Protocol

Study ID: 115055

Official Title of Study: A prospective study to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of the RTS,S/AS01E candidate vaccine.

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CONFIDENTIAL

115055 (EPI-MALARIA-002 VS AME)
Protocol Amendment 7 Final

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

1. PROTOCOL INFORMATION

This protocol is formatted as "PASS protocol" proposed by the European Medicines Agency (EMA) pharmacovigilance guidance [European Medicines Agency, 2012]. However, this study is not a safety study but will serve to collect baseline information necessary to prepare the PASS study EPI-MALARIA-003 VS AME (115056) (referred to as EPI-MAL-003 in the remainder of the document) that will start upon the implementation of the RTS,S/AS01$_E$ vaccine in Sub-Saharan Africa.

Title:	A prospective study to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of the RTS,S/AS01$_E$ candidate vaccine.
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Opinion Holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Research question and objectives:	**Co-Primary Objectives:** • To estimate the incidence of adverse events of special interest, and of other adverse events leading to hospitalisation or death, in children, prior to implementation of RTS,S/AS01$_E$. • To estimate the incidence of aetiology-confirmed meningitis, in children, prior to implementation of RTS,S/AS01$_E$. Objectives related to malaria are considered as secondary objectives.

Countries of study:	Sites in sub-Saharan Africa (SSA) countries have been selected for EPI-MAL-002 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system census and of vaccine registries. Following the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommendations of pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria have started enrolment (Ghana [Kintampo and Navrongo], Kenya [Kombewa], and Burkina Faso [Sapone, Nouna]). In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GSK Phase IV studies have been, or will be, selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented As a consequence, Burkina Faso sites, that had already started EPI-MAL-002, early terminated the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance since 06 June 2018, with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI. All study activities are planned to be terminated by Q2 2019. A description of data from these sites will be presented in the progress reports up to Q4 2019, but none of these data will be part of the statistical analyses for the interim and final reports.

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2. OPINION HOLDER

Opinion holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium

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LIST OF ABBREVIATIONS

ADEM	Acute Disseminated Encephalo-Myelitis
AE	Adverse Event
AESI	Adverse Event Of Special Interestw
AMP	Agence de Médecine Préventive
AS01	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome
ATP	According To Protocol
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLS	Clinical Laboratory Services
CRP	C-Reactive Protein
CS	Circumsporozoite
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic Acid
DTP	Diphtheria, Tetanus, Pertussis trivalent vaccine
DTP-HepB	DTP-Hepatitis B tetravalent vaccine
DTPw/HepB/Hib	Diphtheria-tetanus-whole-cell pertussis-hepatitis B-Haemophilus influenza type b pentavalent vaccine
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EPI	Expanded Program on Immunization
EU PAS	European Union Post-Authorisation Studies
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline

HBsAg	Hepatitis B surface antigen
HDSS	Health and Demographic Surveillance System
HHE	Hypotonic Hyporesponsive Episode
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
MPAC	Malaria Policy Advisory Committee
MPL	3-O-desacyl-4'- monophosphoryl lipid A (produced by GSK)
MTI	Malaria Transmission Intensity
MVIP	Malaria Vaccine Implementation Programme
OPV	Oral Poliovirus Vaccine
P. falciparum	Plasmodium falciparum
PATH REC	Program for Appropriate Technology in Health Research Ethics Committee
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
pIMD	potential Immune-Mediated Disorders
PT	Preferred Term
PY	Person-Years

QS-21	QS-21 QS-21 = Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RAFT	Réseau en Afrique Francophone pour la Télémédecine
RDT	Rapid Diagnostic Test
RMP	Risk Management Plan
RR	Relative Risk
RTS	Hybrid protein comprising HBs (hepatitis B surface antibody) and CS protein portions
RTS,S	Particulate antigen, containing both RTS and HBs antigen (S) proteins
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAP	Statistical Analysis Plan
SDV	Source Document Verification
SOC	System Organ Class
SPM	Study Procedures Manual
SSA	Sub-Saharan Africa
WHO	World Health Organization

3. RESPONSIBLE PARTIES

GSK Biologicals has the overall responsibility for the conduct of the study.

PPD (DVM, MSc, PhD; Senior Epidemiology Lead - Malaria) and PPD PPD (PhD; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact persons for this study.

4. ABSTRACT

Title

A prospective study to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of the RTS,S/AS01$_E$ candidate vaccine.

115055 (EPI-MALARIA-002 VS AME),

Amendment 7: 05 May 2020

Main author

PPD, Senior Epidemiology Lead – Malaria and PPD, Epidemiology Lead - Malaria

Rationale and background

GSK Biologicals has developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01$_E$, for routine immunisation of infants and children living in malaria-endemic countries of sub-Saharan Africa (SSA). RTS,S/AS01$_E$ will be the first vaccine to be implemented for the prevention of malaria and it will be the first AS01-adjuvanted vaccine used in the paediatric population.

In July 2015, the European Medicines Agency (EMA) issued a positive opinion for the RTS,S/AS01$_E$ vaccine, and in October 2015 recommendations about RTS,S/AS01$_E$ were issued by the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC). In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document.

The safety and efficacy of RTS,S/AS01$_E$ have been evaluated during pre-authorisation clinical trials conducted mainly in SSA.

The RTS,S/AS01$_E$ vaccine will be implemented only in malaria endemic countries of SSA. Most of these countries have no baseline incidence data on rare diseases such as those that may be reported as adverse events (AE) following vaccination.

Data generated from EPI-MALARIA-002 VS AME (115055) (referred to as EPI-MAL-002 in the remainder of the document) will fill this gap and provide data that serve as baseline data for the post-implementation safety study (EPI-MAL-003) that will evaluate the safety of RTS,S/AS01$_E$ as reflected in the co-primary and secondary objectives. Therefore, the primary

aims of the EPI-MAL-002 study are to provide reliable estimates of the rates of occurrence of diseases specified as adverse events of special interest (AESI), of other AE leading to hospitalisation or death, and of meningitis cases (reported as a potential risk in the MALARIA-055 Phase III study) in preparation for the post-implementation safety study EPI-MAL-003. Additionally, vaccine impact measures (indirect, total and overall effects) are included in EPI-MAL-002 and EPI-MAL-003. Therefore, all malaria events (morbidity, mortality and hospitalisation) will be monitored throughout the study. Background incidence rates of any malaria and severe malaria, including cerebral malaria, will be collected. The mortality rate, overall and by gender, will also be estimated.

Research question and objectives

Co-primary objectives

- To estimate the incidence of AESI[1], and of other AE leading to hospitalisation or death, in children, prior to implementation of RTS,S/AS01$_E$.
- To estimate the incidence of aetiology-confirmed meningitis, in children, prior to implementation of RTS,S/AS01$_E$.

Secondary objectives

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- To estimate the incidence of aetiology-confirmed, and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To describe risk factors for AESI, other AE leading to hospitalisation or death, meningitis and malaria.
- To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria).

[1] Acute disseminated encephalomyelitis, encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode, generalised convulsive seizure.
Intussusception, hepatic failure, renal insufficiency.
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease.
Diabetes mellitus type I, thrombocytopenia, anaphylaxis.

- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following administration of routine EPI vaccines.
- To estimate the incidence of any malaria (including *P. falciparum* malaria) using rapid diagnostic test (RDT) and/or microscopy.
- To estimate the incidence of severe malaria (including *P. falciparum* malaria) using RDT and/or microscopy.
- To estimate the incidence of cerebral malaria (malaria diagnosed by RDT and/or microscopy***)***.
- To estimate the prevalence of anaemia among hospitalised children.
- To estimate the incidence of all-cause hospitalisations and hospitalisations attributed to malaria (including *P. falciparum*).
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*])**,** overall and by gender.

Study design

- A disease surveillance study with prospective cohort event monitoring among infants and young children living in a demographic census in SSA countries.
- The design will include active surveillance (home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities) and enhanced hospitalisation surveillance (continuous monitoring of hospitalisations).
- The study targets enrolling 30,000 children in active surveillance, with about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Among the 30,000 children, approximately 15,000 children (with about 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 6-12 weeks group (to collect background data in this age group) and approximately 15,000 children (with about 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 5-17 months group (to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group).
- For EPI-MAL-002 and EPI-MAL-003, the study sites were chosen based on existing infrastructure to identify the study population.

- The diseases under surveillance for safety include AESI, other AE leading to hospitalisation or death, and meningitis, and will be monitored among children enrolled in active surveillance and in enhanced hospitalisation surveillance. To estimate vaccine impact, several measures of malaria burden will be monitored among children in the active surveillance. The mortality rate, overall and by gender, will also be estimated.
- Active surveillance will last 44 months for each subject (mimicking 24 months of active follow-up after the 4th dose of RTS,S/AS01$_E$ in EPI-MAL-003), except for subjects enrolled from Burkina Faso sites for whom their participation in the study has been early terminated.

Population, including the setting and study population

Subjects < 5 years of age living in a geographically limited area with a health and demographic surveillance system (HDSS) or equivalent surveillance system in place, and an existing infrastructure to monitor population health and vaccination programmes. Sites in SSA countries have been selected for EPI-MAL-002 based on the existence of a HDSS from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system census and of vaccine registries.

Following the SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria have started enrolment (Ghana [Kintampo and Navrongo], Kenya [Kombewa], and Burkina Faso [Sapone and Nouna]).

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. In order to align with the MVIP, the study sites for the GSK Phase IV studies have been, or will be, selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented**.** As a consequence, Burkina Faso sites, that had already started EPI-MAL-002, stopped the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance on 06 June 2018, with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI. All study activities are planned to be terminated by Q2 2019. A description of data from these sites will be presented in the progress reports up to Q4 2019, but none of these data will be part of the statistical analyses for the interim and final reports.

Variables

Co-primary endpoints

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of AESI.
- Occurrence of other AE leading to hospitalisation or death.
- Occurrence of aetiology-confirmed meningitis.

Secondary endpoints

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of probable meningitis (final classification).
- Occurrence of clinically suspected meningitis (final classification).
- Occurrence of meningitis cases identified at site level (first line laboratory).
- Occurrence of hospitalisation (including those attributed to an AESI, other AE, meningitis, or malaria) or death.
- Occurrence of febrile convulsions during the 7-day period (Days 0-6) and 1-month period (Days 0-29) following administration of routine EPI vaccines.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following any routine vaccination and foot positional deformation.
- Occurrence of episodes of malaria using RDT and/or microscopy
  - Any malaria (including *P. falciparum* malaria).
  - Severe malaria (including *P. falciparum* malaria).
  - Cerebral malaria.
- Occurrence of anaemia at hospital entry among hospitalised children.
- Occurrence of hospitalisation
  - All causes and hospitalisations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria.

- Occurrence of death
  - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death).
  - AE attributed deaths.

Data sources

HDSS *(or equivalent surveillance system)*

- Listings of all children living in the study area based on the demographic census;
- Total number of children < 5 years of age recorded at the beginning of the study, at least once a year during the study duration, and at the end of the study;
- Other demographic data (cause and date of deaths, migrations);
- Information related to vaccination.

Active surveillance (enrolment)

- Socio-demographic data;
- Active participation in any trial with an investigational product.

Active surveillance (home visits)

- Vaccination types and dates;
- Health history;
- Malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards;
- Verbal autopsy report.

Active surveillance (outpatient visits and hospitalisations at all health care facilities)

- Data on visits at primary health care facilities and hospitals since enrolment or last home visit.

Enhanced hospitalisation surveillance (hospitalisation*s*)

- Socio-demographic data;
- Active participation in any trial with an investigational product;
- Health history;
- Malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards;

- Type of health care facility;
- Final diagnosis for the hospitalisation visit on discharge for all children;
- Data relevant to the diagnosis of AESI, other AE leading to hospitalisation or death, meningitis and malaria (including cerebral malaria);
- Vaccination types and dates;
- Autopsy report.

Study conclusion (home visit*)*

- Vital status;
- Verbal autopsy report;
- Vaccination types and dates;
- Health history since last visit.

Malaria Transmission Intensity Study EPI-MALARIA-005 BOD AME (116682) (referred to as EPI-MAL-005 in the remainder of the document)

- Estimation of annual parasite prevalence;
- Changes in diagnostic practices;
- Malaria control and prevention measures on the community and individual level.

Study size

The study targets enrolling 15,000 children per group (i.e. 6-12 weeks group and 5-17 months group; with about 10,000 children of 15,000 in each group enrolled where the RTS,S/AS01$_E$ vaccine will be implemented), for a total of 30,000 children (about 20,000 children enrolled where the vaccine will be implemented). For some of the AESI the incidence could be very rare (around 1/100,000 person years [PY]) and the period at-risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis. The 95% confidence interval (CI) around an observed incidence of 25.2 per 100,000 PY (corresponding to 1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], based on 10,000 subjects) will be [0.6, 140.2].

Data analysis

- The incidence rate of each AESI and other AE leading to hospitalisation or death will be calculated by dividing the number of subjects reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable.

- The person-time for an event of interest (e.g. juvenile chronic arthritis) will be calculated as the time between the reference date (date of first administration of Diphtheria-tetanus-whole-cell pertussis-hepatitis B-Haemophilus influenza type b pentavalent vaccine [DTP/HepB/Hib] or date of first virtual vaccination, corresponding to the week before first visit) and the end of the at-risk period or the earliest of the followings:
  - Date of first diagnosis of event of interest (e.g. first episode of juvenile chronic arthritis).
  - Date of end of study period.
  - Date of enrolment in EPI-MAL-003 (when applicable).
  - Date when child reaches 5 years.
  - Date of last contact (Lost-to follow-up).
  - Date of death.
- Each AESI will be grouped after case ascertainment (for both confirmed and non-confirmed cases).
- The incidence rate of aetiology-confirmed meningitis and of cerebral malaria will be computed with 95% CI using the same approach as described above.

