for both women and men. As per MFDS (Korea) requirements, this post-marketing surveillance (PMS) is being conducted to collect safety information on the use of *Cervarix* upon the expanded indication to anal cancer in both women and men, in at least 600 Korean women and men within 30 days after the vaccination when administered according to the approved Prescribing Information (PI) in Korea in a real health care setting over a 4-year period.

2. OBJECTIVE (AMENDED: 14 MAY 2018)

To assess the safety of GSK Biologicals' HPV vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant, in terms of frequency and intensity of adverse events (AEs) and serious adverse events (SAEs) when administered according to the local PI.

Refer to Section 11.1 for the definition of the endpoint.

3. PMS DESIGN OVERVIEW (AMENDED: 14 MAY 2018)

Sequential Allocation of Subject Numbers					
Cervarix (N ~ 600)					
Vaccination Dose 1	Follow-up 30-day follow-up after Dose 1	Vaccination Dose 2	Follow-up 30-day follow-up after Dose 2	Vaccination Dose 3	Follow-up 30-day follow-up after Dose 3

N: Number of subjects planned to be enrolled
PMS conclusion will depend on the concluding visit of the subject in the PMS.
Definition of Conclusion of PMS for a subject: Subjects who have completed 30-day follow-up after at least one dose, regardless of the number of doses, are considered to have completed the PMS.
Note: Eligible subjects can be enrolled at any stage in the PMS regardless of *Cervarix* dose(s) received previously. Follow-up for AEs will continue for 30 days after receiving each vaccine dose(s) in the PMS. Follow-up of SAEs will continue from the date of Visit 1 until 30 days after the last dose received in the PMS. *Cervarix* will be vaccinated according to local practice

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 8), are essential and required for study conduct. ***This PMS will be conducted by a continuous surveillance method.***

- PMS design: A prospective, observational, non-comparative, multi-centre PMS in Korea.
- Study population: 9-25 years old males and females.
- Vaccination schedule: *Cervarix* will be administered as per the local PI in Korea.

The recommended schedule is as follows:

  - Vaccination: The 9-25 years old subjects should be administered *Cervarix* with 3 doses ***(0.5mL each)***, 0, 1, and 6 months schedule. The 9-14 years old subjects can be vaccinated with 2 doses, 0 and 6***-12*** months schedule. ***In the 2-dose schedule, if the second dose is administered before 5 months after the first dose, the third dose vaccination is required. In the 3 doses schedule, if the vaccination schedule requires flexibility, the second dose can be administered between 1 and 2.5 months and the third dose can be administered between 5 and 12 months after the first dose.***

Note: The subject/subject's parent's/LAR's signature in the Informed Consent Form (ICF)/Informed Assent Form (IAF) signifies enrolment of the subject into the PMS. The ICF/IAF is for the collection and handling of safety information and **not** for the vaccination procedure.

- Safety monitoring:
  - Recording of all AEs during the 30 day period ***(Day 1 to Day 30)*** using diary cards after each dose of *Cervarix* is administered.
  - Recording of SAEs, adverse drug reactions (ADRs) and Pregnancy from the date of Visit 1 until 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* administered during the subject's participation in the PMS.
- Blood Samples: No blood samples will be collected in this PMS.
- Primary completion Date: last visit of Epoch 1.

  Refer to GLOSSARY OF TERMS for the definition of PCD.
- End of Study (EoS): Last subject last visit (Follow up after the last dose)

  Refer to GLOSSARY OF TERMS for the definition of EoS.
- Duration of the PMS: The intended duration of this study is approximately 4 years.
  - Epoch 001: Prospective data collection starting at vaccination dose 1 and ending at follow up after ***last dose***.

The below table presents the study group and the epoch foreseen in the PMS study.

- **Study groups**: The study groups and epoch foreseen in the study are provided in Table 1.

Table 1 Study group and epoch foreseen in the study

Study groups	Number of subjects	Age at Dose 1 (Min/Max)	Epoch 001
HPV Group	Approx. 600	9/25 years	X

- Type of PMS: Self-contained.
- Data collection: Standardised hard copy Case Report Form (CRF). SAEs, ADRs and pregnancy information will be collected by using the SAE, ADR and Pregnancy Reporting Form.

3.1. Discussion of PMS design (Amended: 14 May 2018)

All adverse events reported during the 30-day post-vaccination follow-up period and all SAEs reported throughout the PMS period up to 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* administered during the subject's participation in the PMS, will be collected as part of safety data in this PMS. These adverse events will be further classified by GSK at the time of statistical analyses as expected/unexpected based on the locally approved Prescribing Information.

4. STUDY POPULATION

4.1. Number of subjects/centres (Amended: 14 May 2018)

As per the MFDS (Korea) requirements, safety information from a total of at least 600 evaluable subjects is needed for this PMS. Therefore, a total of at least 600 evaluable subjects will be enrolled over a period of 4 consecutive years.

4.1.1. Recruitment of PMS centres

Overview of the recruitment plan:

- This prospective, observational PMS will be conducted at multiple centres ***in*** private clinics and hospitals ***(department of pediatrics and obstetrics & gynecology, etc.)*** in Korea for a period of 4 years.
- PMS population: Subjects who receive at least one dose of *Cervarix* as a part of routine practice at a clinic or hospital. Only subjects to whom *Cervarix* will be prescribed in routine clinical practice will be invited to participate in the surveillance.
- Eligible subjects may join the PMS after the ICF/IAF has been signed by the subject/subject's parent/LAR.
- The PMS is required to be conducted in at least one hospital [with Institutional Review Board (IRB) oversight] in order for the PMS to be conducted in private clinics (without IRB).
- Target enrolment: A total of at least 600 subjects will be enrolled over a period of 4 years
- The vaccine will be purchased by the subject/subject's parents/LAR.
- The recruitment will be monitored by the PMS monitor.

Table 2 Expected enrolment plan of subject

Period	*Tentative calendar dates*	*Planned No. of enrolled subject**
1st Year	*2017.07.28 ~ 2018.07.27*	*0*
2nd Year	*2018.07.28 ~ 2019.07.27*	*280*
3rd Year	*2019.07.28 ~ 2020.07.27*	*300*
4th Year	*2020.07.28 ~ 2021.07.27*	*20*
Total		*600***

**** Approximate number***
***** At least 600 evaluable subjects will be recruited for the PMS.***
Note: The above plan may be modified depending on conditions such as progress

4.2. Inclusion criteria for enrolment

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

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

- Subject or/and subjects whose parent(s)/Legally Acceptable Representative(s) [LAR(s)], in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., complete the diary cards, return for follow-up visits).
- Korean male or female subjects aged 9-25 years who are eligible for the series of *Cervarix* according to the locally approved PI.
- Written informed consent obtained from the subject/from the parent(s)/LAR of the subject.

4.3. Exclusion criteria for enrolment

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

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

- At the time of PMS entry, the contraindications and precautions of use indicated in the locally approved PI. PI should be checked and the subject must not be included in the PMS if there is any contraindication. Any changes in the locally approved PI must be implemented immediately.
- Subjects who had previous administration of a HPV vaccine other than *Cervarix* will not be enrolled into the study
- Subjects who are not eligible for vaccination with *Cervarix* according to the medical judgement of physician.
- Child in care. Please refer to the GLOSSARY OF TERMS for the definition of child in care.

5. CONDUCT OF THE PMS

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

The PMS will be conducted in accordance with the ICH Guideline for GCP or other applicable guidelines (local rules and regulations of the country (MFDS) (Korea) and relevant GSK SOPs/Policies and Guidance), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

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

GSK will obtain favourable opinion/approval to conduct the PMS from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the PMS in that country.

