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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice.
eTrack study number and Abbreviated Title	207350 (EPI-HPV-070 VS CN PMS)
Scope:	All data pertaining to the above study. The analysis plan for demography and safety endpoints.
Date of Statistical Analysis Plan	Final draft: 04NOV2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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LIST OF ABBREVIATIONS

AE	Adverse event
AEFI	Adverse Events Following Immunization
CI	Confidence Interval
eCRF	Electronic Case Report Form
ES	Exposed Set
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan
PI	Prescribing Information
pIMD	Potential Immune Mediated Disease
PO	Pregnancy Outcomes
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
04NOV2020	first version	Amendment 1: 27 JUNE 2018

2. OBJECTIVES/ENDPOINTS

The aim of this post marketing surveillance study is to assess the safety of *Cervarix* among healthy female Chinese subjects aged between 9 and 45 years, who were vaccinated on a voluntary basis as per standard practice.

2.1. Objectives

2.1.1. Primary objective

- To assess the safety of *Cervarix* in terms of medically attended AEFIs occurring within 30 days (Day 1-30) following each immunisation, in all enrolled subjects.

2.1.2. Secondary objectives

- To assess the safety of *Cervarix* in terms of serious AEFIs occurring during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- To assess the safety of *Cervarix* in terms of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- To assess the safety of *Cervarix* in terms of PO when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- To assess the safety of *Cervarix* in terms of congenital anomalies when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

2.2. Endpoints

2.2.1. Primary endpoint

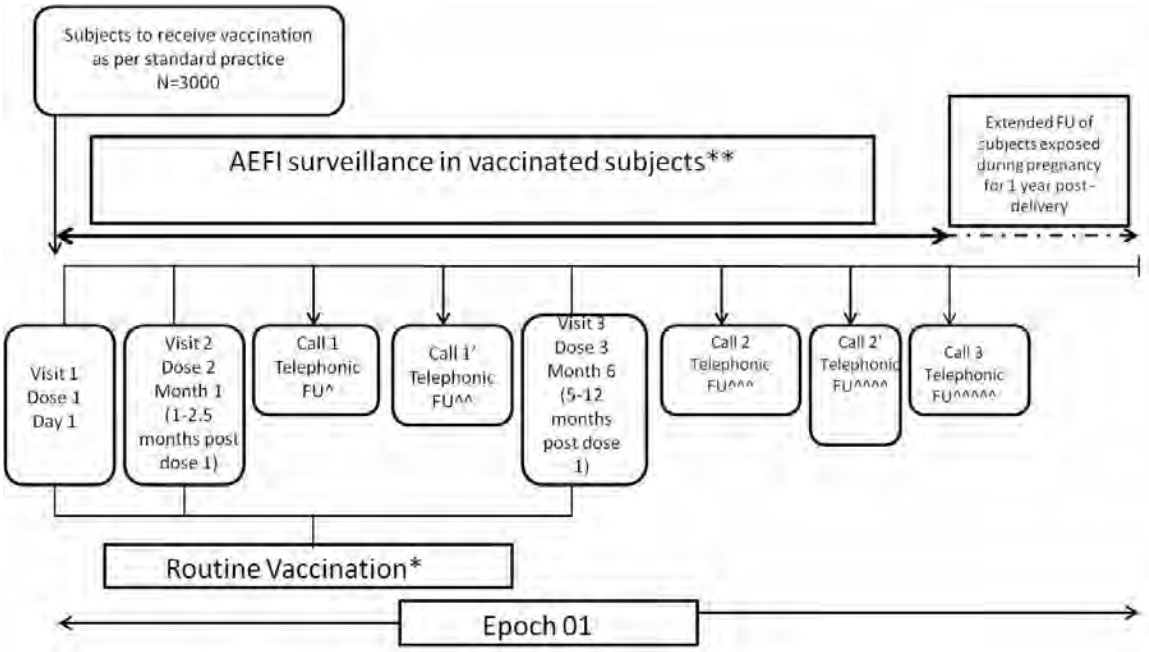
- Occurrence, intensity and causal relationship to vaccination, of medically attended AEFIs reported during the 30-day period (Day 1-30) following each immunisation with *Cervarix*.