Milestones

The study started in Q4 2015, and is planned to end in Q1 2022. Progress reports will be generated every 6 months. An interim report is planned to be written by Q3 2019

5. AMENDMENTS AND UPDATES

Final: 31 May 2012

Amendment 1 Final: 22 October 2013

Amendment 2 Final: 03 June 2014

Amendment 3 Final: 19 March 2015

Amendment 4 Final: 11 December 2015

Amendment 5 Final: 11 October 2017

Amendment 6 Final: 06 July 2018

The rationale for the protocol amendments 1, 2, 3, 4, 5 6 and ***7,*** and the summary of changes are provided in Annex 7
(Amended 5 May 2020)

6. MILESTONES

Milestone	Planned date
Start of data collection	Q4 2015*
End of data collection	Q1 2022
Study progress report	1 progress report every 6 months
Interim report	Q3 2019
Final report of study results	Q4 2022

*Actual date

7. BACKGROUND AND RATIONALE

7.1. Background

The devastating morbidity and mortality, particularly in children under five years of age, that results from malaria in sub-Saharan Africa (SSA) is well documented [WHO World Malaria Report, 2012]. In 2010 there were approximately 174 million cases of malaria in the African region, 98% due to *Plasmodium (P.) falciparum*, causing approximately 596,000 deaths, 91% of which were in children under five years of age [WHO World Malaria Report, 2012]. During the past decade, renewed international commitment and increased funding to scale-up proven malaria control interventions have resulted in morbidity and mortality reductions in several African countries [Steketee, 2010]. The development of efficacious malaria vaccines has been identified by national and international health authorities as a key component of a sustainable malaria control programme which will consequently have significant benefits in terms of health and the economy [Malaria Vaccine Technology Roadmap, 2013].

GSK Biologicals has developed a pre-erythrocytic *P. falciparum* malaria vaccine, RTS,S/AS01$_E$, for routine immunisation of infants and children living in malaria-endemic countries of SSA. RTS,S/AS01$_E$ will be the first vaccine to be implemented for the prevention of malaria and it will be the first AS01-adjuvanted vaccine used in the paediatric population.

The vaccine antigen, RTS,S, consists of sequences of the *P. falciparum* circumsporozoite (CS) protein and hepatitis B surface antigen (HBsAg) adjuvanted with AS01$_E$ that consists of two immune enhancers MPL (3'-O-desacyl-4'-monophosphoryl-lipid A) and QS-21 (Quillaja saponaria Molina, fraction 21), in a liposomes suspension.

The pre-authorisation clinical development has been conducted mainly in SSA countries. The main clinical study supporting efficacy and safety is the large Phase III study, MALARIA-055, conducted at 11 study sites in seven countries across SSA, which enrolled 15,459 children. This clinical trial was conducted in two age categories. Infants aged 6-12 weeks at first dose received RTS,S/AS01$_E$, in co-administration with other childhood vaccinations (diphtheria-tetanus-whole-cell pertussis-hepatitis B/*Haemophilus influenza* type b pentavalent vaccine [DTPwHepB/Hib] and oral poliovirus vaccine [OPV]), within the context of the Expanded Program on Immunization (EPI). The comparator group received meningococcal C conjugate vaccine in co-administration with the same EPI vaccines. At Month 20, infants vaccinated with RTS,S/AS01$_E$ in co-

administration with other childhood vaccinations received either a fourth dose of RTS,S/AS01$_E$ with OPV, or meningococcal C conjugate vaccine with OPV. Infants in the comparator group received meningococcal C conjugate vaccine with OPV. Children aged 5-17 months at first dose received RTS,S/AS01$_E$ without co-administration of other vaccines. The comparator group received human diploid-cell rabies vaccine. At Month 20, children vaccinated with RTS,S/AS01$_E$ received either a fourth dose of RTS,S/AS01$_E$ or meningococcal C conjugate vaccine. Children in the comparator group received meningococcal C conjugate vaccine at the time of the fourth dose. Children aged 5 to 17 months at first dose were followed for approximately 48 months after Dose 1 and infants aged 6 to 12 weeks at first dose for approximately 38 months after Dose 1.

In July 2015, the European Medicines Agency (EMA) issued a positive opinion for the RTS,S/AS01$_E$ vaccine [European Medicines Agency, 2015(a); European Medicines Agency, 2015(b)], and in October 2015 recommendations about RTS,S/AS01$_E$ were issued by the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) [WHO, 2015(a)] (see Section 9.1.1).

The EMA issued a positive opinion for the RTS,S/AS01$_E$ vaccine with the following indication: "*Mosquirix* is indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B. The use of *Mosquirix* should be based on official recommendations considering *Plasmodium falciparum* malaria epidemiology in different geographical areas" [European Medicines Agency, 2015(a); European Medicines Agency, 2015(b)]. These policy recommendations will be defined by the WHO and public health authorities in the malaria endemic SSA countries where the vaccine would be used.

The WHO's SAGE and MPAC recommended pilot implementations of RTS,S/AS01$_E$ in children of 5–17 months of age, in parts of 3-5 sub-Saharan African countries, administering 3 doses of the vaccine to children aged 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose 15-18 months later. They did not recommend the use of the malaria vaccine in the 6–12 weeks age group [WHO, 2015(a)]. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme [WHO, 2017], referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document (see section 9.2).

The study protocol has been adapted to take into account implementation of a 4th dose of RTS,S/AS01$_E$ 18 months after the 3rd dose. Although SAGE/MPAC recommended the use of the RTS,S/AS01$_E$ vaccine in the 5-17 months age group only, the study will enrol children in the two age groups in which the Phase III study MALARIA-055 was conducted (6-12 weeks at first dose and 5-17 months at first dose). This will allow collection of background data in both age groups. In the post-implementation safety study EPI-MAL-003, only the 5-17 months age group will be kept.

7.2. Safety results of the clinical development of RTS,S/AS01$_E$

In the large, pivotal Phase III study (MALARIA-055), adverse events (AEs) including serious adverse events (SAEs) were collected throughout the trial in all subjects. Seizures occurring within 7 days after vaccination were collected proactively and were analysed according to Brighton Collaboration Guidelines. Potential immune-mediated disorders (pIMDs) were collected as SAEs throughout the trial. Information was collected on all unsolicited reports of AEs that occurred within 30 days after vaccination and on reactogenicity within 7 days after vaccination among the first 200 children in both age categories at each study site. This study was overseen by an Independent Data Monitoring Committee. Safety results are shown below for the intention-to-treat population.

In the 5-17 month old group at Month 20 post Dose 1, at least one SAE was reported in 1,108 children out of 5,949 vaccinated with RTS,S/AS01$_E$ (18.6%; 95% confidence interval [CI]: 17.6, 19.6) and in 676 children out of 2,974 who received the rabies vaccine (control group) (22.7%; 95% CI: 21.1, 24.3) [The RTS,S Clinical Trials Partnership, 2014]. At least one SAE related to vaccination (judged by the study investigator) was reported in 10 children (0.2%) vaccinated with RTS,S/AS01$_E$ and in one child (0.0%) receiving the rabies vaccine.

Over the same surveillance period in the 6-12 week old group, at least one SAE was reported in 959 infants among 4,358 who were vaccinated with RTS,S/AS01$_E$ (22.0%; 95% CI: 20.8, 23.3) and in 503 infants among 2,179 who received the meningococcal C conjugate vaccine (control group) (23.1%; 95% CI: 21.3, 24.9) [The RTS,S Clinical Trials Partnership, 2014]. SAEs were judged to be related to vaccination by the study investigator for 4 children (0.1%) vaccinated with RTS,S/AS01$_E$ and 3 infants (0.1%) receiving the meningococcal C conjugate (control group).

Pneumonia, gastroenteritis, malaria, anaemia and febrile convulsions were the most frequently reported SAEs in both study groups.

Up to study end, in the 5-17 month old group, at least one SAE was reported in 720 children out of 2,976 vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (24.2%; 95% CI: 22.7, 25.8), in 752 children out of 2,972 vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose (25.3%; 95% CI: 23.7, 26.9) and in 846 children among 2,974 who received the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose (control group) (28.4%; 95% CI: 26.8, 30.1). At least one SAE related to vaccination was reported in 8 children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, in 4 children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal conjugate vaccine at the time of the 4th dose, and in one child receiving the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015].

In the 6-12 week old group, over the same surveillance period, at least one SAE was reported in 580 infants among 2,180 who were vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (26.6%; 95% CI: 24.8, 28.5), in 602 children among 2,178 who were vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose (27.6%; 95% CI: 25.8, 29.6), and in 619 infants among 2,179 who received meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose (control group) (28.4%; 95% CI: 26.5, 30.4). At least one SAE related to vaccination was reported in 6 infants vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, in one infant vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and in 3 infants receiving the meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015].

Potential immune-mediated disorders (pIMDs):

In the 5-17 month old group and up to Month 20 post Dose 1, 3 cases of pIMDs were reported among children vaccinated with RTS,S/AS01$_E$ (2 cases of encephalitis, one case of erythema multiforme) and 2 cases among children receiving the rabies vaccine (2 cases of encephalitis). In the 6-12 week old group, 3 cases were reported among infants vaccinated with RTS,S/AS01$_E$ (encephalitis, glomerulonephritis acute, Langerhans' cell histiocytosis) and 2 cases among children receiving the meningococcal C conjugate vaccine (encephalitis, glomerulonephritis).

Post 4th dose of RTS,S/AS01$_E$ / meningococcal C conjugate vaccine, no case of pIMD was reported in the 6-12 week old group, and 6 cases were reported in the 5-17 month old group: 3 cases among children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (2 cases of encephalitis and one case of encephalomyelitis), 1 case among children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose (encephalitis), and 2 cases among children receiving the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose (vitiligo, Stevens-Johnson syndrome).

Meningitis:

- An imbalance was observed for meningitis in the 5-17 month category (Table 1). During the 20 months period post Dose 1, in children aged 5-17 months, 16 meningitis cases (9 no aetiology, 4 meningitis meningococcal, 1 meningitis viral, 1 meningitis pneumococcal, 1 *Haemophilus influenza* meningitis) occurred in the RTS,S/AS01$_E$ group and 1 (no aetiology) in the control vaccine group (Relative Risk [RR] = 8.0 [95% CI: 1.1, 60.3]). Among infants aged 6-12 weeks, 9 meningitis cases (3 no aetiology, 3 meningitis pneumococcal, 3 meningitis due to salmonella) occurred in the RTS,S/AS01$_E$ group and 3 (2 no aetiology, 1 meningitis pneumococcal) in the control group (RR = 1.5 [95% CI: 0.4, 5.5]) [The RTS,S Clinical Trials Partnership, 2014]. Most of the meningitis cases were observed during the 12 months period post-Dose 3 (23 out of 29 cases, 79.3%), no clear risk window was identified in study MALARIA-055. The meningitis cases were mainly observed in 2 trial sites, Lilongwe in Malawi and Kombewa in Kenya.

Table 1 Meningitis cases observed in MALARIA-055 over 20 months post first dose (MedDRA preferred terms including meningitis and meningitis with any aetiologies)

Analysis available	Follow up (post dose 3)	Age category	Number of cases in RTS,S/AS01$_E$ (Number of RTS,S/AS01$_E$ study participants)	Number of cases in control (Number of control study participants)	RR	95% CI
June 2014	18 months	6-12w	9 (4358)	3 (2179)	1.5	0.4-5.5
		5-17m	16 (5949)	1 (2974)	8.0	1.1-60.3

Between administration of the 4th dose of RTS,S/AS01$_E$ / meningococcal C conjugate vaccine and study end, in children aged 5-17 months, 2 meningitis cases occurred among children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, and 3 cases among children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose. No case occurred in the control vaccine group (rabies vaccine for primary vaccination and meningococcal C conjugate vaccine at the time of the 4th dose). In infants aged 6-12 weeks, 2 meningitis cases occurred among infants vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 3 cases among infants receiving meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015]. Therefore, meningitis was considered as a potential risk.

Febrile convulsions:

- Among children aged 5-17 months, the occurrence of generalised convulsive seizures with fever within 7 days following primary vaccination in RTS,S/AS01$_E$ recipients was 1.04 case/1000 doses compared to recipients of control vaccine (0.57 case/1000 doses). Among infants aged 6-12 weeks, the incidence of febrile convulsions was 0.16 case/1000 doses of RTS,S/AS01$_E$ vaccine versus 0.47 case/1000 doses of control vaccine. Although the increase in febrile convulsions was observed within 7 days of vaccination in children, the overall rate of febrile convulsions reported as a SAE was not increased in the RTS,S/AS01$_E$ group compared to the control group over 30 days post vaccination (0.8%% in RTS,S/AS01$_E$ versus 0.8% in control) and over 18 months of follow-up (3.8% in RTS,S/AS01$_E$ versus 3.8% in controls) [The RTS,S Clinical Trials Partnership, 2011]. The incidence of febrile convulsions after administration of the 4th dose of RTS,S/AS01$_E$ / meningococcal C conjugate vaccine was 2.5 cases/1000 doses in children aged 5-17 months, vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, 1.2 case/1000 doses in children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 0.4 case/1000 doses in the control vaccine group (rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose). Among infants aged 6-12 weeks, the incidence of febrile convulsions was 2.2 cases/1000 doses in infants vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, no case/1000 doses in infants vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose and

0.5 case/1000 doses in the control vaccine group [The RTS,S Clinical Trials Partnership, 2015]. Therefore, febrile convulsions were considered as an identified risk.

Severe malaria including cerebral malaria:

In the MALARIA-055 study, there was a higher susceptibility to severe malaria in 5-17 months recipients of a primary course of RTS,S/AS01$_E$ without a 4th dose (R3C) relative to the control group (C3C) after Month 20. This finding was considered to be related to a potential rebound effect and has been included in the Risk Management Plan (RMP) as a potential risk. In order to further investigate this finding, an additional analysis was conducted in MALARIA-055 to examine clinical syndromes and outcomes of cases of severe malaria.

The cases of severe malaria disease according to the secondary case definition 1 (P. falciparum > 5000 parasites per µL AND with one or more marker(s) of disease severity including co-morbidities: pneumonia, meningitis, sepsis, gastroenteritis) were classified by syndrome using the markers of severe malaria disease. GSK Biologicals has considered the definition for cerebral malaria cases as: parasitaemia > 5000 per µL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL. It should be noted that whereas this is a commonly used definition, low coma score can be the outcome of many diseases processes and is not pathognomic of sequestration of parasitized red cells in the cerebral microvasculature.