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

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

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

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

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

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

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

6. DETAILED PMS PROCEDURES

6.1. Subject identification

Subject numbers will be assigned sequentially to subjects who participate/whose parents/LARs consent to allow their children to participate in the PMS, according to the range of subject numbers allocated to each PMS centre.

6.2. General PMS aspects

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

6.3. Outline of PMS procedures (Amended: 14 May 2018)

Table 3 presents the list of PMS procedures.

Table 3 List of PMS procedures

Epoch	Epoch 001		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3 [c]**
Informed consent *	●		
Check inclusion/exclusion criteria *	●		
Check contraindications	●	●	●
Check warnings and precautions	●	●	●
Collect demographic data	●		
Medical history *	●		
Medication/Vaccination history **	●		
Physical examination	●	O	O
Pre-vaccination body temperature	●	●	●
Record vaccination information	●	●	●
Distribution of diary cards	O	O	O
Recording of adverse events within 30 days post-vaccination, by physician	●	●	●
Return of diary cards [a]		O	O
Diary card transcription by physician		●	●
Record any concomitant medication/vaccination	●	●	●
Record any intercurrent medical conditions		●	●
Reporting of serious adverse events / ADRs/Pregnancy Information	●	●	●
PMS Conclusion [b]	●	●	●

● is used to indicate a PMS procedure or a vaccination-related non-PMS procedure that requires documentation in the individual CRF.
○ is used to indicate a PMS procedure that does not require documentation in the individual CRF.
* For the subjects who have received *Cervarix* previously and are enrolled in the PMS, procedures for Informed Consent/Check inclusion/exclusion criteria/Medical history/Vaccination history can be conducted at the first PMS-related visit.
** ***Medication***/Vaccination history (within 30-days prior to the *Cervarix* vaccination)
For subjects who have received one or two dose/s of *Cervarix* before the PMS enrolment, previous *Cervarix* vaccination history will be reported starting at the first PMS-related visit onwards irrespective of the number of dose subject received during the PMS.
[a] – The subjects will be instructed to return the completed diary card to the physician on their next PMS visit or phone or mail, to report any AEs/SAEs/ADRs/Pregnancy during the 30 day period ***(Day 1 to Day 30)*** using diary cards after each dose of *Cervarix* is administered.
[b] –PMS CRF Conclusion section to be completed depending on the available concluding visit of the subject in the PMS. The CRF conclusion will be 30 days after the last dose.
[c]–The visit 3 can be omitted as 9-14 years old can be vaccinated with two dose schedule.

It is the physician's responsibility to ensure that the dosing intervals are followed as described in the locally approved PI. However, if circumstances dictate other intervals, this will not lead to the exclusion of the subject from the analysis.

6.4. Detailed description of PMS procedures (Amended: 14 May 2018)

6.4.1. Check inclusion and exclusion criteria

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

6.4.2. Informed consent

The ICF/IAF for this PMS is for the collection and handling of personal and safety information after vaccination with *Cervarix*. Diary card(s) will be used to collect safety information and for source document verification. The ICF/IAF for this PMS will not include consent for vaccination as vaccination is at the discretion of subject/ parent(s)/LAR and the physician.

The signed/witnessed/thumb printed informed consent of the subject or subject's parent(s)/LAR(s) must be obtained before study participation. The signed informed assent of a subject below the age of consent (i.e., minor) should be obtained in addition to the signed informed consent by her parent(s)/LAR(s) according to local rules and regulations. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

6.4.3. Collect demographic data

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

6.4.4. Record medical history

Obtain the subject's medical history ***such as status (past/current), diagnosis, classify (renal/liver disease/other)*** by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the PMS in the CRF.

6.4.5. Physical examination

Perform a physical examination of the subject. Collected information ***(weight, height)*** needs to be recorded in the CRF.

At each study visit subsequent to the first ***visit***, a physical examination will only be performed if the subject indicates during questioning that there may be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this PMS or by referral to an appropriate health care provider.

6.4.6. *Medication/*Vaccination History

Collect information regarding all ***medicines/***vaccines administered to the subject 30 days prior to vaccination with *Cervarix* during the PMS.

6.4.7. Check and record medication/vaccination

Concomitant medication/vaccination must be recorded in the CRF (see Section 7.4).

6.4.8. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination are to be checked at the beginning of each vaccination visit (see Section 7.2)

6.4.9. Assess body temperature as pre-vaccination

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to *Cervarix* administration as routine practice. The preferred route for recording temperature in this PMS will be axillary/tympanic. If the subject has fever [fever is defined as temperature 37.5°C on oral, axillary or tympanic setting, or 38.0°C on rectal setting] on the day of vaccination, the vaccination visit will be rescheduled.

6.4.9.1. Vaccination

After completing the prerequisite procedures prior to vaccination, one dose of *Cervarix* will be administered according to the PI (refer to Section 7.1).

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

6.4.10. Distribution, return and transcription of diary cards

The physician will provide the diary card to the subjects or subject's parent(s)/LAR(s) to record e. g. Medication taken, AE, SAE, and pregnancy until next visit/contact. The subjects or 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 subjects or subject's parent(s)/LAR(s) at the subsequent visit/contact. Any unreturned diary cards will be sought from the subjects or subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure. The Physician will transcribe the collected information into the CRF in English

After each vaccination, diary cards will be provided to the subjects or subject's parent(s)/LAR(s) to record any AEs (i.e. on the day of vaccination and during the next 29 days) occurring after vaccination. The subjects or subjects' parent(s)/LAR(s) will be instructed to return the completed diary card to the physician on their next PMS visit or provide details during the telephonic interview from physicians or by postal mail. Site staff will try to contact subject or subject's parent(s)/LAR(s) through telephone call(s) ***(at least 3 attempts)*** for any unreturned diary for follow up. Information collected will be treated confidentially and for the purpose of reporting SAE(s) to MFDS (Korea), and for publication, if required.

Collection of pregnancy outcome information from pregnant subjects who received *Cervarix*, at 6-8 weeks after the Estimated Date of Delivery, if possible.

6.4.11. Recording of AEs, ADRs and SAEs

Refer to Section 8.3 for procedures for the Physician to record AEs, ADRs and SAEs and to Section 8.3 for guidelines on how to report these AEs /ADRs /SAEs to GSK Biologicals.

The subjects or 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.

6.4.12. Procedures during follow-up visits/contacts

Note that some of the procedures to be performed during the follow-up visits/contacts (recording of AEs/SAEs) and are described in Section 6.4.7 up to Section 6.4.11.

Following-up to return and transcription of diary cards (refer to Section 6.4.7).

Checking for pregnancy within 30 days after *Cervarix* vaccination ***as applicable.***

6.4.13. PMS conclusion

The physician will review safety data collected to ensure accuracy and completeness and will complete the PMS Conclusion page in the CRF.

7. DESCRIPTION OF *CERVARIX*

All marketed vaccines to be used have been developed and manufactured by GSK Biologicals.

Refer to the locally approved PI for information on the formulation and presentation of the *Cervarix* vaccine to be used in this PMS.

7.1. Dosage and administration of *Cervarix*

The vaccine should be administered as an intramuscular injection. The preferred sites are deltoid muscle in upper arms. Refer to the locally approved PI for more detailed information.

7.2. Contraindications to subsequent vaccination

The events that constitute absolute contraindications to further administration of *Cervarix* are listed in the locally approved PI. If any of these events occur during the surveillance, the subject must not receive additional doses of vaccine but may continue other PMS procedures at the discretion of the physician and any applicable local recommendations.