2.2.2. Secondary endpoints

- Occurrence, intensity and causal relationship to vaccination of serious AEFI reported during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- Occurrence, intensity and causal relationship of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.

- Occurrence of PO when *Cervarix* is administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- Occurrence of any congenital anomalies when *Cervarix* is administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

3. STUDY DESIGN



N= Number of subjects planned to be enrolled
AEFI: Adverse Event Following Immunisation
* Three doses of the vaccine administered intramuscularly according to the Prescribing Information (PI) for China
** Data pertaining to medically attended AEFIs, PO and pIMDs will be collected through
- patient interview and observation at immunisation visits (events that have occurred since the previous visits or that occur during or just after the visit),
- structured telephonic FU
- direct reporting by the subjects/subjects parent(s)/LAR(S)
- reporting by physician not part of this study: A physician can report a suspected AEFI by contacting the study investigator or his/her delegate).

FU: Follow-up
^ Call 1 will occur 31-45 days post second immunisation (if second immunisation was done according to PI schedule within 2.5 months post first immunisation) or 2.5 months post first immunisation if second immunisation was not done by Month 2.5.
^^ Call 1' will be scheduled 31-45 days post second immunisation in case the second immunisation occurs more than 2.5 months following the first immunisation
^^^ Call 2 will occur 31-45 days following the third immunisation
^^^^ Call 2' will be scheduled 31-45 days post third immunisation in case the third immunisation occurs more than 12 months following the first immunisation.
^^^^^ Call 3 will occur either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first)

- Type of design: A prospective, descriptive, self-contained, multi-centre cohort study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).

- Study population: The study will involve approximately 3000 female Chinese subjects aged between 9 and ***45*** years of age, vaccinated voluntarily as per standard practice.
- *Cervarix* will be administered as per standard practice according to the PI for China (please refer to sections on dosage and administration, instructions for administration, contraindications, warning and precautions, pregnancy, nursing mothers, drug interactions in the PI) [*Cervarix* Product Information, 2018].
- Vaccination schedule: Chinese female subjects aged between 9 and 45 years, who consented to participate in the study, are expected to receive three doses of *Cervarix* at 0, 1 and 6 months. The second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose. The vaccine will be administered intra-muscularly, in the deltoid region of the upper arm.

  Note: Cervarix will be available for purchase at immunisation centres or Point of Vaccination (POV).
- Data collection: electronic Case Report form (eCRF) will be used to collect data.
- Study duration: The follow-up will be performed from enrolment until either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first). This represents an individual subjects' total follow-up time between 18 and 24 months for subjects completing the immunisation course (3 doses) as per *Cervarix* PI schedule. Subjects who report exposure to *Cervarix* during pregnancy or pregnancy onset up to 60 days following the last immunisation will be followed-up till end of pregnancy, to observe the PO and for any possible congenital anomalies diagnosed during the first 12 months of the child's life. Thus, in such cases, an extended follow-up beyond 24 months may occur.
- Epoch 001: Prospective data collection (for each subject) starting at Visit 1 (Day 1) and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix*, whichever occurs first.

The study cohorts and epoch foreseen in the study are presented in Table 1.

Table 1 Study groups and epochs foreseen in the study

Study Group	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
HPV group	3000	09 years - 45 years	x

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

Group order in tables	Group label in tables	Group definition for footnote
1	HPV	Subjects who have received *Cervarix*

4. ANALYSIS SETS

4.1. Exposed Set (ES)

The exposed set (ES) will include all subjects exposed to at least one dose of *Cervarix.*

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

Code 900 (invalid informed consent or fraudulent data) and code 1030 (No administration of any dose of *Cervarix*) will be used for identifying subjects eliminated from ES

5. STATISTICAL ANALYSES

That standard data derivation rules and stat methods are described in section 10. All analyses will be performed on the exposed set.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Number of subjects vaccinated, completed and withdrawn with reason for withdrawal will be tabulated.