In a post-hoc analysis of the Phase III study MALARIA-055, the distribution of the markers of severity used in the case definition of severe malaria were analysed by study group. Of the 1038 severe malaria cases according to the secondary case definition 1, 73 cases met the definition of cerebral malaria (parasitaemia > 5000 per µL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL) in both age categories over the entire study period. An imbalance was observed for cerebral malaria in the 5-17 month category (Table 2).

Table 2 Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 5-17 month age category; from MALARIA-055 study)

Time Period	Syndrome	RTS,S group (R3C + R3R) N=5948		Control group (C3C) N=2974	
		N	Died	N	Died
M0-M20	All Cases	205	6	158	2
	Cerebral	16	3	5	1
	Cerebral + Anaemia	6	1	1	0
	Anaemia	25	0	29	1
	Other	157	2	123	0
	Missing	1	0	0	0

Time period	Syndrome	3-dose schedule (R3C) N=2719		4-dose schedule (R3R) N=2681		Control (C3C) N=2702	
		N	Died	N	Died	N	Died
M21-SE	All Cases	103	6	76	3	76	2
	Cerebral	9	4	11	2	2	0
	Cerebral + Anaemia	0	0	1	0	2	1
	Anaemia	18	1	11	0	17	0
	Other	75	1	53	1	54	1
	Missing	1	0	0	0	1	0

R3C group: children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a dose of a meningococcal C conjugate vaccine at study month 20
R3R group: children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a 4th dose of RTS,S/AS01$_E$ at study month 20
C3C group: children and infants to receive 3 doses of a control vaccine on a 0-1-2-month schedule + a dose of a control vaccine at study month 20
SE = Study end (Month 48)
All cases: Secondary case definition 1 (> 5000 parasites/µL and at least 1 marker of severe disease, including comorbidities)
Cerebral: > 5000 parasites/µL and BCS ≤ 2 and a haemoglobin level of ≥ 5 g/dL
Anaemia: > 5000 parasites/µL and BCS > 2 and a haemoglobin level of < 5 g/dL
Cerebral+Anaemia: > 5000 parasites/µL and BCS ≤ 2 and a haemoglobin level of < 5 g/dL
Other severe disease: > 5000 parasites/µL, a BCS >2, a haemoglobin level of ≥ 5 g/dL and another marker of severe disease (prostration, respiratory distress, seizures, hypoglycemia [< 2.2 mmol/L], acidosis [BE ≤ -10.0 mmol/L], lactate ≥ 5.0 mmol/L)
Missing: Haemoglobin or BCS unavailable so syndrome classification could not be determined

- During the 20 months period post Dose 1, in children aged 5-17 months, 16 cerebral malaria cases (parasitaemia > 5000 per µL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL) occurred in the RTS,S/AS01$_E$ group, among 5948 children, and 5 cerebral malaria cases occurred in the control vaccine group, among 2974 children. In addition, cerebral malaria and anaemia (parasitaemia > 5000 per µL, Blantyre Coma Score ≤ 2 and haemoglobin level of < 5 g/dL) were observed for 6 subjects in the RTS,S/AS01$_E$ group and 1 subject in the control vaccine group.
- Between administration of the 4th dose of RTS,S/AS01$_E$ / meningococcal C conjugate vaccine and study end, in children aged 5-17 months, 9 cerebral malaria cases occurred among 2719 children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose. No cerebral malaria with anaemia was observed in this group. 11 cerebral malaria cases occurred among 2681 vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (plus

one case of cerebral malaria with anaemia), and 2 cerebral malaria cases occurred among 2702 children receiving rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose (plus 2 cases of cerebral malaria with anaemia).

Taking into consideration the fact that the numbers were small, that no clinical diagnosis was performed by the investigators (no clinical case definition used), that there is no known biological plausibility of a pre-erythrocytic vaccine to directly cause cerebral malaria, the most likely explanation of the imbalance is a possible rebound effect and/or shift of age linked to the efficacy of the intervention. Therefore GSK Biologicals considers cerebral malaria as a safety concern that requires further evaluation, and has therefore categorized it as an important potential risk in the RMP.

Overall mortality by gender:

Ad-hoc analysis of mortality by gender based on the completed Phase III study MALARIA-055 data was performed at the request of WHO, in the context of their policy making pertaining to the potential use of Mosquirix in SSA [WHO, 2016(a); WHO, 2016(b)].

In this analysis all-cause mortality in the girls who received RTS,S/AS01$_E$ was ≈2-fold higher than in the girls who received the control vaccine (123/5091 [2.4%] versus 33/2603 [1.3%]; for both age categories pooled); while in boys, all-cause mortality was slightly lower in the group that received RTS,S/AS01$_E$ compared to the boys in the control group (95/5215 [1.8%] versus 55/2550 [2.2%]).

It is GSK's position that this should not be considered a safety signal because:

- Low fatality rate overall in study MALARIA-055 compared to what could be expected: 1 to 2% in each group, while in real-life setting under 5 mortality in SSA is estimated to be 3% (WHO) to 5% (World bank);
- An investigator-initiated case control study in one site showed a 70% reduction in all-cause mortality in children enrolled in the study, as compared to children living in the same area but not enrolled in MALARIA-055;
- Background mortality rates per gender vary significantly across SSA countries. Under circumstances where boys and girls have the same access to resources such as food and medical care, boys have higher mortality rates than girls during childhood. Western Africa had the most countries (five) with evidence of excess female child mortality in the 2000s as well as several countries of Eastern Africa and Middle Africa [United Nations, 2011].
- The overall trend for differences in mortality rates in girls between the RTS,S/AS01$_E$ and control groups is also observed in the subgroup analyses of the potential confounding factors including administration of recommended EPI vaccines (measles, yellow fever, etc), human immunodeficiency virus (HIV) status and different access to medical care and/or proper nutrition. These differences are in-line with the observed imbalance in overall mortality and it is difficult to understand whether they actually contributed to the overall mortality differences between girls in the RTS,S/AS01$_E$ treatment groups and girls in the control group. Therefore, these

additional analyses only seem to support the hypothesis that the observed imbalance in mortality in girls (i.e. active versus control) is likely to be a chance finding (given the small numbers involved and the fact that clinical trials are not designed to evaluate impact on mortality, especially for a disease like malaria that is perfectly treatable).

However, GSK Biologicals considers that gender-specific mortality requires further evaluation, and has therefore categorized it as missing information in the RMP.

In summary, meningitis is considered/reported as a potential risk in the RMP of RTS,S/AS01$_E$. The occurrence of febrile convulsions is considered/reported as an identified risk associated during the 7 days following vaccination with RTS,S/AS01$_E$. The imbalance observed for cerebral malaria following a post-hoc analysis of the MALARIA-055 study is considered as a safety concern that requires further evaluation and is therefore categorized as an important potential risk in the RMP. At present, GSK Biologicals does not consider excess/increased mortality in females as a potential risk. Additional data need to be generated; for now it has been categorized in the RMP as missing information.

7.3. Efficacy results of the clinical development of RTS,S/AS01$_E$

Efficacy results of the Phase III study, MALARIA-055, are shown below for the intention-to-treat population. Efficacy against all episodes of clinical malaria in children aged 5 to 17 months over 12 months after Dose 3 was estimated to be 55.1% (95% CI: 50.5, 59.3) [The RTS,S Clinical Trials Partnership, 2011]. Over 18 months after Dose 3 it was estimated to be 45.1% (95% CI: 41.4, 48.7) [The RTS,S Clinical Trials Partnership, 2014]. In infants aged 6-12 weeks, efficacy against all episodes of clinical malaria over 12 months was 32.9% (95% CI: 26.3, 38.8) [The RTS,S Clinical Trials Partnership, 2012] and over 18 months was 27.0% (95% CI: 21.1, 32.5) [The RTS,S Clinical Trials Partnership, 2014].

In both age groups, vaccine efficacy for clinical malaria waned over time (Schoenfeld residuals p<0. 001). In children 5-17 months, the reduction in malaria by 6 month time intervals following Dose 3 was reported as: 68% (95% CI: 64, 72) over the first 6 months of follow-up; 41% (95% CI: 36, 46) over the subsequent 6 months of follow-up; and 26% (95% CI: 19, 33) over the last 6 months of follow-up [The RTS,S Clinical Trials Partnership, 2014]. In infants 6-12 weeks, the corresponding reduction was reported to be 47% (95% CI: 39, 54), 23% (95% CI: 15, 31), and 12% (95% CI: 1, 21), respectively [The RTS,S Clinical Trials Partnership, 2014].

Long-term follow-up efficacy data and data following administration of a 4th dose of RTS,S/AS01$_E$ 18 months post Dose 3 show a decline in efficacy against clinical and severe malaria with time in both children and infants who did not receive a 4th dose of the RTS,S/AS01$_E$ vaccine. Administration of a 4th dose of RTS,S/AS01$_E$ enhanced protection against clinical malaria in infants and children as well as the efficacy against severe malaria in children. In children aged 5 to 17 months who did not receive a 4th dose of RTS,S/AS01$_E$, efficacy against all episodes of clinical malaria over 30 months post Dose 3 was estimated to be 35.2% (95% CI: 30.5, 39.5). In children who were administered a 4th dose of RTS,S/AS01$_E$, efficacy against all episodes of clinical malaria over 30 months was 43.9% (95% CI: 39.7, 47.8). For severe malaria, efficacy over 30 months in children aged 5 to 17 months was 4.5% (95% CI: -20.6, 24.5) when no 4th dose of RTS,S/AS01$_E$ was administered and 34.9% (95% CI: 15.6, 50.0) when a 4th dose of RTS,S/AS01$_E$ was administered. In infants aged 6-12 weeks, efficacy against all episodes of clinical malaria over 30 months was 20.3% (95% CI: 13.6, 26.5) without administration of a 4th dose of RTS,S/AS01$_E$ and 27.8% (95% CI: 21.7, 33.4) with administration of a 4th dose of RTS,S/AS01$_E$. Efficacy against severe malaria over 30 months was 7.9% (95% CI: -23.3, 31.2) without administration of a 4th dose of RTS,S/AS01$_E$ and 11.9% (95% CI: -18.3, 34.5) with administration of a 4th dose of RTS,S/AS01$_E$ [The RTS,S Clinical Trials Partnership, 2015]. These data support the benefit of a 4th dose of RTS,S/AS01$_E$ administered 18 months post Dose 3.

A potential rebound effect was observed in children aged 5-17 months. Throughout the period 18 months post Dose 3 to study end, an increased incidence of severe malaria was observed in children who did not receive a 4th dose of RTS,S/AS01$_E$, compared to controls: efficacy was -41.0% (95% CI: -98.5, -0.8). Among children who were administered a 4th dose of RTS,S/AS01$_E$ efficacy against severe malaria throughout the same period was -4.0% (95% CI: -50.0, 27.8). In infants aged 6-12 weeks, efficacy against severe malaria during the period 18 months post Dose 3 to study end was 11.2% (95% CI: -31.3, 40.2) when no 4th dose of RTS,S/AS01$_E$ was administered and 32.4% (95% CI: -3.2, 56.2) when a 4th dose of RTS,S/AS01$_E$ was administered. In contrast, clinical malaria disease showed no period of increased incidence compared to controls. The impact of RTS,S/AS01$_E$ against clinical malaria and severe malaria varied substantially by study site and the rebound effect was mainly observed in medium and high transmission settings [The RTS,S Clinical Trials Partnership, 2015].

7.4. Rationale for the study

The RTS,S/AS01$_E$ vaccine will be implemented only in malaria endemic countries of SSA. Most of these countries have no baseline incidence data on rare diseases such as those that may be reported as AE following vaccination. Lack of baseline data would compromise the interpretation of any AE detected following the implementation of the RTS,S/AS01$_E$ vaccine in the paediatric population.

GSK Biologicals has developed a set of studies to address this paucity of data, and to ensure optimal collection of information related to the occurrence of those events before and after implementation of the RTS,S/AS01$_E$ vaccine. EPI-MAL-002, a pre-implementation study (i.e. before vaccine implementation), is intended primarily as a surveillance study to collect background incidence rates of protocol-defined events of

special interest, other events leading to hospitalisation or death, and meningitis cases in preparation for EPI-MAL-003. In the post-implementation study EPI-MAL-003, the events of special interest have been defined as adverse events of special interest (AESI), and events leading to hospitalisation or death have been defined as AE leading to hospitalisation or death. The events measured in EPI-MAL-002 and EPI-MAL-003 are based on results from MALARIA-055 or are events that have historically been associated with vaccines other than RTS,S/AS01$_E$, or may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines. They will be monitored the same way in EPI-MAL-002 and EPI-MAL-003. In order to harmonize the terminology between the two studies, the terms AESI and AE will be used even for EPI-MAL-002.

Additionally, vaccine impact measures (indirect, total and overall effects) are included in EPI-MAL-002 and EPI-MAL-003 to take advantage of the capacity developed for the safety component in the study sites and of the data collected on any malaria and severe malaria, including cerebral malaria, during EPI-MAL-002. Therefore malaria morbidity and mortality will also be monitored. The mortality rate, overall and by gender, will also be estimated.

The EPI-MAL-002 study started in Q4 2015 and will last for approximately 5 years (depending on recruitment timelines). EPI-MAL-003 ***started in Q1 2019*** when the vaccine ***became*** available in the study sites that are exposed clusters after its implementation according to WHO guidelines in the framework of the MVIP (first vaccine introduction ***was*** foreseen in 2018, see section 9.2).
(Amended 5 May 2020)

In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MAL-005) is conducted to measure malaria transmission intensity (MTI) and other malaria control interventions at community level in the study site areas. This study began in Q4 2014, at the first malaria transmission peak season in the West African sites with peak malaria transmission in the second half of the year, and will run through the completion of EPI-MAL-003. It is taking place in similar if not identical settings as EPI-MAL-002 and EPI-MAL-003.