7.3. Warnings and precautions

Refer to the approved product label/package insert.

7.4. Concomitant medication/vaccination (Amended: 14 May 2018)

All concomitant vaccinations according to local practice are allowed during the PMS***. Collected information for concomitant medication/vaccination such as trade/generic name, route, frequency, total daily dose (dose, unit), start date, end date, indication etc. needs to be recorded in the CRF.*** The ***medication/***vaccination history (within 30-days prior to the *Cervarix* vaccination) should be documented in the CRF. For subjects who have received any of their dose/s of *Cervarix* outside the PMS and appear for the subsequent dose/s in this PMS, previous *Cervarix* vaccination history will be reported starting at first visit onwards irrespective of the dose subject has appeared for in the PMS. (Refer to the Table 1).

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

7.4.1. Recording of concomitant medications/products and concomitant vaccination

The following concomitant medications/products/vaccines must be recorded in the eCRF/CRF or the ***SAE/ADR*** Report if administered during the indicated recording period:

- All concomitant medication/vaccination, 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, or ≥ 38.0°C (100.4°F) on rectal 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 PMS SAE report form, as applicable. Refer to Section 8.1.3 for the definition of a SAE.

7.4.2. 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 each dose of *Cervarix* and ending 30 days ***(Day 1 to Day 30)*** after each dose of *Cervarix* must be recorded in the CRF.
- Any vaccine not foreseen in the PMS protocol administered in the period beginning 30 days (Day – ***29*** to Day ***1***) preceding each dose of *Cervarix* and ending 30 ***(Day 1 to Day 30)*** days after each dose of *Cervarix* must be recorded in the CRF.

- Any investigational medication or vaccine administered throughout the PMS (i.e. from 30 days before the first dose of the vaccine and 30 days after the last dose of the vaccine) must be recorded in the CRF.

8. SAFETY

The physician or site staff is/are responsible during the PMS for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in this protocol.

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

8.1. Safety definitions

8.1.1. Definition of an adverse event

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

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 an AE include

- Significant or unexpected worsening or exacerbation of the condition/indication under PMS.
- 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 *Cervarix* administration.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy) the condition that leads to the procedure is an AE/SAE.
- 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 PMS that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the PMS. These events will be recorded in the medical history section of the CRF (i.e. prior to the first PMS vaccination).

An Expected/Unexpected AE defined as below;

- Expected AE: The presence/occurrence/intensity of an AE that is expected from the subjects during the post-vaccination follow-up period as described in the locally approved Prescribing Information.
- Unexpected AE: Any AE that is not described in the approved Prescribing Information. Unexpected AEs are therefore not expected to occur during the post-vaccination follow-up period.

8.1.2. Definition of adverse drug reaction

Adverse drug reaction (ADR) represents adverse, unintended reactions from normal administration/use of the pharmaceuticalscannot be excluded. Of the voluntarily reported adverse events, those with no known causal relationship with the pharmaceutical are deemed to be adverse drug reactions.

8.1.3. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence 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 AE.

d. Results in disability/incapacity,

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.

or

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

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

8.2. Events or outcomes not qualifying as AEs or SAEs (Amended: 14 May 2018)

8.2.1. Pregnancy

Female subjects who are either pregnant or lactating and who inadvertently received *Cervarix* may continue other PMS procedures according to the locally approved Prescribing Information.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or an SAE.

Note: The pregnancy itself should always be recorded on a paper pregnancy report

The following should always be considered as an SAE and will be reported as described in Sections 8.4.1.

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/ at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations may be different.

- Any early neonatal death (i.e., death of a live born infant occurring within the first seven days of life).

  – Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a PMS subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion

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

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. hepatomegaly, jaundice, pallor, edema, bradycardia, facial edema, loss of hearing, tachycardia, increased intracranial pressure, lymphadenopathy, etc.) 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 8.1.1, or of an SAE, as defined in Section 8.1.3. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the PMS or are present at baseline and significantly worsen following the start of the PMS 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 PMS 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.

8.3. Detecting and recording AEs, ADRs and SAEs (Amended: 14 May 2018)

8.3.1. Time period for detecting and recording AEs, ADRs and SAEs

All AEs and SAEs starting immediately following administration of each dose of *Cervarix* must be recorded onto the CRF and all SAEs must be reported using the PMS 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 first receipt of *Cervarix* in the PMS and will end 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* administered during the subject's participation in PMS. See Section 8.4 for instructions on reporting and recording SAEs.

An overview of the protocol-required reporting periods for AEs, ADRs and SAEs is given in ***Table 4.***

Table 4 Reporting periods for AEs, ADRs and SAEs

PMS activity	V1	29 days post-V1		V2	29 days post-V2		V3	29 days post-V3
Reporting of AEs (expected & unexpected)								
Reporting of SAEs/ADRs and Pregnancy*								

V: vaccination; Post-V: post-vaccination

* For subjects who become pregnant after receiving *Cervarix* during PMS, 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 adverse events will be collected and reported only for *Cervarix* doses received within the PMS (after signing the ICF). Any adverse events collected after *Cervarix* doses received outside of this PMS shall be reported as a spontaneous report and shall follow guidance for reporting of spontaneous report.

All AEs reported within 30 days of each dose of the vaccine administered within the PMS and all SAEs reported throughout the PMS period up to 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* administered during the subject's participation in the PMS need to be recorded in the CRF. These AEs/ SAEs will be classified as expected/unexpected at the time of statistical analyses (refer to GLOSSARY OF TERMS for definitions of expected/unexpected adverse events).

All AEs reported during the 30 day ***(Day 1 to Day 30)*** follow-up period after each vaccine dose will be recorded using diary cards provided to the subjects or parent/LAR(s) of the subject. The AEs/SAEs will be analysed in the PMS report according to the expectedness and unexpectedness criteria as defined in the locally approved Prescribing Information (also refer to GLOSSARY OF TERMS).

Note: Assessment of causality and outcome will be done as defined in the MFDS (Korea) guidelines. According to the current version of MFDS (Korea) guidelines, causality will be assessed as: Certain; Probable/Likely; Possible; Unlikely; Conditional/Unclassified; Unassessible/Unclassifiable. Outcome will be assessed as recovered; not recovered; recovering; resolved with sequelae; fatal; unknown.

A post-surveillance AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 3. Physicians are not obligated to actively seek AEs/SAEs in former PMS participants. However, if the physician learns of any SAE, including a death, at any time after a subject has been discharged from the PMS, and he/she considers the event reasonably related to the *Cervarix*, the physician will promptly notify the Contact for Reporting SAEs.

8.3.2. Evaluation of AEs, ADRs and SAEs

8.3.2.1. Active questioning to detect AEs, ADRs and SAEs

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 subjects or subject's parent(s)/LAR(s) should be asked a non-leading question such as:

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

When an AE/ADR/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 the AE/SAE on the CRF or ADR Report Form, SAE Report Form as applicable. The physician is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the CRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. 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/SAE and not the individual signs/symptoms.

8.3.2.2. Assessment of severity

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 AEs (SAEs) recorded during the PMS. The assessment will be based on the physician's clinical judgement.

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

1 (mild)	=	An AE/SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. For fever: ≥37.5°C to ≤38.0°C (Oral/Axillary/ Tympanic temperature).
2 (moderate)	=	An AE/SAE which is sufficiently discomforting to interfere with normal everyday activities. For fever: >38°C to ≤39.0°C (Oral/Axillary/ Tympanic temperature).
3 (severe)	=	An AE/SAE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice). For fever: >39.0°C (Oral/Axillary/ Tympanic temperature).