The mean age (plus range and standard deviation) and race will be tabulated.

The vaccination history, the percentage of subjects who received any vaccination within 12 months preceding Visit 1 will also be presented.

The distribution of subjects vaccinated in different centres will be tabulated.

5.1.2. Additional considerations

Demographic characteristics of subjects will be described using percentages for categorical variables and mean (standard deviation) or median (min-max) for continuous variables. The same variables will be presented descriptively, overall and by age group; 9-15, 16-17, 18-25, 26-45, >=46 years old.

The percentage of subjects who had any pre-existing conditions, signs or symptoms that have started before first vaccination (general medical history) will be tabulated overall. The tabulation will be done using the MedDRA classification of System Organ Class.

5.2. Important protocol deviations

Code	Condition under which the code is used
900	Invalid informed consent or fraudulent data
1030	No administration of any dose of *Cervarix*.

5.2.1. Additional considerations

Table and listing of summaries of important protocol deviations not leading to elimination from any analyses will be generated based on the PD sheet. Table will be generated only if at least 1% of subjects from the exposed set reporting important PDs in the PD sheet.

Below are the PDs identified important, not leading to elimination in this study as per the PDMP.

Deviation Category	Sub-category
Eligibility Criteria Not Met	Related to other criteria
Eligibility Criteria Not Met	Related to vaccination
Failure to report safety events per protocol	SAE
Failure to report safety events per protocol	AEs of special interest
Failure to report safety events per protocol	Pregnancy
Failure to report safety events per protocol	Failure to confirm causality assessment
Failure to report safety events per protocol	Other

5.3. Exposure

5.3.1. Analysis of exposure planned in the protocol

Not applicable

5.3.2. Additional considerations

The percentage of subjects who have been administered with the study vaccine will be tabulated overall. In addition, the percentage of subjects will be summarized, based on each vaccine dosage received. For example, the percentage of subjects who received only one dose, two doses and/or three doses of *Cervarix*

The percentage of subjects, who were administered any vaccine(s) other than the study vaccine (concomitant vaccination), during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), will be reported and documented as per protocol.

The percentage of subjects, who have used any concomitant medications, will also be tabulated.

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis for Primary endpoint

The analysis will be based on the ES.

The percentage of subjects with at least one medically attended AEFI occurring within the 30-day (Day 1-30) follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The tabulation will be done using the MedDRA classification of System Organ Class and Preferred term.

The same tabulation will be performed for medically attended AEFI causally related to vaccination occurring within the 30-day (Day 1-30) follow-up period.

5.4.2. Analysis for Secondary endpoints

The analysis will be based on the ES.

The occurrence of serious AEFIs will be assessed throughout the entire follow-up period. Serious AEFIs will be further evaluated for their clinical relevance and relationship to vaccination.

The percentage of subjects with serious AEFI occurring within the 30-day (Day 1-30) follow-up period will be tabulated with exact 95% CI after any dose.

The occurrence of pIMD(s) will be collected and summarized through the entire follow-up period in all exposed subjects.

The PO and congenital anomalies will be summarized when *Cervarix* is administered within 60 days before pregnancy onset or any time during pregnancy. In addition, the PO will be summarized by the time of the vaccination, such as vaccination before the pregnancy, vaccination during the first trimester (LMP through week 13) of the pregnancy, vaccination during the second trimester (week 14 through week 27) of the pregnancy, vaccination during the third trimester (week 28 through term) of the pregnancy.

All secondary endpoints (serious AEFIs, pIMDs and POs) will be summarized by percentage of subjects reporting the endpoint with exact 95% CI.

5.4.3. Additional considerations

The percentage of subjects with at least one medically attended non-serious AEFI occurring within the 30-day (Day 1-30) follow-up period will be tabulated with exact 95% CI after any dose.

The percentage of subjects, who have used any medications, that was required to be reported as per protocol, during the whole study period will be tabulated. Medications will be coded using the GSKDRUG dictionary.