Finally, describing the overall morbidity and mortality in this population is thought to have broader utility beyond these malaria studies, and could serve as baseline data for other disease control and prevention studies.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To estimate the incidence of AESI[2], and of other AE leading to hospitalisation or death, in children, prior to implementation of RTS,S/AS01$_E$.
- To estimate the incidence of aetiology-confirmed meningitis, in children, prior to implementation of RTS,S/AS01$_E$.

8.2. Secondary objectives

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- To estimate the incidence of aetiology-confirmed, and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To describe risk factors for AESI, other AE leading to hospitalisation or death, meningitis and malaria.
- To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria).
- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following administration of routine EPI vaccines.
- To estimate the incidence of any malaria (including *P. falciparum* malaria) using rapid diagnostic test (RDT) and/or microscopy.
- To estimate the incidence of severe malaria (including *P. falciparum* malaria) using RDT and/or microscopy.
- To estimate the incidence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- To estimate the prevalence of anaemia among hospitalised children.

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[2] Acute disseminated encephalomyelitis, encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode, generalised convulsive seizure.
Intussusception, hepatic failure, renal insufficiency.
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease.
Diabetes mellitus type I, thrombocytopenia, anaphylaxis.

- To estimate the incidence of all-cause hospitalisations and hospitalisations attributed to malaria (including *P. falciparum*).
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.

9. RESEARCH METHODS

9.1. Study design

The aim of this study is to estimate the incidence of protocol-defined AESI in a setting without existing surveillance systems designed to capture those rare events. The study also aims to estimate the incidence of other AE leading to hospitalisation or death, meningitis, severe malaria, including cerebral malaria, and malaria morbidity and mortality at the same time. The mortality rate, overall and by gender, will also be estimated. Therefore, the design of the study is defined as a disease surveillance study with prospective cohort event monitoring. The cohort is technically dynamic, as children will be entering and leaving the cohort throughout the study period. The design incorporates both active surveillance and enhanced hospitalisation surveillance. The study uses multiple data sources, to increase the opportunity to capture the events of interest.

Active surveillance:

Approximately 30,000 children will be recruited within the collaborating study sites, and enrolled into active surveillance, with about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. These children will be actively followed up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. Among these children, approximately 15,000 children will be enrolled in the 6-12 weeks group (with about 10,000 children in sites where the vaccine will be implemented) and approximately 15,000 children will be enrolled in the 5-17 months group (with about 10,000 children in sites where the vaccine will be implemented; see Section 9.2.1.1). For the purpose of this study, the 6-12 weeks group and the 5-17 months group are defined as follows:

6-12 weeks group:

- Children identified at first administration of DTP/HepB/Hib vaccine (usually given at 6, 10 and 14 weeks of age) and for whom the home visits will be conducted according to the EPI schedule.

5-17 months group:

- 5-17 months group, enrolled at first DTP: Children identified at first administration of DTP/HepB/Hib vaccine (usually given at 6, 10 and 14 weeks of age), for whom the home visits will be scheduled from 6 months of age onwards (mimicking administration of RTS,S/AS01$_E$ in the 5-17 months group). In case a child is first seen during hospitalisation, before first administration of DTP/HepB/Hib vaccine, and meeting the inclusion criteria for active surveillance, the child can be enrolled in active surveillance (5-17 months group, enrolled at first DTP) during hospitalisation and home visits will be scheduled from 6 months of age onwards.

- 5-17 months group, catch-up: Children aged 5 to <18 months, identified at first encounter with the study staff, for whom the home visits will be scheduled from the first encounter with the study staff onwards (mimicking administration of RTS,S/AS01$_E$ in the 5-17 months group). In case a child aged 5 to <18 months is first seen during hospitalisation and meeting the inclusion criteria for active surveillance, the child can be enrolled in active surveillance (5-17 months group, catch-up) during hospitalisation and home visits will be scheduled after being discharged from the hospital.

Enrolled children will be followed up through home visits for a total period of 44 months (see Figure 1 and Section 9.2.7.1) except for subjects enrolled from Burkina Faso sites for whom their participation in the study has been early terminated. This follow-up period corresponds to the follow-up period of the children enrolled in EPI-MAL-003 (i.e. 24 months after the 4th dose of RTS,S/AS01$_E$).

In addition to the home visits, in children enrolled in the active surveillance, all visits to health care facilities (primary health care and hospital level) for any diseases, signs and symptoms will be reported to the study staff up to the end of the active follow-up period for each individual child (see Section 9.4.2). Thereafter there will be continuous monitoring of hospitalisations only, up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) (Figure 1).

Note: There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003. Therefore, children enrolled in active surveillance of EPI-MAL-002 and who meet the eligibility criteria for the EPI-MAL-003 study may have their study conclusion for the EPI-MAL-002 study before the end of the 44 months of active follow-up if enrolled in EPI-MAL-003 (see Section 9.2.7.1.12).

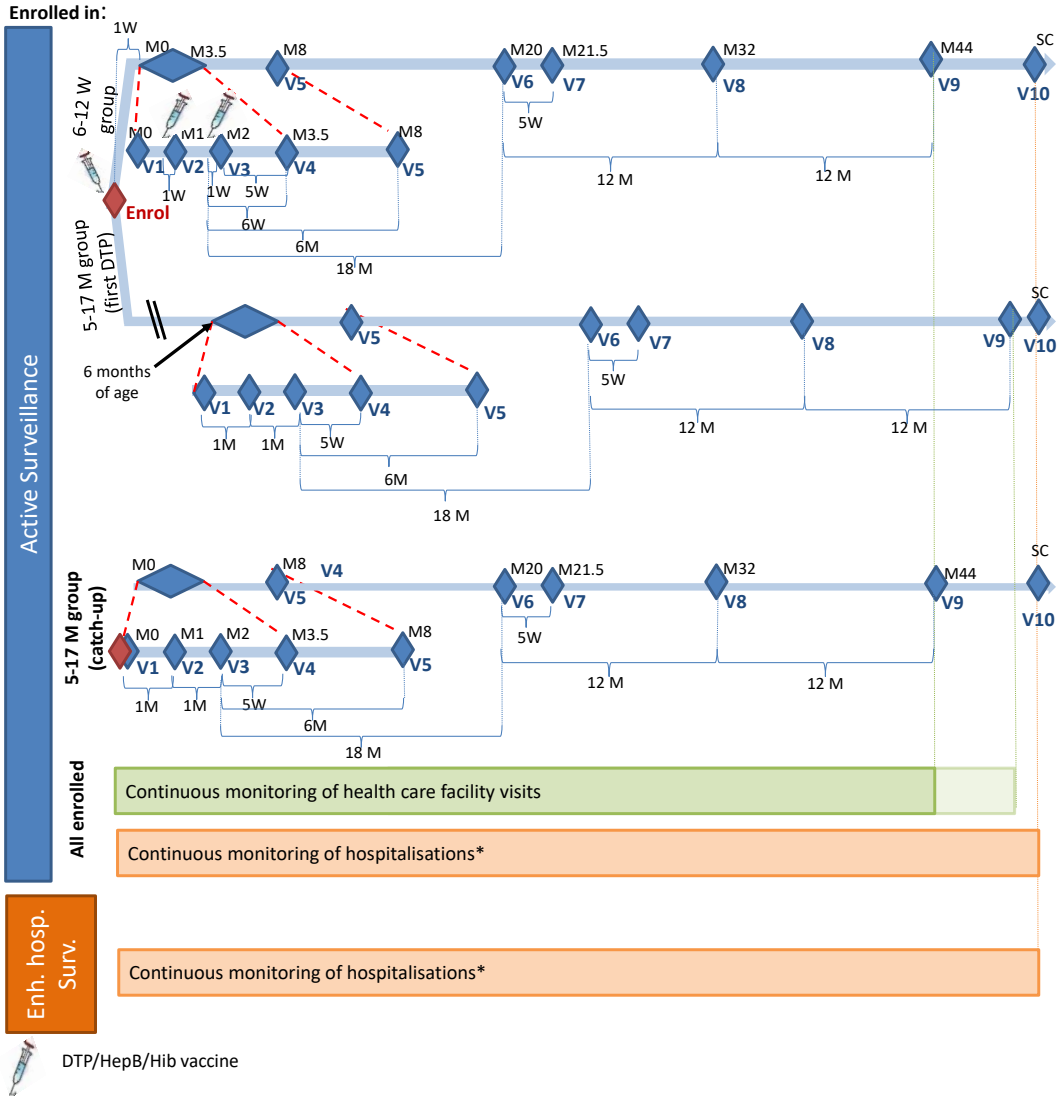
Enhanced hospitalisation surveillance:

All children under the age of 5 years of age, within the study areas, not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance, are eligible for enrolment in enhanced hospitalisation surveillance during any hospitalisations throughout the whole study period, to allow data collection regarding those hospitalisations (see Figure 1 and Section 9.2.7.2). For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

In this protocol, active surveillance will refer to children who are enrolled in active surveillance, and enhanced hospitalisation surveillance will refer to children who are enrolled in enhanced hospitalisation surveillance. Data collected regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

Because of a possible overlap of studies EPI-MAL-002 and EPI-MAL-003, study conclusion of EPI-MAL-002 for children enrolled in enhanced hospitalisation surveillance will be done at start of study EPI-MAL-003 (as the RTS,S/AS01$_E$ vaccine becomes available in the sites that are exposed clusters).

Figure 1 Study design overview



* Hospitalisation is defined as spending at least one night at a health care facility

V = visit; W = week(s); M = month(s); SC = study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first); Enrol = enrolment.

For the children enrolled in active surveillance in the 6-12 weeks group, enrolment is at first administration of DTP/HepB/Hib vaccine. The home visits will take place approximately 1 week after administration of each dose of DTP/HepB/Hib vaccine (V1, V2, V3), and 6 weeks (V4) and 6 months (V5) after administration of the third dose. These visits will be followed by a visit (V6) approximately 18 months after administration of the third dose, and visits approximately 5 weeks (V7), 12 months (V8) and 24 months (V9) after V6. A last home visit (V10) will be conducted at study conclusion.

The 5-17 months group of the active surveillance will include a group of selected children identified at first administration of DTP/HepB/Hib vaccine, or first seen during hospitalisation, before first administration of DTP/HepB/Hib vaccine, and meeting the inclusion criteria for active surveillance, and a group of children aged 5 to <18 months, corresponding to a catch-up. The first visit (V1) for selected children identified at first administration of DTP/HepB/Hib vaccine will be at 6 months of age, and for children aged 5 to <18 months, corresponding to a catch-up, at time of their first encounter with study staff or approximately 1 week later. The following visits will be scheduled in a similar way as for the 6-12 weeks group.

Continuous monitoring of outpatient visits at health care facilities will be done up to the end of active follow-up (V9) for all children enrolled in the active surveillance.

Continuous monitoring of hospitalisations will be done throughout the whole study period.

9.1.1. Rationale for the study design

The target population for this study is defined as infants and young children < 5 years of age. The active surveillance will include approximately 15,000 children in the 6-12 weeks group (with about 10,000 children where the RTS,S/AS01$_E$ vaccine will be implemented; to collect background data in this age group) and approximately 15,000 children in the 5-17 months group (with about 10,000 children where the RTS,S/AS01$_E$ vaccine will be implemented; to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group). The active follow-up will be based on administration of a primary schedule of 3 doses of RTS,S/AS01$_E$ administered at 1-month intervals, with a 4th dose 18 months after last primary dose, and 24 months of active follow-up after the last dose. Refer also to Section 9.9 for details about limitations.

The safety, effectiveness and impact of RTS,S/AS01$_E$ vaccination is planned to be evaluated through EPI-MAL-003. To collect comparable baseline information, this study, EPI-MAL-002, must collect data as similarly as possible as described in the EPI-MAL-003 protocol. EPI-MAL-003 will recruit subjects from a population of children less than 5 years of age living within a study catchment area. EPI-MAL-002 utilises a similar approach in similar if not identical settings for comparability of data.

The main outcomes of the EPI-MAL-002 study are the incidence of AESI, other AE leading to hospitalisation or death, and meningitis**.** The AESI were selected because they have been historically associated with vaccines other than RTS,S/AS01$_E$, or may be hypothetically associated with RTS,S/AS01$_E$ because this vaccine has components which are new compared to current widely used vaccines. Meningitis was identified in the Phase III efficacy trial, MALARIA-055, as a potential risk. Therefore, the estimation of the incidence of meningitis (classified as aetiology-confirmed, probable or clinically suspected meningitis - see case definitions in Section 9.2.5.3) has been added as specific safety objective in this protocol. The diseases under surveillance for safety will be monitored among children enrolled in active surveillance and in enhanced hospitalisation surveillance.

All malaria events (morbidity, mortality and hospitalisation) will be monitored throughout the study. Background incidence rates of any malaria and severe malaria, including cerebral malaria, will be collected. This will enable the investigation of the impact (indirect, total and overall effect) of the RTS,S/AS01$_E$ vaccine by comparing all malaria events in EPI-MAL-002 to all malaria events in unvaccinated children in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children in EPI-MAL-003 (overall effect); for children enrolled in the active surveillance. The mortality rate, overall and by gender, will also be estimated.

Since RTS,S/AS01$_E$ is only protecting against *P. falciparum*, all analyses done for any malaria cases and for severe malaria cases regardless of the plasmodium species will be repeated for episodes with evidence of the *P. falciparum* parasite only. Analyses will also be performed for cerebral malaria due to *P. falciparum*, which is a complication of severe *P. falciparum* malaria (see Section 9.2.5.5 for case definitions).

Active surveillance

In order to detect the events of interest, active surveillance will be conducted among enrolled subjects through a series of home based visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities. For children in the 6-12 weeks group (identified at the first administration of DTP/HepB/Hib vaccine) these home visits will take place approximately 1 week after administration of each dose of DTP/HepB/Hib vaccine (V1, V2, V3), and 6 weeks (V4), 6 months (V5) and 18 months (V6) after administration of the last dose of DTP/HepB/Hib vaccine, followed by visits approximately 5 weeks (V7), 12 months (V8) and 24 months (V9) after V6, to mimic the potential active follow-up in study EPI-MAL-003 (Figure 1).