An AE that is assessed as Grade 3 (severe) 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 8.1.3.

8.3.2.3. Assessment of causality

The Physician is obligated to assess the relationship between *Cervarix* 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 the administration of *Cervarix* will be considered and investigated. The Physician will also consult the local Prescribing Information (Summary of Product Characteristics, SPC) to ensure an accurate assessment.

There may be situations when a SAE has occurred and the Physician has minimal information to include in the initial report to GSK Biologicals. 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 Biologicals. The Physician may change his/her opinion of causality in light of follow-up information, and update 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 *Cervarix*?

If an event meets the criteria to be determined as 'serious' (see Section 8.1.3), 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable.
- Erroneous administration
- Other cause (specify).

Assessment of causality of these AEs will be done to reflect the requirement of MFDS (Korea) to assess the relationship of the AEs.

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

As per MFDS (Korea) requirements, causality will be assessed as:

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. Unlikely:

   It is a transitory case which may not have causality with the administration and use of the drug, it is also able to be explained reasonably by other medications, chemical substances or latent disease.

5. Conditional/Unclassified:

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

6. Unassessible/Unclassifiable:

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

If the physician judges that the causal relationship is 1. Certain, 2. Probable/Likely, 3. Possible, 5. Conditional/Unclassified, or 6. Unassessible/Unclassifiable, they should classify the relevant event as an ADR according to the GSK Reporting Procedure and prepare an ADR Report.

8.3.2.4. Assessment of the outcomes

Outcome of any non-serious AE occurring within 30 days post-vaccination or any SAE reported during the entire PMS will be assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.
- Fatal.
- Unknown.

8.3.2.5. Medically attended visits

For each adverse event the subject experiences, subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalisation or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the CRF.

8.4. Reporting of SAEs, Pregnancies and other events *related to Cervarix* (Amended: 14 May 2018)

8.4.1. Prompt reporting of SAEs related to PMS participation/ related to *Cervarix*, pregnancies and other events to GSK

SAEs that occur in the time period defined in Section 8.3.1 will be reported promptly to GSK within the timeframes described in Table 5 once the physician determines that the event meets the protocol definition of an SAE.

Non-serious AEs related to the vaccine that occur in the time period defined in Section 8.3.1 will be reported promptly to GSK Biologicals within the timeframes described in ***Table 5*** once the physician determines that the event meets the protocol definition for that event.

Pregnancies that occur in the time period defined in Section 8.3.1 will be reported promptly to GSK within the timeframes described in Table 5 once the physician becomes aware of the pregnancy. The subject will be followed to determine the outcome of the pregnancy.

Table 5 Time frames for submitting SAEs and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours*	SAE report	24 hours*	SAE report
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 physicians after the awareness of the information.

8.4.2. PMS Contact for Reporting SAEs, *ADRs* and pregnancies: Please refer to local PMS contact information

Back-up PMS Contact for Reporting SAEs, *ADRs* and Pregnancies

24/24 hour and 7/7 day availability:

GSK Biologicals Clinical Safety & Pharmacovigilance

Outside US & Canada sites:
Fax: PPD or PPD
Email address: PPD

8.4.3. Regulatory reporting requirements for SAEs

The physician will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. 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 under surveillance. Prompt notification of SAEs by the physician to the PMS Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

8.4.4. Completion and transmission of SAE reports to GSK Biologicals

Once a physician becomes aware that an SAE has occurred in a PMS subject, she/he 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) transmission ***or e-mail delivery*** of the SAE Report Form is the preferred method to transmit this information to the Contact for Reporting SAEs. In rare circumstances and due to failure of facsimile ***or electronic*** 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 ***or e-mail*** must be accompanied by telephone call to the PMS Contact for Reporting SAEs.

8.4.5. Completion and transmission of non-serious AEs related to *Cervarix* reports to GSK

Once a physician becomes aware that a non-serious AE related to vaccine has occurred in a PMS subject, the physician (or designee) must complete an ***ADR*** Report and forward it to GSK within 5 calendar days. The report will always be completed as thoroughly as possible with all available details of the event and then dated and signed by the physician (or designee). Even if the physician does not have all information regarding an AE, the report should still be completed and forwarded to GSK within 5 calendar days. Once additional relevant information is received, the report should be updated and forwarded to GSK within two weeks.

The physician will always provide an assessment of causality at the time of the initial report.

Fax transmission ***or e-mail delivery*** is the preferred method to forward the paper ***ADR*** Report to the PMS Contact for Reporting SAEs. In absence/ dysfunction of fax equipment ***or electronic***, the PMS Contact for Reporting SAEs must be notified by telephone within 5 calendar days. As soon as the fax equipment ***or electronic*** is working again, the physician (or designee) must fax ***or e-mail*** the report to the PMS Contact for Reporting SAEs within 5 calendar days.

8.4.6. Completion and transmission of pregnancy reports to GSK Biologicals

Once the physician becomes aware that a subject is pregnant, the physician (or designee) must complete, date and sign a paper pregnancy notification report and fax ***or e-mail*** it to the PMS Contact for Reporting SAEs (refer to the local PMS contact information document) WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.5. Follow-up of AEs and SAEs (Amended: 14 May 2018)

After the initial AE/SAE report, the physician is required to proactively follow each subject and provide further information to GSK Biologicals 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 PMS.

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 up to 30 days ***(Day 1 to Day 30)*** after the last dose of *Cervarix* administered during the subject's participation in the PMS.

Physicians will follow-up subjects:

- With SAEs or subjects withdrawn from the PMS 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 PMS Monitor.

GSK Biologicals 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 PMS or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

8.5.1. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. 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 Biologicals using the paper pregnancy follow-up report and the ***SAE*** Report if applicable. Generally, the follow-up period does not need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this PMS, if the pregnancy outcome is an SAE, it should always be reported as an SAE.

8.6. Treatment of AEs

Treatment of any adverse event 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.

9. 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 PMS 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 *Cervarix* would likely be omitted in this drug use investigation.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject completion

Subjects who have completed 30-day follow-up after at least one dose, regardless of the number of doses are considered to have completed the PMS.

10.2. Subject withdrawal (Amended: 14 May 2018)

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 8.5).

Withdrawals will not be replaced.

10.2.1. Subject withdrawal from PMS

From an analysis perspective, a 'withdrawal' from the PMS refers to any subject who did not come back for the concluding visit/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 PMS when no PMS 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 ***attempts*** 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 PMS was made by the subject's parent(s) or LAR(s), or by the physician, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event.
- Lost to follow-up.
- Death.
- Other (specify).

11. STATISTICAL METHODS

11.1. Endpoints (Amended: 14 May 2018)

- Occurrence of AEs during the 30-day ***(Day 1 to Day 30)*** follow-up period after each vaccine dose.
- Occurrence of SAEs reported throughout the PMS period up to 30 days ***(Day 1 to Day 30)*** after the last dose administered during the subject's participation in the PMS.

11.2. Determination of sample size

According to MFDS (Korea) regulation requirement, at least 600 evaluable subjects will be recruited for the PMS. Therefore, 660 subjects are expected to be enrolled through the PMS period considering the dropout rate of 10% (out of 600 subjects). Depending on the status, the enrolment plan can be adjusted.

Table 6 presents the exact two-sided 95% confidence interval for a sample size of 600 subjects.

Table 6 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
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.

11.3. Study cohorts to be evaluated

11.3.1. Total Vaccinated cohort

The total vaccinated cohort will include all subjects who receive at least one dose of *Cervarix* in the PMS:

11.3.2. Total Safety cohort

Safety analysis based on all vaccination groups will include all subjects who were vaccinated per product information and have completed 30-day follow-up after at least one dose, regardless of the number of dose.