All primary and secondary endpoints (medically attended AEFIs, serious AEFIs, , casually related AEFIs , grade 3 AEFIs, pIMDs and POs) will be summarized by percentage of subjects and percentage of doses reporting the symptoms with exact 95% CI.

Incidence and nature of reported AEFIs following each dose and overall will be presented. The analysis will be done for any AEFI, medically attended AEFI within 30 days follow-up period and serious AEFI.

Adverse events will be coded using medical dictionary for regulatory activities - MedDRA classification of System Organ Class and Preferred term.

Serious AEFIs will be summarised with the rationale for identification, intensity and the outcome. The similar summary will be presented for the serious AEFIs causally related to the vaccination.

Summary of infant information (infant sex, length, weight, Apgar score) will be tabulated.

Listings of serious AEFIs, pIMDs, concomitant vaccination(for the subjects with at least one medically attended AEFI causally related to the vaccine), pregnancies and infants (with / without congenital anomalies) will be generated.

6. ANALYSIS INTERPRETATION

All analyses are descriptive.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

A final analysis of all data collected up to either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), will be conducted. This will include final analysis of safety. In case of regulatory submission before license renewal, interim report(s)/progress report(s) will be prepared. The analysis for the annual progress reports will be performed on the dataset that will be as cleaned as possible that includes cumulative number of subjects recorded in the clinical database until the date of data lock point.
The data to be analysed will be selected based on date of consent (demography), date of completion/withdrawal (disposition), dates of administration (study vaccine, concomitant vaccines/medications) or onset dates (AEFI, pregnancy outcomes) prior to or on the date of data lock point, as applicable.

Since the study started on May 31, 2018, the DLP (Data Lock Point) was set as May 31, 2019 for the ADR report 2019 and May 31, 2020 for the ADR report 2020. The dates of clinical database freeze will be adjusted accordingly following data cleaning and SAE (Serious Adverse Events) reconciliation, thus may encompass data beyond DLP as this is a living database.

After the DBF of final analysis, If there are any additional information collected during the infant follow up on potential congenital anomalies when the child is about 12 months old, the listing related to adverse events of infants will be updated post another DBF.

7.2. Statistical considerations for interim analyses

Since there is no hypothesis testing, no adjustment of type I error is required. A final report will be prepared when the follow-up of all enrolled subjects has been completed.

The following table details the analyses (tables and figures) to be included in each analysis (interim and final analysis)

Description	Analysis ID	Disclosure Purpose	Dry run review needed (Y/N)	Study Headline Summary (SHS)	Reference for TFL
Analysis of all data	E1_01	Study report	Yes	Yes	All tables from TFL TOC
Analysis of data as of DLP = 31May2019	E1_02	*Comprehensive* report to be submitted to ADR	No	No	Additional analysis request Amendment dated 01-Oct-2019
Analysis of data as of DLP = 31May2020	E1_03	*Comprehensive* report to be submitted to ADR	No	No	Additional analysis request Amendment dated 01-Oct-2019

NA: Not applicable

8. CHANGES FROM PLANNED ANALYSES

All analyses related to primary and secondary endpoints except on study attrition will be done on the exposed set instead of all enrolled subjects as planned in the protocol.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

Not applicable.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

- Adverse event start dates with missing day:
    - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
    - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or

only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10.1.2.2. Laboratory data

Not applicable.

10.1.2.3. Daily recording of solicited adverse events

Not applicable.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

10.1.3.3. Distinction of adverse events in mother and infant cases

For the pregnant subjects with pregnancy outcome, in case if there are any adverse events collected for both mother and infants, adverse events of the infants will be prefixed with the term – 'INFANT' to distinguish between the AEs of mother and the infant. Analysis of primary and secondary endpoints (AEs of the subjects), data needs to be considered accordingly. (E.g., If the analysis is based on the AE of the subjects, then we need to exclude the AE's prefixed with the word 'Infant'.)

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
    - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

    - The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
    - Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (like age) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.2. TFL TOC

The Table Figure Listing (TFL) Table of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

11. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

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Cervarix Summary of Product Characteristics. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Product_Information/human/000721/WC500024632.pdf. Accessed on 21 September 2017.