The 5-17 months group of the active surveillance will include a group of selected children identified at first administration of DTP/HepB/Hib vaccine, or first seen during hospitalisation, before first administration of DTP/HepB/Hib vaccine, and meeting the inclusion criteria for active surveillance, and a group of children aged 5 to <18 months, corresponding to a catch-up (see Section 9.2.1.1). The first visit (V1) for selected children identified at first administration of DTP/HepB/Hib vaccine will be at 6 months of age and for children aged 5 to <18 months, corresponding to a catch-up, at time of their first encounter with study staff or approximately 1 week later. The visits will be scheduled in a similar way as for the 6-12 weeks group (Figure 1). The intent for the 5-17 months group is to mirror the home visits of infants of the 6-12 weeks group, to capture events in a uniform manner and, for the children in the 5-17 months group identified at first administration of DTP/HepB/Hib vaccine, to mimic the potential immunisation schedule in study EPI-MAL-003 in the 5-17 months age group. For all children enrolled in active surveillance, a last home visit will be conducted at study conclusion (V10).

In addition to the home visits, any diseases, signs and symptoms in children enrolled in the active surveillance will also be reported to the study staff by all health care facilities (primary health care and hospital level) up to the end of the active follow-up period for each individual child, and will thereafter be continuously monitored up to study conclusion during hospitalisations only.

An important additional function of the active surveillance component is to ensure referral of sick children to the health care facilities.

Enhanced hospitalisation surveillance

For the purpose of this study, and of EPI-MAL-003, enhanced hospitalisation surveillance corresponds to case detection during hospitalisation through monitoring of medical records and registries. Enhanced hospitalisation surveillance is included to supplement the active surveillance to capture events in children whose parents/ Legally Acceptable Representatives (LARs) declined enrolment in active surveillance, in children who were not enrolled in active surveillance as recruitment had been completed or in children not eligible for active surveillance. Throughout the whole study period, all children under the age of 5 years within the study areas who are hospitalised, not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active

surveillance, are eligible for enrolment in enhanced hospitalisation surveillance, to allow for data collection regarding that hospital visit and any subsequent hospital visits until study conclusion (see also Section 9.2.1.1). Children already enrolled in active surveillance will have hospitalisations monitored as part of the procedures related to the active surveillance and will therefore not be enrolled in enhanced hospitalisation surveillance.

To assess the operational conduct of both enhanced hospitalisation surveillance and active surveillance, two control outcomes have been included in the study protocol. Abscess at injection site (after routine vaccination) is included as a positive control and positional foot deformation is included as a negative control (see case definitions in Section 9.2.6). These conditions are relatively easy to diagnose and could be used to assess changes in the performance of health care systems to diagnose disease.

Selected study sites are expected to have a health and demographic surveillance system (HDSS) or equivalent surveillance system in place. If a site does not have an equivalent surveillance system in place, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites. In addition, being part of the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) (or seeking membership to INDEPTH) is an asset to ensure standard health and demographic surveillance practices, thereby enabling standardised calculation of incidence rates.

9.2. Setting

The three studies EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005 are planned to be anchored when possible on the INDEPTH HDSS platform (http://www.indepth-network.org) or equivalent surveillance system to provide both population and health facility linkage [INDEPTH, 2015]. INDEPTH provides an international platform of sentinel HDSS centres in low and middle income countries designed to longitudinally follow populations and provide demographic and health information. For this study, the HDSS or equivalent surveillance system provides the population and its characteristics, from which a cohort may be identified. The cohort will be a subset of the total eligible population of children specified within the geographic catchment area of the study sites. The cohort is considered dynamic, as newborns and immigrants are included in the cohort and the birth or in-migration date is recorded. Similarly, deaths and out-migrations are recorded.

The process begins with a census of the population and proceeds with regularly scheduled (at least once a year) monitoring of vital events (births, deaths), migration, selected health outcomes, and other demographic and lifestyle variables. The census serves as the source document for the initial screening for study population eligibility.

Note: If a site is not part of the INDEPTH network, or does not have an equivalent surveillance system in place, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites.

Initially, seven sites in five SSA countries were planned to participate in the EPI-MAL-002 study. Following SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria [WHO, 2015(a)], some of the initially chosen sites located in low endemicity settings had to be terminated. For this reason, other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01$_E$ vaccine is planned to be implemented according to the MVIP, were added to the already defined study sites as described below.

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. The 3 countries were selected to participate in the pilot programme based on the following criteria: high coverage of long-lasting insecticidal-treated nets, well-functioning malaria and immunisation programmes, a high malaria burden even after scale-up of long-lasting insecticidal-treated nets, and participation in the Phase III RTS,S/AS01$_E$ malaria vaccine trial. Each of the 3 countries will decide on the districts and regions to be included in the MVIP. High malaria burden areas will be prioritized [WHO, 2017]. GSK baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) being fully embedded in the MVIP, selection of the clusters that are/will participate in those studies depends on the cluster identification process led by the Ministries of Health according to WHO guidance. They have been, or will be, selected as follows:

- ***EPI-MAL-002 study sites:*** currently, a total of 5 sites (2 in Ghana [Kintampo, Navrongo], 1 in Kenya [Kombewa] and 2 in Burkina Faso [Sapone, Nouna]) have enrolled study participants in the EPI-MAL-002 study.
  - Since sites have been, or will be, selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented, Burkina Faso sites that started EPI-MAL-002 have early terminated the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance on 06 June ***2018***, with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI (see sections 9.2.7.4.1, 9.2.7.4.2 and 9.2.7.4.5). All study activities are planned to be terminated by Q2 2019. A description of data from these sites will be presented in the progress reports up to Q4 2019, but none of the data from these sites will be part of the statistical analyses for the interim and final reports (neither in the before/after comparison analyses of the EPI-MAL-002 and EPI-MAL-003 studies, nor in any other indicators planned to be generated by EPI-MAL-002 data to inform analyses of the EPI-MAL-003 study [e.g. background incidence of meningitis for study sample size and the exposure to other vaccines]). Burkina Faso sites will not be included in EPI-MAL-003 because the MVIP will not take place in the country.

    (Amended 5 May 2020)

  - Two sites in Malawi have fulfilled the criteria of the study feasibility assessment and were planned to initiate the EPI-MAL-002 study in Q1-Q2 2018. Considering the RTS,S/AS01$_E$ vaccine implementation date in Malawi, currently planned in October 2018, the baseline data that might be collected in

Malawi in the EPI-MAL-002 study would be too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment observed from sites in Kenya (Kombewa) and Ghana (Kintampo) and extending recruitment in Ghana (Navrongo).

- EPI-MAL-003 study sites: as currently planned in the MVIP and according to WHO guidance, 4 study sites (corresponding to 4 clusters of the MVIP) in each of the 3 countries selected for the RTS,S/AS01$_E$ pilot implementation programme (12 study sites/clusters in total) are planned to be part of EPI-MAL-003: 2 of them should become exposed clusters and 2 of them should become unexposed clusters (see Annex 3 for definitions of exposed and unexposed clusters). In order to allow the before-after comparison of study endpoints and according to WHO guidance, study sites from Ghana and Kenya included in the EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters.
- EPI-MAL-005 study sites: being an ancillary study to EPI-MAL-002 and EPI-MAL-003 studies, EPI-MAL-005 is/will be conducted in study sites conducting EPI-MAL-002 and/or EPI-MAL-003.
- Of note, all study sites are submitted to a comprehensive scientific and operational study site assessment conducted by GSK, which will determine study feasibility in those sites. Exposed and unexposed clusters will be comparable in terms of malaria transmission, health facilities level, geographical region and population size.
- A replacement strategy has also been elaborated in case one or more of the sites conducting EPI-MAL-002 cannot participate in EPI-MAL-003. It could consist in extending the recruitment period in the remaining sites (depending on vaccine implementation strategy).

9.2.1. Study population

The study population is defined as those children living in the study areas who are < 5 years old.

Following SAGE/MPAC recommendations, sites with moderate-to-high transmission of malaria have started enrolment. In order to reach a birth cohort of about 17,250 children per year (with about 11,500 children per year where the RTS,S/AS01$_E$ vaccine will be implemented), other sites in SSA settings with moderate-to-high transmission of malaria, from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented (see Section 9.2), were added to the already defined study sites.

The assumption of such a birth cohort was done to allow recruitment of about 30,000 children in active surveillance in 16 months, with about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented.

Although participation rates are thought to be high in these study sites, taking into account the potential refusal of parents/LARs for their children to join the study, the

targeted number of 30,000 children to be enrolled into active surveillance is feasible. Among the 30,000 children recruited for active surveillance with about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented, approximately 15,000 will be part of the 6-12 weeks group (with about 10,000 children enrolled in sites where the vaccine will be implemented) and approximately 15,000 will be part of the 5-17 months group (with about 10,000 children enrolled in sites where the vaccine will be implemented).

In addition to the children enrolled for active surveillance, events of interest will also be collected through the enhanced hospitalisation surveillance.

9.2.1.1. Participant recruitment

Active surveillance

All children will be identified through HDSS or equivalent surveillance system review. Parents/LARs of potentially eligible children will be invited to enrol their children into active surveillance and the informed consent form (ICF) for active surveillance will be signed or witnessed and thumb printed.

Participant recruitment is expected to be done as follows, based on the birth cohort:

- Parents/LARs of children presenting for the first administration of DTP/HepB/Hib vaccine (usually given at 6, 10 and 14 weeks of age) will be proposed to enrol their child in active surveillance. Among children whose parents/LARs accept to enrol their child into active surveillance, two out of three children will be included in the 6-12 weeks group and the remaining children (one out of three) will be included in the 5-17 months enrolled at first DTP group until the enrolment target of the 5-17 months (first DTP) group is reached. Thereafter, all children whose parents/LARs accept enrolment in active surveillance will be included in the 6-12 weeks group, until the expected number of children is reached. An expected number of 15,000* children will be enrolled in the 6-12 weeks group, and of 6,375* children in the 5-17 months enrolled at first DTP group. The first visit (V1) for the 6-12 weeks group will be approximately 1 week after the first administration of DTP/HepB/Hib vaccine. For the 5-17 months enrolled at first DTP group the first visit (V1) will be at the age of 6 months.
- Parents/LARs of children aged 5 to <18 months will be contacted by the study staff and invited to enrol their child into active surveillance. Children whose parents/LARs accept to enrol their child into active surveillance will be included in the 5-17 months catch-up group. The first visit (V1) for the 5-17 months catch-up group will be at time of their first encounter with study staff or approximately 1 week later, depending on site. Recruitment will be done until the expected number of children is reached (expected number of children in this group: 8,625*).

  * Based on a birth cohort of 17,250 children (see Section 9.2.1), which is a conservative estimate knowing that the birth cohort is increasing.

- In case a child is first seen during hospitalisation, before first administration of DTP/HepB/Hib vaccine (usually given at 6, 10 and 14 weeks of age), and meeting the inclusion criteria for active surveillance, within the recruitment period, the child can be enrolled in active surveillance in the 5-17 months enrolled at first DTP group. The first visit (V1) will be at the age of 6 months. In case a child aged 5 to <18 months is first seen during hospitalisation and meeting the inclusion criteria for active surveillance, within the recruitment period, the child can be enrolled in active surveillance in the 5-17 months catch-up group. The first visit (V1) will be 1 week after being discharged from the hospital. The ICF for active surveillance will be signed or witnessed and thumb printed during hospitalisation.

In case a subject enrolled in active surveillance is returning to the study area having previously been declared as an emigrant (migration being defined as spending more than 3 months outside the study area) this subject will keep the same subject study number and continue the original follow-up.

In each site, a proportion of approximately 50% children enrolled in the 6-12 weeks group and 50% children enrolled in the 5-17 months group is expected.

Note: As part of routine EPI vaccination programmes, the standard DTP/HepB/Hib vaccinations usually given at 6, 10 and 14 weeks of age will be administered by the National EPI system in the study area (in some countries the EPI schedule may differ by a few weeks). Vaccination types and dates will be recorded, but no vaccination will be administered as part of this study.

Parents/LARs should be prompted to attend EPI if their child is late in receiving their first dose of the EPI three dose vaccines usually given at 6, 10 and 14 weeks of age.

Enhanced hospitalisation surveillance

Parent(s)/LAR(s) from all children who are hospitalised, who are under the age of 5 and who can be linked to the HDSS or equivalent surveillance system census, will be approached to enrol their child into this study:

- If a child, who is first identified during hospitalization by study staff, fulfills the eligibility criteria for enrolment in active surveillance (within the recruitment period), enrolment in active surveillance will be proposed. If the parents/LARs decline enrolment in active surveillance enrolment in enhanced hospitalisation surveillance will be proposed.
- If a child, who is first identified during hospitalization by study staff, is not eligible for enrolment in active surveillance but fulfills the eligibility criteria for enrolment in enhanced hospitalisation surveillance, enrolment in enhanced hospitalisation surveillance will be proposed.

  Note: ‘first identified during hospitalization by study staff’ means ‘not already enrolled in the study’.

In case a subject enrolled in enhanced hospitalisation surveillance is returning to the study area having previously been declared as an emigrant (migration being defined as spending more than 3 months outside the study area) this subject will keep the same subject study number and continue the original follow-up.

Enrolment into the study, as documented by signed or witnessed and thumb printed ICF, will allow for the collection of data that were generated during the hospitalisation under the local standards of care. In case a subject is hospitalised more than once during the study duration, the subject will be enrolled only once and followed for all hospitalisations occurring throughout the study duration or until he/she reaches 5 years of age.

Hospitalisation is defined as spending at least one night at a health care facility, for a subject registered in the study area.

Some primary health care facilities have beds available for overnight monitoring; these stays are considered to be “hospitalisations” for protocol purposes. There may be a difference in the degree of severity of cases admitted in the hospital and those hospitalised at primary health care facilities as the latter may include children with non-severe disease who live too far to be sent home on the same day. On the other hand, hospitalisations in primary health care facilities may also include cases that under European conditions would normally be referred to the hospital, such as: parental refusal to refer the child to a hospital, difficulties of transport or local standard practice. This issue will be addressed by identifying the type of health care facility (either hospital or primary health care facility) in case of hospitalisation. The type of health care facility will be included as covariate in the analyses, where appropriate.