11.4. 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 PMS report.

11.4.1. Sequence of analyses

Analysis will be performed bi-annually for the first two years and annually for the remaining follow-up years (based on pre-defined cut-off date for enrolment). A comprehensive analysis will be performed at the end of the PMS. The analysis, including individual data listings, will be based on the cohort for vaccinated subjects for whom the PMS conclusion page has been received at GSK before the pre-defined cut-off date.

Bi-annual PMS reports will be written for the first two years and annual PMS reports will be written for the remaining years. A comprehensive PMS report will be written at the end of the PMS. All analyses described will be performed on cleaned data for each bi-annual/annual report. All reports will be sent to the GSK Biologicals' Central Safety and Pharmacovigilance (VCSP) and to MFDS (Korea).

11.4.2. Statistical considerations for interim analyses

As this is a descriptive PMS 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 PMS conduct.

11.5. Statistical methods (Amended: 14 May 2018)

11.5.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, gender, and ethnicity) ***and weight, height*** of the PMS cohort will be tabulated using descriptive statistics. Mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage will be calculated for categorical variables.

The medical history ***by disease classification and per past/current status*** and vaccination history of the vaccinated subjects will also be presented.

The distribution of subjects vaccinated among the PMS centres by years will be tabulated.

11.5.2. Analysis of safety

Safety analysis based on total vaccinated cohort, will include all subjects who were vaccinated per product information and have completed 30-day follow-up after at least one dose, regardless of the number of dose. Analysis of AE/SAE data reported after each dose will be performed separately.

11.5.2.1. Within group assessment

The AEs/ SAEs will be analysed in the PMS 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% confidence interval (CI), of any AEs occurring within 30 days ***(Day 1 to Day 30)*** will be tabulated, for each dose, for overall doses and by number of subjects. The same calculations will be done for any adverse events according to the severity and for those assessed as causally related to vaccination.

The verbatim reports of signs and symptoms will be matched and coded according to the appropriate WHO-ART Preferred Term. The PMS physician will review and confirm the appropriate WHO-ART Preferred Term by responding to data queries if any discrepancies are reported while coding. The percentage of subjects with AEs occurring within 30 days ***(Day 1 to Day 30)*** with its exact 95% CI will be tabulated by preferred term. Similar tabulation will be done for AEs with relationship to vaccination and for AEs rated as grade 3.

The number and percentage of subjects who received concomitant medication/ vaccination at least once during the 30-day ***(Day 1 to Day 30)*** follow-up period will be tabulated after each vaccine dose and overall, with exact 95% CI. Similar tabulations will be done for the number of subjects by types of medication/ vaccination during the entire PMS period.

The outcome of pregnancy (reported in the pregnancy report form) for subjects who become pregnant subjects during PMS will be presented, If possible.

Serious adverse events and withdrawals due to adverse events reported during the PMS period (each subject receiving the vaccine up to 30 days after the last dose) will be described in detail.

12. ADMINISTRATIVE MATTERS (AMENDED: 14 MAY 2018)

To comply with GEP, acceptable ethical principles, applicable local regulatory requirements, LSOP and administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. Safety data is used for analysis and GSK does not forward personally identifiable information***. In the PMS report, subject number which is a number identifying a subject will be reported to MFDS (Korea).***

12.1. Case Report Form

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

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

While completed CRFs are reviewed by a GSK Biologicals' PMS Monitor at the PMS 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 PMS data collected.

Any questions or comments related to the CRF should be directed to the assigned PMS 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 investigational site.

12.2. Monitoring by GSK Biologicals

Monitoring visits by a GSK PMS Monitor are for the purpose of confirming that GSK Biologicals' sponsored PMS are being conducted in accordance with the acceptable ethical principles and the applicable 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 PMS).

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

Direct access to all PMS-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document Verification (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 PMS monitor and physician and should be filed in the monitor's and physician's PMS 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, and GSK procedures, GSK monitors will contact the site prior to the start of the PMS to review with the site staff the protocol, PMS requirements, and their responsibilities to satisfy regulatory, ethical, and GSK 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 PMS to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- PMS is conducted in accordance with the currently approved protocol and any amendments, any other PMS agreements, GSK POL/SOP/Bio Guidance Document, 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 PMS, the monitor will conduct site closure activities with the physician or site staff, as appropriate, in accordance with applicable regulations, and GSK procedures.

12.3. Archiving of data at PMS sites

Following closure of the PMS, the physician must maintain all site PMS 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 PMS, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; 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.

12.4. Audits

To ensure compliance with GSK Vaccines' procedures and 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 PMS. Such audits/inspections can occur at any time during or after completion of the PMS. 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.

12.5. Posting of information on public registers

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

12.6. Ownership, confidentiality and publication (Amended: 14 May 2018)

12.6.1. Ownership

All information provided by GSK and all data and information generated by the site as part of the PMS (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 PMS are the sole property of GSK, and are hereby assigned to GSK.

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

12.6.2. Confidentiality

Documented evidence that a potential physician is aware and agrees to the confidential nature of the information related to the PMS 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 PMS (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 PMS. 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 IEC or IRB solely for the evaluation of the PMS; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a PMS subject; ***(iv)***

information from this PMS may also be combined with results from other research studies to learn more about the vaccine and related diseases; or (***v***) PMS results which may be published as described in the next paragraph. If a written contract for the conduct of the PMS which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

12.6.3. Publication

For multicentre studies, the first publication or disclosure of PMS results shall be a complete, joint multicentre 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 PMS 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 twenty-one working days, or at least fifteen working days for abstracts/posters/presentations). Proposed Publications shall not include either GSK confidential information other than the PMS 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 PMS, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

12.6.4. Provision of PMS results to physicians, posting to the clinical trials registers and publication

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

The results summary will be posted to the GSK Clinical PMS Register no later than 12 months after the last subject's last visit (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 PMS information will be posted to the GSK Clinical PMS 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.

13. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

14. REFERENCES

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APPENDIX A AMENDMENTS ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccines R & D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	208710 (EPI-HPV-077 VS KR PMS)
Administrative change number:	Amendment 1
Administrative change date:	14 May 2018
Co-ordinating author:	PPD Medical Writer from DreamCIS, contractor for GSK Biologicals
Rationale/background for changes: The protocol has been amended to address Ministry of Food and Drug Safety (MFDS) request for adding detailed description of enrolment plan, departments that will participate, method of PMS, collection of information regarding medical history, physical examination, and concomitant medication. In addition, collection of potential immune medicated diseases (pIMD) has been removed as it has not been considered mandatory for PMS, combined with results from other research studies to learn more about the vaccine and related diseases has been added in confidentiality section by referring to current Informed consents form (ICF), changed MFDS reporting method of personally identifiable information and added GSK reporting method of AEs/SAEs has been changed as it has been considered current PMS procedures, clarified vaccination schedule has been changed as it has been based on current prescribing information, and schedule period (such as Day 1 to Day 30) has been changed according to current writing process. **Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:**	
The list of contributing authors has been updated.	
Contributing authors	• PPD ***and*** PPD, Clinical and Epidemiology R&D Project Lead • PPD, Study Delivery Lead • PPD, Safety Physician • PPD, Lead Scientific Writer • PPD ***and*** PPD, Oversight Data Manager • PPD, Statistician • PPD, Regional VP Medical/Clinical GSK Vaccines • PPD, Regional Epidemiologist