9.2.2. Inclusion criteria for enrolment

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

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

- Subjects’ parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Written informed consent provided from either the parent(s) or LAR of the subject.
- Subject living in the HDSS or equivalent surveillance system area.
- For enrolment in the active surveillance: children must be < 18 months of age

  OR

  For enrolment in the enhanced hospitalisation surveillance: children must be < 5 years of age and hospitalised at any time during the study.

Parents/LARs of children first identified during hospitalisation, before first administration of DTP/HepB/Hib vaccine or at the age of 5 to <18 months, must first be proposed enrolment in active surveillance (5-17 months group) within the recruitment period.

Children already enrolled in active surveillance will have hospitalisation monitored as part of the procedures related to the active surveillance and can therefore not be enrolled in enhanced hospitalisation surveillance.

9.2.3. Exclusion criteria for enrolment

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

- Child in care.

  Please refer to Annex 3 for the definition of child in care.

9.2.4. Study period

Recruitment for active surveillance is expected to be done until the enrolment target is reached. Enrolment in enhanced hospitalisation surveillance has been early terminated for the sites where the RTS,S/AS01$_E$ vaccine will not be implemented. For the sites where the RTS,S/AS01$_E$ vaccine will be implemented, the enrolment in enhanced hospitalisation surveillance will end at start of study EPI-MAL-003.

Active surveillance will last 44 months for each subject (mimicking 24 months of active follow-up after the 4th dose of RTS,S/AS01$_E$ in EPI-MAL-003) except for subjects enrolled from Burkina Faso sites for whom their participation in the study has been early terminated. The EPI-MAL-002 study will last for approximately 5 years (depending on recruitment timelines).

Note: There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003, some children enrolled in EPI-MAL-002 may have the possibility to be part of EPI-MAL-003 (see Section 9.2.7.1.12 for more details).

The study began enrolment during Q4 2015.

9.2.5. Case definitions

9.2.5.1. AESI

Adverse events of special interest (AESI) are protocol-defined diseases corresponding to AEs that have historically been associated with vaccines other than RTS,S/AS01$_E$, or may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines.

The list of AESI has been developed in collaboration with a group of paediatricians working in SSA. This group of paediatricians was consulted following an opportunity to receive a scientific advice with the EMA in 2011. Indeed, the Committee for Medicinal Products for Human Use (CHMP) suggested to seek advice from relevant paediatric clinicians on which additional AESI may be of most relevance for SSA countries. In addition, GSK had considered four diseases which have been identified as potential AE with other vaccines and has added these to this list (Intussusception, Kawasaki diseases, Henoch-Schonlein Purpura and Hypotonic Hyporesponsive Episode [HHE]).

When available, the Brighton Collaboration Working Groups case definitions are used. These aim at defining levels of diagnostic certainty of reported events following vaccination. Their global use enhances data comparability within and across clinical trials and surveillance systems and allows for the adaption of the diagnosis based on the health facility's settings. Each case definition is structured in a two or three level of diagnostic certainty format, each level being defined by a set of clinical and/or additional diagnostic criteria.

- Level 1 of diagnostic certainty: most specific and least sensitive level
- Level 2 of diagnostic certainty: intermediate level of specificity and sensitivity
- Level 3 of diagnostic certainty: most sensitive but lower level of specificity.

Job Aids are field guides that act as a reference tool for study staff. For this study, Job Aids have been developed to standardise the definition of each AESI during a collaborative initiative between GSK, Agence de Médecine Préventive (AMP) and Réseau en Afrique Francophone pour la Télémédecine (RAFT). RAFT physicians will provide support for case diagnosis through virtual consultation infrastructure.

The predefined list of AESI and associated clinical information is provided in Table 3 and case definitions are provided in Annex 5.

Table 3 Summary of adverse events of special interest (AESI) by body system

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
Nerves and Central Nervous System				
ADEM	0.6 to 0.8/100,000 PY [Karussis, 2014]; 0.2/100,000 PY (in < 18 yr olds, Canada) [Banwell, 2009]; 0.40, 0.27 and 0.30/100,000 PY (10-14 yr olds, 15-19 yr olds, 20-29 yr olds, respectively, China) [Xiong, 2014]; 0.03/100,000 PY (10-16 yr olds, Germany) [Pohl, 2007]; 0.2/100,000 PY (< 18 yr olds, The Netherlands) [Ketelslegers, 2012]; 0.34/100,000 PY (1-15 yr olds, UK) [Absoud, 2012]; 0.3/100,000 PY (≤ 18 yr olds, US) [Langer-Gould, 2011]; 0.4/100,000 PY (< 20 yr olds, US) [VanLandingham, 2010]	1-2 per million following vaccination against measles, 0.2 per 100,000 following vaccination against Japanese encephalitis, 1 per 300 to 1 per 7,000 following administration of neural vaccine against rabies [Tenembaum, 2007]	NA	BC
Encephalitis	11.1 (95% CI: 10.1, 12.1) and 4.7 (95% CI: 4.3, 5.1) encephalitis-associated hospitalisations /100,000 PY (in <1 yr and 1-4 yr olds, US, respectively) [Vora, 2014]	1396 cases (mean age 23.4 yrs, range 0-89 yrs) in the US from 1990 to 2010 [Al Qudah, 2012]	Onset within 6 wks and 2 wks after vaccination: 65.2% and 50.7% of patients, respectively [Al Qudah, 2012]	BC
Guillain Barré Syndrome	0.7/100,000 PY (in 12-29 yr olds, Tanzania) [Howlett, 1996] 0.38/100,000 PY (in 0-4 yr olds, China) [Chen, 2014] 0.62/100,000 PY (95% CI: 0.52, 0.75) in 0-9 yr olds in a meta-analysis from studies in North America and Europe [Sejvar, 2011]	1 additional case per 10^6 doses with influenza vaccination in US, 1992-1994 [Lasky, 1998] Calculated RR in different studies on influenza vaccination from 1978 to 2005 produced RR values ranging from 0.4 to 1.7 [Sejvar, 2011]	Ranges from 3-5 days to 6-10 wks, and up to a few months and even years [Sejvar, 2011]	BC

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
Generalised convulsive seizure	Unknown	1.04 per 1,000 (95% CI: 0.62, 1.64) after primary vaccination with RTS,S/AS01 in children 5-17 months at first dose [The RTS,S Clinical Trials Partnership, 2011]; 2.5 per 1,000 and 2.2 per 1,000 after 4th dose of RTS,S/AS01 in children 5-17 months at first dose, and in children aged 6-12 weeks at first dose, respectively [The RTS,S Clinical Trials Partnership, 2015]	0-7 days after RTS,S/AS01	BC
Hypotonic Hypo-responsive episode	NA	Reported rates following whole-cell and acellular pertussis component combination vaccines range from 21 to 71 episodes and 7 to 36 episodes per 100,000 doses and 36 to 250 episodes and 4 to 140 episodes per 100,000 children, respectively [Buettcher, 2007]	3–4h but ranges from immediately to 48h post vaccination	BC
Hepato-Gastrointestinal and Renal System				
Intussuscep-tion	Average rate 1 case per 3,300; yearly variations 1:2,500 to 1:5,000 (<1 yr old, Panama) [Sáez-Llorens, 2004] <5/100,000 PY (<9 wks), 62/100,000 PY (26-29 wks), 26/100,000 PY (52 wks) (US) [Tate, 2008] 8.1/100,000 PY (<1 yr Australia) [Justice, 2005]	Overall estimate of risk of IS during the 7 days after vaccination with *Rotarix* 6.8 (95% CI: 2.4, 19.0) and with *RotaTeq* 9.9 (95% CI: 3.7, 26.4) after dose 1. Small increase after dose 2 for both vaccines [Carlin, 2013; Rosillon, 2015]	1 to 7 days after 1st and 2nd doses of *Rotarix* and *RotaTeq* vaccines	BC
Hepatic insufficiency	Unknown	NA	1-10 days	BC
Renal insufficiency	Unknown	NA	1-10 days	BC
Skin and Mucous Membrane & Bone and Joints				
Juvenile chronic arthritis	18/100,000 PY (in ≤16 yr olds, Canada) [Feldman, 2009]; 7/100,000 PY (Germany); 24/100,000 PY (Australia) [Begg, 2007]	NA	≤6 months	P
SJS and TEN	SJS:1-6 per million PY [Roujeau, 1995] TEN: 0.4-1.2 per million PY [Roujeau, 1995]	NA	1-3 weeks	P
Henoch Schonlein purpura	Peak at 70/100,000 PY (in 4-6 yr olds, UK) [Gardner-Medwin, 2002]	NA	NA	P

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
Kawasaki disease	About 215/100,000 PY (in <5 yr olds, Japan) [Nakamura, 2010] 20/100,000 PY (in <5 yr olds, US); 17/100,000 PY (in <5 yr olds, African Americans) [Holman, 2010]; 6.4/100,000 PY (in <5 yr olds, Israel) [Bar-Meir, 2011]	Reporting to VAERS in the US, from 1990 through mid-October 2007: Hib (31 cases of Kawasaki disease), PVC-7 (29 cases), MMR (22 cases), diphtheria and tetanus toxoids and acelluar pertussis (21 cases), inactivated polio (17 cases), rotavirus (16 cases), diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, and inactivated polio combined (16 cases), hepatitis B (13 cases). 0.65 and 0.37 reports /100,000 PY for *RotaTeq* and *Pediarix*, respectively, before label revision of *RotaTeq*, and 2.78 and 2.44/100,000 PY for *RotaTeq* and *Pediarix* , respectively, after label revision [Hua, 2009] PCV-7: 4.6 per 100,000 doses, PCV-13: 5.4 per 100,000 doses [Tseng, 2013] PCV-13: 1 case in 233 vaccinated children, considered not to be related to vaccination [Gutierrez Brito, 2013] Electronically captured health insurance claims in the US, from 2006 to 2007: *RotaTeq*: 1 case within 30 days, 2 cases between 31 and 60 days after vaccination in North Wales. DTaP: 1 case [Loughlin, 2012]	1 month after vaccination	P
Systemic Disease and Haematology				
Diabetes mellitus type 1	0.06/100,000 PY (0.0, 0.13) (in 0-4 yr olds, Tanzania) [Swai, 1993]; 0.9/100,000 PY (in 0-4 yr olds, Sudan) [Karvonen, 2000]; 2.3 to 6.3/100,000 PY (in 0-4 yr olds, Tunisia) [Karvonen, 2000]; 9.06/100,000 PY (0-4 yr olds, Cyprus), 14.15/100,000 PY (5-9 yr olds, Cyprus) [Skordis, 2012]; 3.1/100,000 PY (in <18 yr olds, Egypt) [El-Ziny, 2014];	NA	≤6 months	P

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
	12.9/100,000 PY (0-5 yr olds, Germany), 18.7/100,000 PY (5-10 yr olds, Germany) [Galler, 2010]; 8.59/100,000 PY (0-4 yr olds, Israel), 13.29/100,000 PY (5-9 yr olds, Israel) [Sella, 2011]; 17.1/100,000 PY (0-4 yr olds, Saudi Arabia), 10.9/100,000 PY (5-9 yr olds, Saudi Arabia) [Habeb, 2011]; 4.3/100,000 PY (0-4 yr olds, Turkey), 9.1/100,000 PY (5-9 yr olds, Turkey) [Demirbilek, 2013]			
Thrombo-cytopenia	2.2/100,000 PY (in <16 yr olds, Germany) [Sutor, 2001]	NA	12-25 days median (range 1-83 days)	BC
Anaphylaxis	70/100,000 PY (in 0-19 yr olds, Minnesota, US) [Decker, 2008]	Monovalent measles (12 per 100,000 doses), MMR (1 per 100,000 doses), HPV bivalent (1.4 per million doses) or HPV quadrivalent (from 2.6 per 100,000 to 1.7 per million doses) [Vanlander, 2014] 0.65 (95% CI: 0.21, 1.53) per million doses for the most common vaccines for children and adolescents [Bohlke, 2003]	0-48 hours [Bohlke, 2003]	BC

ADEM= Acute Disseminated Encephalo-Myelitis; AE = adverse event; AESI = adverse event of special interest; Hib = *Haemophilus influenza* type B; HPV = human papilloma virus; MMR = measles, mumps, rubella; PCV = pneumococcal conjugate vaccine; SJS= Stevens Johnson Syndrome; TEN = toxic epidermal necrolysis; NA = not available; PY = person years; RR = relative risk; VAERS = Vaccine Adverse Event Reporting System.

9.2.5.2. Hospitalisations for an AE other than an AESI, meningitis, *any malaria* or severe malaria (including cerebral malaria)

These include all hospitalisations reported by the physician not due to an AESI (Section 9.2.5.1), or to meningitis (Section 9.2.5.3), or to any malaria or to severe malaria (including cerebral malaria) (Section 9.2.5.5).

9.2.5.3. Meningitis

Of note, because meningitis was identified as a potential risk during RTS,S/AS01$_E$ clinical development (see Section 7.2), the disease is identified separately from the other AESI.

- At the site level, a suspected meningitis case based on clinical symptoms and/or signs is defined as [adapted from WHO, 2003]:
  - A child with sudden onset of fever (> 38.0 °C rectal or 37.5 °C axillary) and one or more of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign such as bulging fontanelle in children under one year of age.

  Lumbar puncture will be performed according to routine medical practice for examination of cerebrospinal fluid (CSF). Children with symptoms and/or signs of meningitis will be classified as follows based on first line laboratory results (for monitoring trends over time):
  - If a CSF sample is available and a bacterial agent has been identified, as bacterial confirmed meningitis case;
  - If a CSF sample is available, no bacterial agent has been identified in the CSF, but some abnormalities in the CSF have been detected (such as turbid macroscopic aspect, positive Gram, positive antigen test, pleiocytosis, abnormal glucose or protein levels) or positive blood culture to a bacterial agent, as probable meningitis case;
  - If a CSF sample is available and all examinations are normal at first line laboratory level, or if no CSF sample is available and no alternative diagnosis, as clinically suspected meningitis case.
- Based on second line laboratory results (see Section 9.2.7.3.1 and 9.2.7.3.2) and after external panel of experts review (see Section 9.2.7.4.1), final classification of meningitis cases will be as follows (for the statistical analyses):
  - If a CSF sample is available and any known aetiologic agent (bacterial or not) has been identified, as aetiology-confirmed meningitis case;
  - If a CSF sample is available, no aetiologic agent has been identified in the CSF, but some abnormalities in the CSF have been detected (such as turbid macroscopic aspect, positive Gram, positive antigen test, pleiocytosis, abnormal glucose or protein levels), or positive blood culture to a bacterial agent as probable meningitis case;

– If a CSF sample is available and all laboratory results are normal after second line laboratory results, or if no CSF sample is available and no alternative diagnosis, as clinically suspected meningitis case.

If none of the criteria (no specific clinical symptoms and/or signs or laboratory results) are fulfilled, after review by the external panel of experts, the case will be classified as a no meningitis case.

9.2.5.4. Febrile convulsions

- Adapted from Brighton case definition for generalised seizures (see Annex 5): generalised seizures with measured fever ≥ 37.5 °C (axillary) or reported history of fever.

9.2.5.5. Malaria

Case definitions according to the WHO will be used [WHO, 2015(***b***)]. Any malaria will include uncomplicated and severe malaria cases, including cerebral malaria.

- Uncomplicated malaria [WHO, 2015(***b***)]:

  Plasmodium parasitaemia > 0 detected by microscopy and/or RDT

  AND

  Presence of fever (temperature ≥ 37.5°C), as reported by the parent(s)/LAR(s) or recorded at the time of presentation

  OR

  Occurring in a child who is unwell and brought for treatment to a health care facility.

  AND

  Without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

- Severe falciparum malaria [adapted from WHO, 2015(***b***)]:

  P. falciparum parasitaemia > 0 detected by microscopy and/or RDT

  AND

  One or more of the following, occurring in the absence of an identified alternative cause:

  – Impaired consciousness: a Glasgow coma score < 11 in children ≥ 2 years of age or a Blantyre coma score < 3 in children < 2 years of age;

  – Prostration: generalised weakness so that the person is unable to sit, stand or walk without assistance;

  – Multiple convulsions: more than two episodes within 24 h;

  – Acidosis: a base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).

- Hypoglycaemia: blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL);
- Severe malarial anaemia: haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age with a parasite count > 10,000/µL;
- Renal impairment: plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L;
- Jaundice: plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL;
- Pulmonary oedema: radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation;
- Significant bleeding: including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena;
- Shock: compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill);
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/µL).

- Severe vivax malaria is defined as for severe falciparum malaria but with no parasite density thresholds [WHO, 2015(***b***)].
- Cerebral malaria [adapted from WHO, 2015(***b***)]:

  Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age);

  AND

  If malaria with seizure: coma persisting for > 30 min after the seizure.

  Other treatable causes of coma should be excluded before diagnosing cerebral malaria (e.g. hypoglycaemia, bacterial meningitis).

Note: Suspected malaria cases routinely tested using RDT will have a blood smear for reading by microscopy in parallel, in order to measure sensitivity and specificity. This will be done for all suspected cases presenting at primary health care facilities one day per month during the first year of the study.

9.2.5.6. Anaemia

- All anaemia: haemoglobin <11g/dL [Stoltzfus, 1993].
- Severe anaemia: haemoglobin <7g/dL [Stoltzfus, 1993].

9.2.5.7. Hospitalisation

- Hospitalisations (all causes)

  A subject requiring overnight stay in hospital/inpatient facility.

- Hospitalisation for malaria (including *P. falciparum* malaria)

  A hospitalised subject with malaria (including *P. falciparum* malaria) and for whom malaria is the primary cause of hospitalisation.

9.2.5.8. Deaths

- Deaths – all cause

  A fatality (of any cause).

- Malaria attributed deaths (including *P. falciparum* malaria)

  A fatality for which malaria (including *P. falciparum* malaria) is listed as a contributing cause of death. This is based on verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [INDEPTH, 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.

- Deaths attributed to an AE

  A fatality for which an AE is listed as a contributing cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [INDEPTH, 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.

* If a site is not part of the INDEPTH network, or does not have an equivalent surveillance system in place, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

Deaths, including malaria attributed deaths with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the expert panel to confirm the primary/secondary cause of death (see Section 9.2.7.4.4).

9.2.6. Surveillance quality indicators

To ensure the quality of the surveillance that will be performed in the study sites, two surveillance quality indicators have been added based on discussion with African paediatricians: abscess at injection site during the 7-day period (Days 0-6) after routine vaccination and foot positional deformations.

9.2.6.1. Case definition for abscess at injection site

The diagnosis and monitoring of abscess at the injection site will be used as a positive control, as this is an AE that is relatively frequently observed after routine vaccination in Africa, and is defined as:

- A localised collection of material in subcutaneous tissue, fat, fascia or muscle at the site of immunisation confirmed in spontaneous or surgical drainage of material from the mass or by presence of palpable fluctuance (defined as a wavelike motion on palpation due to liquid content). The abscess may be further classified as due to infectious aetiology, a sterile abscess or not-determined. Abscesses of infectious aetiology may be accompanied by fever/regional lymphadenopathy. Sterile abscesses are not accompanied by fever/regional lymphadenopathy.

9.2.6.2. Case definition for foot positional deformations

The diagnosis and monitoring of foot positional deformations as a birth defect will be used as a negative control (to assess changes in the performance of health care systems to diagnose disease) and is defined as:

- Metatarsus adductus characterised by medial deviation (adduction) of the forefoot while the hindfoot remains in a normal position, thus forming a "C" shape, or concavity of the medial aspect of the foot

  OR

- Positional calcaneovalgus feet characterised by hyperdorsiflexion of the foot with the abduction of the forefoot, which often results in the forefoot resting on the anterior surface of the lower leg

  OR

- Clubfoot characterised by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward.

9.2.7. Study procedures[3]

9.2.7.1. Active surveillance

For children enrolled in active surveillance (i.e. home visits and monitoring of outpatient visits and hospitalisations at all health care facilities), enrolment procedures may be conducted at the time of the first administration of DTP/HepB/Hib vaccine, at the time of first encounter with the study staff, or approximately 1 week later, or during hospitalisation (for children first identified and enrolled during hospitalisation: either before 1st DTP or children aged 5 to < 18 months) (see Section 9.2.1.1).

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

The organisation of visits will be study site dependent and based on the listing obtained through the HDSS or equivalent surveillance system database. The schedule of subject recruitment and first visit should be established just prior to study start and updated using the data collected between and during study area rounds after study start (e.g. for newborns).

In case a child in the 6-12 weeks group has received the first dose of DTP/HepB/Hib vaccine, but is delayed for dose 2 and/or dose 3, parents/LARs should be prompted to attend EPI for completing immunisations and the visits V2 and/or V3 will take place 1 week post vaccination.

If the child does not receive the complete primary schedule, V2 and/or V3 will not take place, but V4, V5 and V6 will be done 6 weeks, 6 months and 18 months after the recommended scheduled visit for the third dose of DTP/HepB/Hib vaccine.

Two attempts should be made to visit the child at home within the month of the scheduled follow-up visit/study conclusion visit before it is abandoned.

Table 4 and Table 5 detail study procedures to be conducted during the visit, both at home visits and during any hospitalisation. Data collected regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

Data collected will be entered into the study database/ electronic case report form (eCRF).

Note: As the study has been early terminated in Burkina Faso, subjects will no longer be followed up (i.e. no more home visits, outpatient visits or hospitalisations). However, the 1, 6, and 12 months follow-up check-ups in case of an already diagnosed meningitis, cerebral malaria or AESI before the early termination should still be done. (See sections 9.2.7.4.1, 9.2.7.4.2 and 9.2.7.4.5).

9.2.7.1.1. Informed consent

Freely given and written or witnessed and thumbprinted informed consent must be obtained from each subject's parent(s)/LAR(s), as appropriate, prior to participation in the study. Refer to Section 10.1 for the requirements on how to obtain informed consent.

Note: In special circumstances (Section 9.2.8), there could be certain restrictions that will make it not possible for parents/LARs to provide written consent. In these special circumstances parents/LARs of subjects enrolled and still under follow up will provide consent verbally.
(Amended 5 May 2020)

9.2.7.1.2. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 9.2.2 and 9.2.3 before enrolment.

9.2.7.1.3. Assign subject study number

Assign subject study number and record in the eCRF. Provide study ID card and study-specific stickers. Study-specific stickers with the subject's study number should be used at health care facilities to identify any visit of the subject in the facility register if no other system is in place. A holder will be provided for carrying the subject's ID card/study stickers together with other records e.g. welfare card, child growth record, immunisation record to avoid double enrolment.

9.2.7.1.4. Collect demographic data

Record socio-demographic data (e.g. date of birth and gender, the number and age of persons in the household) and active participation in any trial with an investigational product in the subject's eCRF.

9.2.7.1.5. Health history

Record brief medical history (e.g. chronic co-morbidities such as known HIV infection or congenital disease, such as known hemoglobinopathies) and perform physical examination at the first visit V1.

9.2.7.1.6. Check and record vaccinations

Record all standard vaccinations administered, including type and dates. Received vaccinations must be recorded during the first visit and updated if needed at all consecutive visits or at study conclusion. See also Section 9.3.3.1 for ascertainment of vaccine history.

9.2.7.1.7. Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards

Record data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated). Record also information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals (see Section 9.3.3).

9.2.7.1.8. Record health care facility visits and hospitalisations

Record any outpatient visits and hospitalisations at all health care facilities between enrolment and Visit 1, or since the last follow-up visit (for subsequent follow-up visits) in the eCRF.

9.2.7.1.9. Physical examination, record of signs and symptoms, record any serious delay in developmental milestones or physical disability

Perform a basic examination of the subject e.g. change in food/milk intake, crying, identification of dehydration, bleeding, oedema, jaundice, neck stiffness to detect any potential signs and symptoms indicating that the child is sick. Record any signs and symptoms detected during examination or in the past 48 hours preceding the visit in the eCRF. At study visits 1, 3 and 10 *(*study conclusion*)*, ask the parent/LAR for any noticed or previously diagnosed abnormalities while checking for developmental milestone delays and presence of physical disability using study specific guidance document (see Annex 6).

Care of any abnormality observed during this examination should be provided according to local medical practice in the study site or by referral to an appropriate health care provider (see Section 9.2.7.5).

Community health workers will use visual aids and other training materials to detect any potential signs and symptoms indicating that the child is sick. They will also be trained to recognise symptoms and signs of AESI, meningitis and will be instructed to measure body temperature systematically of all children. In case of fever, body temperature will be recorded in the eCRF.

9.2.7.1.10. Refer sick children or children with disabilities to outpatient clinic or hospital

Refer children who are sick, have an acute condition or with disabilities to health facilities for further assessment and care, that will be dispensed according to routine medical practice, including consultation, laboratory tests and treatment.

Refer children with fever (≥ 37.5°C) and symptoms suggestive of malaria to the primary health care facility or hospital where diagnosis of malaria will be ensured using RDT and/or microscopy.

Record referral in the eCRF.

9.2.7.1.11. Record cases of death

In the event of death occurring at home, the cause of death will be systematically obtained through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] as is routinely done in the study area.

If a site is not part of the INDEPTH network, or does not have an equivalent surveillance system in place, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

9.2.7.1.12. Study conclusion

Subjects will exit the study when they reach 5 years of age or at study end (whichever occurs first), if not earlier due to migration or in the event of death.

At the study conclusion (home visit, V10), a record will be taken of the subject's health and vital status, any disabilities and all vaccinations received.

The investigator will review collected data to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

Note: There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003. Children enrolled in active surveillance of EPI-MAL-002, and not eligible for RTS,S/AS01$_E$ vaccination or declining vaccination will continue to be followed up to the study conclusion visit in EPI-MAL-002. Children enrolled in active surveillance of EPI-MAL-002, and becoming vaccinated with RTS,S/AS01$_{E,}$ will have their study conclusion of EPI-MAL-002. Thereafter, these children can be eligible and enrolled in EPI-MAL-003 according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures. For children enrolled in enhanced hospitalisation surveillance of EPI-MAL-002, study conclusion of EPI-MAL-002 will be done at start of study EPI-MAL-003 (as the vaccine becomes available in the study sites that are exposed clusters). Thereafter, these children can be eligible and enrolled in active surveillance or in enhanced hospitalisation surveillance of EPI-MAL-003 according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

9.2.7.1.13. Outline of study procedures

Table 4 List of study procedures to be conducted at each visit, and study visit schedule (active surveillance)

Epoch	1										
Type of contact	**Enrolment**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Visit days: 6-12 weeks group [6] (identified at first administration of DTP/HepB/Hib vaccine)		**1 wk (±3 days) after 1st DTP/ HepB/ Hib dose**	**1 wk (±3 days) after 2nd DTP/ HepB/ Hib dose**	**1 wk (±3 days) after 3rd DTP/ HepB/ Hib dose**	**6 wks (±5 days) after 3rd DTP/ HepB/ Hib dose**	**6 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose**	**18 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] (±2 wks)**
Visit days: 5-17 mths group (identified at first administration of DTP/HepB/Hib vaccine)		**At the age of 6 mths *(> 5 mths to* < 7 *mths)***	**4 wks (±3 days) post V1**	**4 wks (±3 days) post V2**	**5 wks (±5 days) post V3**	**6 mths (±2 wks) post V3**	**18 mths (±2 wks) post V3**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] *(±2 wks)***
Visit days: 5-17 mths group (catch-up, enrolled at 5 to <18 mths of age)		**First contact with study staff or 1 wk later**	**4 wks (±3 days) post V1**	**4 wks (±3 days) post V2**	**5 wks (±5 days) post V3**	**6 mths (±2 wks) post V3**	**18 mths (±2 wks) post V3**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7]*(±2 wks*)**
Time point (Month)		**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Informed consent	●[1]										
Check inclusion/exclusion criteria	●[1]										
Assign subject study number	●[1]										
Provide study ID card and study-specific stickers	○[1]										
Record socio-demographic details and active participation in any trial with an investigational product	●[1]										
Record brief medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies)		●									
Record vaccination [2]		●	●	●	●	●	●	●	●	●	●