	• PPD ***and*** PPD, Local Medical Lead, • PPD ***and*** PPD***, Country Clinical Operations Head*** • PPD***, Vaccines Medical Director*** • PPD, Named Safety Contact • PPD, Local Delivery Lead
Sponsor signatory has been updated.	
Sponsor signatory	~~Frank Struyf~~ ***Dorota Borys***, Director, Clinical and Epidemiology R&D Project Lead, HPV and Hepatitis vaccines, RDC Belgium, GlaxoSmithKline Biologicals, SA.
Synopsis has been updated as it has been based on current prescribing information as shown below:	
Indication	*Cervarix* is a vaccine indicated for active immunisation against HPV infection in males and females 9-25 years old as 3 doses, ~~0-1-6~~0***, 1 and*** 6 ***months*** schedule. Children and adolescents 9-14 years old can be vaccinated with 2 doses, ~~0-6~~0 ***and 6-12 months*** schedule.
Section 2. OBJECTIVES has been updated.	
2. OBJECTIVES~~~~ ~~**2.1. Primary objective**~~	
Section 3. PMS DESIGN OVERVIEW has been updated to address MFDS request for method of PMS as shown below:	
Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 8), are essential and required for study conduct. ***This PMS will be conducted by a continuous surveillance method.***	
Section 3. PMS DESIGN OVERVIEW has been updated as it has been based on current prescribing information shown below:	
The recommended schedule is as follows: – Vaccination: The 9-25 years old subjects should be administered ~~0.5 mL dose of~~ *Cervarix* with 3 doses ***(0.5mL each)***, 0, 1, and 6 months schedule. The 9-14 years old subjects can be vaccinated with 2 doses, 0 and 6***-12*** months schedule. ***In the 2 doses schedule, if the second dose is administered before 5 months after the first dose, the third dose vaccination is required. In the 3 doses schedule, if the vaccination schedule requires flexibility, the second dose can be administered between 1 and 2.5 months and the third dose can be administered between 5 and 12 months after the first dose.***	

Section 3. PMS DESIGN OVERVIEW has been updated according to current PMS procedures and writing process as shown below:

Sequential Allocation of Subject Numbers					
Cervarix (N ~~=~~ ~ 600)					
Vaccination Dose 1	Follow-up 30-day follow-up after Dose 1	Vaccination Dose 2	Follow-up 30-day follow-up after Dose 2	Vaccination Dose 3	Follow-up 30-day follow-up after Dose 3

N: Number of subjects planned to be enrolled
PMS conclusion will depend on the concluding visit of the subject in the PMS.
Definition of Conclusion of PMS for a subject: Subjects who have completed 30-day follow-up after at least one dose, regardless of the number of doses, are considered to have completed the PMS.
Note: Eligible subjects can be enrolled at any stage in the PMS regardless of *Cervarix* dose(s) received previously. Follow-up for AEs will continue for 30 days after receiving each vaccine dose(s) in the PMS. Follow-up of SAEs will continue from the date of Visit 1 until 30 days after the last dose ~~(dose 1, 2 or 3)~~ received in the PMS. *Cervarix* will be vaccinated according to local practice

- Safety monitoring:
  - Recording of all AEs during the 30 day period ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** using diary cards after each dose of *Cervarix* is administered.
  - Recording of SAEs, adverse drug reactions (ADRs) and Pregnancy from the date of Visit 1 until 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** after the last dose ~~(dose 1, 2 and 3)~~ of *Cervarix* administered during the subject's participation in the PMS.
  - Duration of the PMS: The intended duration of this study is approximately 4 years.
  - Epoch 001: Prospective data collection starting at vaccination dose 1 and ending at follow up after ~~dose 3~~***last dose***.

Table 1 Study group and epoch foreseen in the study

Study groups	Number of subjects	Age at Dose 1 (Min/Max)	Epoch 001
~~prospective~~***HPV Group***	Approx 600	9/25 years	X

3.1. Discussion of PMS design

All adverse events reported during the 30-day post-vaccination follow-up period and all SAEs reported throughout the PMS period up to 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** after the last dose ~~(dose 1, 2 or 3)~~ of *Cervarix* administered during the subject's participation in the PMS, will be collected as part of safety data in this PMS. These adverse events will be further classified by GSK at the time of statistical analyses as expected/unexpected based on the locally approved Prescribing Information.

Section 4.1 Number of subjects/centres has been updated to address MFDS request for adding detailed description of enrolment plan and departments that will participate as shown below:

Overview of the recruitment plan:

- This prospective, observational PMS will be conducted at multiple centres ***in*** private clinics and hospitals ***(department of pediatrics and obstetrics & gynecology, etc.)*** in Korea for a period of 4 years.
- PMS population: Subjects who receive at least one dose of *Cervarix* as a part of routine practice at a clinic or hospital. Only subjects to whom *Cervarix* will be prescribed in routine clinical practice will be invited to participate in the surveillance.
- Eligible subjects may join the PMS after the ICF/IAF has been signed by the subject/subject's parent/LAR.
- The PMS is required to be conducted in at least one hospital [with Institutional Review Board (IRB) oversight] in order for the PMS to be conducted in private clinics (without IRB).
- Target enrolment: A total of at least 600 subjects will be enrolled over a period of 4 years.
- The vaccine will be purchased by the subject/subject's parents/LAR.
- The recruitment will be monitored by the PMS monitor.

Table 2 Expected enrolment plan of subject

Period	*Tentative calendar dates*	*Planned No. of enrolled subject**
1st Year	*2017.07.28 ~ 2018.07.27*	*0*
2nd Year	*2018.07.28 ~ 2019.07.27*	*280*
3rd Year	*2019.07.28 ~ 2020.07.27*	*300*
4th Year	*2020.07.28 ~ 2021.07.27*	*20*
Total		*600***

**** Approximate number***
***** At least 600 evaluable subjects will be recruited for the PMS.***
Note: The above plan may be modified depending on conditions such as progress

Section 6.3. Outline of PMS procedures has been updated as it has been considered current PMS procedures as shown below:

~~**Table 2***Table 3*~~ presents the list of PMS procedures.

~~**Table 2***Table3 List of PMS procedures*~~

Epoch	Epoch 001		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3** [c]
Informed consent *	●		
Check inclusion/exclusion criteria *	●		
Check contraindications	●	●	●
Check warnings and precautions	●	●	●
Collect demographic data	●		
Medical history*	●		
Medication/Vaccination history **	●		
Physical examination	●	O	O
Pre-vaccination body temperature	●	●	●
Record vaccination information	●	●	●
Distribution of diary cards	O	O	O
Recording of adverse events within 30 days post-vaccination, by physician	●	●	●
Return of diary cards [a]		O	O
Diary card transcription by physician		●	●
Record any concomitant medication/vaccination	●	●	●
Record any intercurrent medical conditions		●	●
Reporting of serious adverse events / ADRs/Pregnancy Information	●	●	●
PMS Conclusion [b]	●	●	●

● is used to indicate a PMS procedure or a vaccination-related non-PMS procedure that requires documentation in the individual CRF.
○ is used to indicate a PMS procedure that does not require documentation in the individual CRF.
* For the subjects who have received *Cervarix* previously and are enrolled in the PMS, procedures for Informed Consent/Check inclusion/exclusion criteria/Medical history/Vaccination history can be conducted at the first PMS-related visit.
** ***Medication***/Vaccination history (within 30-days prior to the *Cervarix* vaccination)
For subjects who have received one or two dose/s of *Cervarix* before the PMS enrolment, previous *Cervarix* vaccination history will be reported starting at the first PMS-related visit onwards irrespective of the number of dose subject received during the PMS.
[a] – The subjects will be instructed to return the completed diary card to the physician on their next PMS visit or phone or mail, to report any AEs/SAEs/ADRs/Pregnancy during the 30 day period ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** using diary cards after each dose of *Cervarix* is administered.
[b] –PMS CRF Conclusion section to be completed depending on the available concluding visit of the subject in the PMS. The CRF conclusion will be 30 days after the last dose. ~~(dose 1, 2, 3).~~
[c] –***The visit 3 can be omitted as 9-14 years old can be vaccinated with two dose schedule.***

Section 6.4. Detailed description of PMS procedures has been updated to address MFDS request for collection of information regarding medical history, physical examination, and concomitant medication as shown below:

6.4.3. Collect demographic data

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

6.4.4. Record medical history

Obtain the subject's medical history ***such as status (past/current), diagnosis, classify (renal/liver disease/other)*** by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the PMS in the CRF.

6.4.5. Physical examination

Perform a physical examination of the subject. Collected information ***(weight, height)*** needs to be recorded in the CRF.

6.4.6. *Medication*/Vaccination History

Collect information regarding all ***medicines/***vaccines administered to the subject 30 days prior to vaccination with *Cervarix* during the PMS.

Section 6.4. Detailed description of PMS procedures has been updated as it has been considered current PMS procedures as shown below:

6.4.5. Physical examination

At each study visit subsequent to the first ***visit***, a physical examination will only be performed if the subject indicates during questioning that there may be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

6.4.10. Distribution, return and transcription of diary cards

After each vaccination, diary cards will be provided to the subjects or subject's parent(s)/LAR(s) to record any AEs (i.e. on the day of vaccination and during the next 29 days) occurring after vaccination. The subjects or subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the physician on their next PMS visit or provide details during the telephonic interview from physicians or by postal mail. Site staff will try to contact subject or subject's parent(s)/LAR(s) ~~at least 3 attempts~~ through telephone call(s) ***(at least 3 attempts)*** for any unreturned diary for follow up. Information collected will be treated confidentially and for the purpose of reporting SAE(s) to MFDS (Korea), and for publication, if required.

6.4.12. Procedures during follow-up visits/contacts

Following-up to return and transcription of diary cards (refer to Section 6.4.7).
~~Collection and verification of completed diary card during discussion with the subjects or subject's parent(s)/LAR(s) at the subsequent visit/contact. Any unreturned diary cards will be sought from the subjects or subject's parent(s)/LAR(s) 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 30 days after *Cervarix* vaccination~~, if possible~~ ***as applicable.***

Section 7.4. Concomitant medication/vaccination has been updated as it has been considered current PMS procedures and current writing process as shown below:

All concomitant vaccinations according to local practice are allowed during the PMS ~~and administration of these should be documented in the CRF~~***. Collected information for concomitant medication/vaccination such as trade/generic name, route, frequency, total daily dose (dose, unit), start date, end date, indication etc. needs to be recorded in the CRF.*** The ***medication/***vaccination history (within 30-days prior to the *Cervarix* vaccination) should be documented in the CRF. For subjects who have received any of their dose/s of *Cervarix* outside the PMS and appear for the subsequent dose/s in this PMS, previous *Cervarix* vaccination history will be reported starting at first visit onwards irrespective of the dose subject has appeared for in the PMS. (Refer to the Table 1).

7.4.1. Recording of concomitant medications/products and concomitant vaccination

The following concomitant medications/products/vaccines must be recorded in the eCRF/CRF or the ~~Expedited Adverse Event~~***SAE/ADR*** Report if administered during the indicated recording period:

7.4.2. 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 each dose of *Cervarix* and ending 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** after each dose of *Cervarix* must be recorded in the CRF.
- Any vaccine not foreseen in the PMS protocol administered in the period beginning 30 days ~~(Day 29 to Day 0)~~ ***(Day –29 to Day 1)*** preceding each dose of *Cervarix* and ending 30 ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** days after each dose of *Cervarix* must be recorded in the CRF.

Section 8.2.3. Reporting adverse events of specific interest to GSK has been removed as it has not been considered mandatory for PMS

~~**Section 8.2.3. Reporting adverse events of specific interest to GSK**~~

~~Several adverse events of specific interest including but not limited to potential immune medicated diseases (pIMD) and postural orthostatic tachycardia Syndrome (POTS), chronic regional pain syndrome (CRPS) following the Cervarix vaccination require close monitoring and further assessment. pIMD list is provided in .~~

Table 8 List of pIMDs

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy, - Multifocal motor neuropathy - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: - Diffuse Scleroderma - CREST syndrome • Idiopathic inflammatory myopathies, including: - Dermatomyositis - Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: - Juvenile Idiopathic Arthritis - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing Spondylitis, - Reactive Arthritis (Reiter's Syndrome), - Undifferentiated Spondyloarthritis, - Psoriatic Arthritis, - Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).
Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis including: - Giant Cell Arteritis (Temporal Arteritis), - Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa, - Kawasaki's disease, - Microscopic Polyangiitis, - Wegener's Granulomatosis (granulomatosis with polyangiitis),	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: - IgA nephropathy, - Glomerulonephritis rapidly progressive, - Membranous glomerulonephritis, - Membranoproliferative glomerulonephritis, - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome.

~~Vasculitis~~	~~Blood disorders~~	~~Others~~
~~- Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis),~~ ~~- Buerger's disease (thromboangiitis obliterans),~~ ~~- Necrotizing vasculitis (cutaneous or systemic),~~ ~~- anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),~~ ~~- Henoch-Schonlein purpura (IgA vasculitis),~~ ~~- Behcet's syndrome,~~ ~~- Leukocytoclastic vasculitis.~~		~~• Ocular autoimmune diseases including:~~ ~~- Autoimmune uveitis~~ ~~- Autoimmune retinitis.~~ ~~• Autoimmune myocarditis.~~ ~~• Sarcoidosis.~~ ~~• Stevens-Johnson syndrome.~~ ~~• Sjögren's syndrome.~~ ~~• Alopecia areata.~~ ~~• Idiopathic pulmonary fibrosis.~~ ~~• Goodpasture syndrome.~~ ~~• Raynaud's phenomenon.~~
~~Liver disorders~~	~~Gastrointestinal disorders~~	~~Endocrine disorders~~
~~• Autoimmune hepatitis.~~ ~~• Primary biliary cirrhosis.~~ ~~• Primary sclerosing cholangitis.~~ ~~• Autoimmune cholangitis.~~	~~• Inflammatory Bowel disease, including:~~ ~~- Crohn's disease,~~ ~~- Ulcerative colitis,~~ ~~- Microscopic colitis,~~ ~~- Ulcerative proctitis.~~ ~~• Celiac disease.~~ ~~• Autoimmune pancreatitis.~~	~~• Autoimmune thyroiditis (Hashimoto thyroiditis).~~ ~~• Grave's or Basedow's disease.~~ ~~• Diabetes mellitus type I.~~ ~~• Addison's disease.~~ ~~• Polyglandular autoimmune syndrome.~~ ~~• Autoimmune hypophysitis.~~

~~If the subject develops adverse event of specific interest during the surveillance period, the physician shall report it as an AE and follow up the subject to collect information using Targeted Follow-Up Questionnaires (TFUQ) provided by GSK. GSK may request additional information in such cases.~~

Section 8. SAFETY has been updated as it has been considered current PMS procedures and writing process as shown below:

8.3. Detecting and recording AEs, ADRs and

8.3.1. Time period for detecting and recording AEs, ADRs and SAEs

The standard time period for collecting and recording SAEs will begin at the first receipt of Cervarix in the PMS and will end 30 days ~~(Day 0 to Day 29)~~***(Day 1 to Day 30)*** after the last dose ~~(dose 1, 2 or 3)~~ of Cervarix administered during the subject's participation in PMS. See Section 8.4 for instructions on reporting and recording SAEs.

An overview of the protocol-required reporting periods for AEs, ADRs and SAEs is given in Table 4.

All AEs reported within 30 days of each dose of the vaccine administered within the PMS and all SAEs reported throughout the PMS ~~PMS~~ period up to 30 days ~~(Day 0 to Day 29)~~***(Day 1 to Day 30)*** after the last dose ~~(dose 1, 2, 3)~~ of Cervarix administered during the subject's participation in the PMS~~, and received within the PMS~~ need to be recorded in the CRF. These AEs/ SAEs will be classified as expected/unexpected at the time of statistical analyses (refer to GLOSSARY OF TERMS for definitions of expected/unexpected adverse events).

All AEs reported during the 30 day ~~(Day 0 to Day 29)~~***(Day 1 to Day 30)*** follow-up period after each vaccine dose will be recorded using diary cards provided to the subjects or parent/LAR(s) of the subject. The AEs/SAEs will be analysed in the PMS report according to the expectedness and unexpectedness criteria as defined in the locally approved Prescribing Information (also refer to GLOSSARY OF TERMS).

8.4. Reporting of SAEs, Pregnancies and other events *related to Cervarix*

8.4.2. PMS Contact for Reporting SAEs, *ADRs* and pregnancies: Please refer to local PMS contact information

Back-up PMS Contact for Reporting SAEs, *ADRs* and Pregnancies
24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Outside US & Canada sites: Fax: PPD or PPD Email address: PPD

8.4.4. Completion and transmission of SAE reports to GSK Biologicals

Facsimile (Fax) transmission ***or e-mail delivery*** of the SAE Report Form is the preferred method to transmit this information to the Contact for Reporting SAEs. In rare circumstances and due to failure of facsimile ***or electronic*** 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 ***or e-mail*** must be accompanied by telephone call to the PMS Contact for Reporting SAEs.

8.4.5. Completion and transmission of non-serious AEs related to *Cervarix* reports to GSK

Once a physician becomes aware that a non-serious AE related to vaccine has occurred in a PMS subject, the physician (or designee) must complete an ~~Expedited Adverse Event~~***ADR*** Report and forward it to GSK within 5 calendar days. The report will always be completed as thoroughly as possible with all available details of the event and then dated and signed by the physician (or designee). Even if the physician does not have all information regarding an AE, the report should still be completed and forwarded to GSK within 5 calendar days. Once additional relevant information is received, the report should be updated and forwarded to GSK within two weeks.

The physician will always provide an assessment of causality at the time of the initial report.

Fax transmission ***or e-mail delivery*** is the preferred method to forward the paper ~~Expedited Adverse Event~~ ***ADR*** Report to the PMS Contact for Reporting SAEs. In absence/ dysfunction of fax equipment ***or electronic***, the PMS Contact for Reporting SAEs must be notified by telephone within 5 calendar days. As soon as the fax equipment ***or electronic*** is working again, the physician (or designee) must fax ***or e-mail*** the report to the PMS Contact for Reporting SAEs within 5 calendar days.

8.4.6. Completion and transmission of pregnancy reports to GSK Biologicals

Once the physician becomes aware that a subject is pregnant, the physician (or designee) must complete, date and sign a paper pregnancy notification report and fax ***or e-mail*** it to the PMS Contact for Reporting SAEs (refer to the local PMS contact information document) WITHIN 2 WEEKS.

8.5. Follow-up of AEs and SAEs

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 up to 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** after the last dose ~~(dose 1, 2 or 3)~~ of *Cervarix* administered during the subject's participation in the PMS.

8.5.1. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. 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 Biologicals using the paper pregnancy follow-up report and the ~~Expedited Adverse Event~~***SAE*** Report if applicable. Generally, the follow-up period does not need to be longer than six to eight weeks after the estimated date of delivery.

Section 10.2. Subject withdrawal has been updated as it has been considered current PMS procedures as shown below:

10.2.1. Subject withdrawal from PMS

From an analysis perspective, a 'withdrawal' from the PMS refers to any subject who did not come back for the concluding visit/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 PMS when no PMS 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~~***attempts*** 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 PMS was made by the subject's parent(s) or LAR(s), or by the physician, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event.
- ~~Moved from the PMS area.~~
- Lost to follow-up.
- Death.
- Other (specify).

Section 11. STATISTICAL METHODS has been updated as it has been considered current PMS procedures as shown below:

11.1. Endpoints

- Occurrence of AEs during the 30-day ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** follow-up period after each vaccine dose.
- Occurrence of SAEs reported throughout the PMS period up to 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** after the last dose ~~(dose 1, 2 or 3)~~ administered during the subject's participation in the PMS.

11.5. Statistical methods

11.5.2.1. Within group assessment

The number and percentage, with exact 95% confidence interval (CI), of any AEs occurring within 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** will be tabulated, for each dose, for overall doses and by number of subjects. The same calculations will be done for any adverse events according to the severity and for those assessed as causally related to vaccination.

The verbatim reports of signs and symptoms will be matched and coded according to the appropriate WHO-ART Preferred Term. The PMS physician will review and confirm the appropriate WHO-ART Preferred Term by responding to data queries if any discrepancies are reported while coding. The percentage of subjects with AEs occurring within 30 days ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** with its exact 95% CI will be tabulated by preferred term. Similar tabulation will be done for AEs with relationship to vaccination and for AEs rated as grade 3.

The number and percentage of subjects who received concomitant medication/ vaccination at least once during the 30-day ~~(Day 0 to Day 29)~~ ***(Day 1 to Day 30)*** follow-up period will be tabulated after each vaccine dose and overall, with exact 95% CI. Similar tabulations will be done for the number of subjects by types of medication/ vaccination during the entire PMS period.

11.5.1. Analysis of demographics/baseline characteristics has been updated to address MFDS request for collection of information regarding medical history, physical examination, and concomitant medication as shown below:

Demographic characteristics (age, ~~weight,~~ gender, and ethnicity) ***and weight, height*** of the PMS cohort will be tabulated using descriptive statistics. Mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage will be calculated for categorical variables.

The medical history ***by disease classification and per past/current status*** and vaccination history of the vaccinated subjects will also be presented.

The distribution of subjects vaccinated among the PMS centres by years will be tabulated.

Section 12. ADMINISTRATIVE MATTERS has been updated as it has been considered current PMS procedures as shown below:

To comply with GEP, acceptable ethical principles, applicable local regulatory requirements, LSOP and administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. ~~Blinding of subject initials when safety~~***Safety*** data is used for analysis and ~~for GSK LOC to accurately provide the subject initials on the PMS report before submission to MFDS (Korea).(~~GSK does not forward personally identifiable information***. In the PMS report, subject number which is a number identifying a subject will be reported to MFDS (Korea).*** ~~requires reporting of PMS subject's initials in the PMS report).~~

12.6. Ownership, confidentiality and publication has been updated in confidentiality section by referring to current Informed consents form (ICF).

12.6.2. Confidentiality

All information provided by GSK and all data and information generated by the site as part of the PMS (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 PMS. 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 IEC or IRB solely for the evaluation of the PMS; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a PMS subject; ***(iv) information from this PMS may also be combined with results from other research studies to learn more about the vaccine and related diseases;*** or (***v***) PMS results which may be published as described in the next paragraph. If a written contract for the conduct of the PMS which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.