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Epoch	**1**										
Type of contact	**Enrolment**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Visit days: 6-12 weeks group [6] (identified at first administration of DTP/HepB/Hib vaccine)		**1 wk (±3 days) after 1st DTP/ HepB/ Hib dose**	**1 wk (±3 days) after 2nd DTP/ HepB/ Hib dose**	**1 wk (±3 days) after 3rd DTP/ HepB/ Hib dose**	**6 wks (±5 days) after 3rd DTP/ HepB/ Hib dose**	**6 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose**	**18 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] (±2 *wks*)**
Visit days: 5-17 mths group (identified at first administration of DTP/HepB/Hib vaccine)		**At the age of 6 mths *(> 5 mths to* < 7 *mths)***	**4 wks (±3 days) post V1**	**4 wks (±3 days) post V2**	**5 wks (±5 days) post V3**	**6 mths (±2 wks) post V3**	**18 mths (±2 wks) post V3**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] *(±2 wks)***
Visit days: 5-17 mths group (catch-up, enrolled at 5 to <18 mths of age)		**First contact with study staff or 1 wk later**	**4 wks (±3 days) post V1**	**4 wks (±3 days) post V2**	**5 wks (±5 days) post V3**	**6 mths (±2 wks) post V3**	**18 mths (±2 wks) post V3**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7]*(±2 wks*)**
Time point (Month)		**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Record information about malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards		●	●	●	●	●	●	●	●	●	
Record any outpatient visits and hospitalisations at all health care facilities		●	●	●	●	●	●	●	●	●	
Conduct physical examination, including systematic measurement of body temperature		●	●	●	●	●	●	●	●	●	
Record any detected signs and symptoms (including AESI, other AE leading to hospitalisation or death, meningitis, malaria, abscess at injection site, foot positional deformations)		●	●	●	●	●	●	●	●	●	

Epoch	1										
Type of contact	**Enrolment**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Visit days: 6-12 weeks group [6] (identified at first administration of DTP/HepB/Hib vaccine)		**1 wk (±3 days) after 1st DTP/ HepB/ Hib dose**	**1 wk (±3 days) after 2nd DTP/ HepB/ Hib dose**	**1 wk (±3 days) after 3rd DTP/ HepB/ Hib dose**	**6 wks (±5 days) after 3rd DTP/ HepB/ Hib dose**	**6 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose**	**18 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] (±2 *wks*)**
Visit days: 5-17 mths group (identified at first administration of DTP/HepB/Hib vaccine)		**At the age of 6 mths *(> 5 mths to* < 7 *mths)***	**4 wks (±3 days) post V1**	**4 wks (±3 days) post V2**	**5 wks (±5 days) post V3**	**6 mths (±2 wks) post V3**	**18 mths (±2 wks) post V3**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] *(±2 wks)***
Visit days: 5-17 mths group (catch-up, enrolled at 5 to <18 mths of age)		**First contact with study staff or 1 wk later**	**4 wks (±3 days) post V1**	**4 wks (±3 days) post V2**	**5 wks (±5 days) post V3**	**6 mths (±2 wks) post V3**	**18 mths (±2 wks) post V3**	**5 wks (±5 days) post V6**	**12 mths (±2 wks) post V6**	**24 mths (±2 wks) post V6**	**At 5 yrs of age or study end [7] *(±2 wks)***
Time point (Month)		**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Record any serious delay in developmental milestones or physical disability [3]		●		●							●
Refer sick children or children with disabilities to outpatient clinic or hospital according to clinical diagnosis [4]		●	●	●	●	●	●	●	●	●	
If death, record verbal autopsy diagnosis [5]		●	●	●	●	●	●	●	●	●	●
Study conclusion											●

Children in 6-12 weeks group: subjects identified at first administration of DTP/HepB/Hib vaccine
Children in 5-17 months group: subjects identified at first administration of DTP/HepB/Hib vaccine or subjects 5 to <18 months (catch-up)
V= Visit; Wks = weeks; mths = months; yrs = years
● is used to indicate a study procedure that requires documentation in the individual eCRF
○ is used to indicate a study procedure that does not require documentation in the eCRF

1. Procedures at Enrolment visit may be conducted at Visit 1 for children in the 6-12 weeks group and children in the 5-17 months catch-up group.
2. All immunisations will be recorded
3. See Annex 6

4. See Annex 5
5. Using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] for children who died at home. If a site is not part of the INDEPTH, or does not have an equivalent surveillance system in place, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.
6. In case a child in the 6-12 weeks group has received the first dose of DTP/HepB/Hib vaccine, but is delayed for dose 2 and/or dose 3, parents/LARs should be prompted to attend EPI for completing immunisations and the visits V2 and/or V3 will take place 1 week post vaccination. If the child does not receive the complete primary schedule, V2 and/or V3 will not take place, but V4, V5 and V6 will be done 6 weeks, 6 months and 18 months after the recommended scheduled visit for the third dose of DTP/HepB/Hib vaccine.
7. Because of a possible overlap of studies EPI-MAL-002 and EPI-MAL-003, study conclusion of EPI-MAL-002 will be done for children enrolled in active surveillance and becoming vaccinated with RTS,S/AS01$_E$

(Amended 5 May 2020)

9.2.7.2. Enhanced hospitalisation surveillance

Table 5 provides details on the procedures to be conducted for children enrolled in enhanced hospitalisation surveillance at or around the time of hospitalisation.

Data collected regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

9.2.7.2.1. Informed consent (for subjects not enrolled previously, i.e. for previous hospitalisation or for active surveillance)

Freely given and written or witnessed and thumb printed informed consent must be obtained from each subject's parent(s)/LAR(s), as appropriate, prior to participation in the study. Refer to Section 10.1 for the requirements on how to obtain informed consent.

In case routine procedures are performed before the ICF signature, collection of those data for the study CRF will be done retrospectively once the ICF is signed or witnessed and thumb printed. No study specific procedures will be performed before the ICF is signed or witnessed and thumb printed.

9.2.7.2.2. Check inclusion and exclusion criteria (for subjects not enrolled previously)

Check all applicable inclusion and exclusion criteria as described in Sections 9.2.2 and 9.2.3 before enrolment.

9.2.7.2.3. Assign subject study number (for subjects not enrolled previously)

Provide study ID cards and assign subject study number and record in the eCRF for all newly enrolled subjects (for subjects already enrolled - previous hospitalisation or for active surveillance - the same subject study number applies). A holder will be provided for carrying the subject's ID card/study stickers together with other records e.g. child growth record, immunisation record to avoid double enrolment.

In the event a child is first detected during hospitalisation (before 1st DTP or aged 5 to < 18 months) before the active surveillance recruitment is terminated, parents/ LARs will be invited to enrol their child in active surveillance. If consenting, they will be provided with study-specific stickers and a follow-up visit will be scheduled for active surveillance (see Section 9.2.7.1). For all subjects enrolled into active surveillance, study-specific stickers with the subject's study number should be used at health care facilities to identify any visit of the subject in the facility register if no other system is in place.

9.2.7.2.4. Collect demographic data (for subjects not enrolled previously)

Record socio-demographic data (e.g. date of birth and gender, the number and age of persons in the household) and active participation in any trial with an investigational product, in the subject's eCRF.

9.2.7.2.5. Record type of health care facility

Record type of health care facility.

9.2.7.2.6. Record any serious delay in developmental milestones or physical disability (for subjects not enrolled previously and at study conclusion)

Perform an assessment of developmental milestones and physical disabilities according to the study specific guidance document (see Annex 6).

9.2.7.2.7. Health history

Record medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies), and perform a physical examination. Ask the parent/LAR for any noticed or previously diagnosed abnormalities. Record any pre-existing conditions present in a subject prior to the start of the study.

9.2.7.2.8. Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards

Record data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated). Record also information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals (see Section 9.3.3).

9.2.7.2.9. Record standard vaccinations

Record all immunisations received, including type and dates, in the eCRF. Update if needed with vaccinations received since the last visit. See also Section 9.3.3.1 for ascertainment of vaccine history.

9.2.7.2.10. Record diagnosis

Record main diagnosis and any secondary diagnoses made by the physicians in the eCRF.

9.2.7.2.11. Record haemoglobin measurement

For all hospitalised subjects, measurement of haemoglobin concentration, if available, at hospital entry will be recorded in the eCRF.

9.2.7.2.12. Record deaths

In the event of death occurring at the hospital, the cause of death from the medical record or the death certificate will be recorded in the eCRF.

9.2.7.2.13. Record cases of suspected AESI, other AE leading to hospitalisation or death, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations

For all suspected AESI or any meningitis case, details of risk factors, medication history and results of the clinical examination and diagnostic testing (see Annex 5) will be recorded in the eCRF. A blood sample will be taken for storage for all AESIs and meningitis (see Section 9.2.7.3.1). For all cases suspected of meningitis or neurological AESIs, a part of the CSF sample, collected according to routine practice, will be stored for further confirmatory testing (see Section 9.2.7.3.1). Final diagnosis will be recorded in the eCRF.

Children diagnosed with meningitis, cerebral malaria or with an AESI will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

Note: Although the study has been early terminated for subjects from the sites in Burkina Faso, this follow-up check-up should still be done in case the diagnosis with meningitis, cerebral malaria or with an AESI occurred before the termination.

For all hospitalisations, details of risk factors, medication history and results of the clinical examination as well as the final diagnosis will be recorded in the eCRF.

For suspected malaria, malaria microscopy and/or RDT or other results, such as retinoscopy for cerebral malaria (refer to Section 9.2.7.3.1) will be recorded in the eCRF.

For foot positional deformations and abscess at injection site after routine vaccination, record in the eCRF.

9.2.7.2.14. Record serious adverse events related to a study procedure

Record any SAE occurring as a result of the blood draw for a suspected AESI or meningitis (see Section 11.1.1).

Refer to Section 11.2 for procedures for the investigator to record SAEs that are related to study participation and to Section 11.3 for guidelines on how to report these SAEs to GSK Biologicals.

9.2.7.2.15. Study conclusion

Subjects will exit the study when they reach 5 years of age or at study end (whichever occurs first), if not earlier due to migration or in the event of death.

At the study conclusion (home visit), a record will be taken of the subject's health and vital status, any disabilities and all vaccinations received. The investigator will review collected data to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

Note: There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003. For children enrolled in enhanced hospitalisation surveillance of EPI-MAL-002, study conclusion of EPI-MAL-002 will be done at start of study EPI-MAL-003 (as the vaccine becomes available in the study sites that are exposed clusters). Thereafter, these children can be eligible and enrolled in active surveillance or in enhanced hospitalisation surveillance of EPI-MAL-003 according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

9.2.7.2.16. Outline of study procedures

Table 5 List of study procedures to be conducted in the event of hospitalisation

Epoch	**1**	
Type of contact	**Hospitalisation Visit**	**Study Conclusion Visit (At 5 years of age or study end, whichever occurs first)[7] *(±2 wks)***
Informed consent (for subjects not enrolled previously in either active surveillance or enhanced hospitalisation surveillance)	●	
Check inclusion/exclusion criteria (for subjects not enrolled previously)	●	
Assign subject study number (for subjects not enrolled previously)	●	
Provide study ID card (to all subjects not enrolled previously) and study-specific stickers (only to subjects identified before 1st DTP or aged 5 to <18 months not enrolled previously and enrolled before the active surveillance recruitment is terminated)	○	
Record socio-demographic details and active participation in any trial with an investigational product (for subjects not enrolled previously)	●	
Record type of health care facility	●	
Record medical history	●	
Record information about malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards	●	
Record any serious delay in developmental milestones or physical disability[1]	●[6]	●
Record all vaccinations[2]	●	●

Epoch	**1**	
Type of contact	**Hospitalisation Visit**	**Study Conclusion Visit (At 5 years of age or study end, whichever occurs first)[7] *(±2 wks)***
For all subjects		
Identify if specific signs and symptoms present (standard for AESI screening among all hospitalisations)	●	
Record diagnosis with major symptoms and test results	●	
Record measurement of haemoglobin concentration	●	
Record any cases of death and cause of death	●	
Record risk factors	●	
Record medication history	●	
Confirm diagnoses at discharge	●	
Only for subjects with suspected AESI, cerebral malaria or meningitis		
Consult specialised health care professional, if required[3]	●	
Record clinical examination and additional testing according to clinical diagnosis for suspected AESI[4], cerebral malaria or meningitis	●	
For each diagnosis of an AESI or meningitis, collect approx. 5 mL of whole blood and store serum [5]	●	
For each diagnosis of a neurological AESI or meningitis, where a CSF sample has been taken as part of routine practice, store part of the CSF sample (minimum 500 µL)[5]	●	
Record any SAE occurring as a result of blood draw for a suspected AESI or meningitis	●	
Follow-up children up to study conclusion, by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge	●	
Only for subjects with suspected malaria		
For suspected malaria, record malaria microscopy and/or RDT or other result	●	
Study conclusion		●

Hospitalisation visits: subjects aged < 5 years, to include subjects referred in between active surveillance visits.
● is used to indicate a study procedure that requires documentation in the individual eCRF
○ is used to indicate a study procedure that does not require documentation in the eCRF

1. See Annex 6
2. All immunisations will be recorded
3. See Study Procedures Manual (SPM)
4. See Annex 5
5. See Section 9.2.7.3.1
6. For subjects not enrolled previously
7. Because of a possible overlap of studies EPI-MAL-002 and EPI-MAL-003, study conclusion of EPI-MAL-002 for children enrolled in enhanced hospitalisation surveillance will be done at start of study EPI-MAL-003 (as the RTS,S/AS01$_E$ vaccine becomes available in the sites that are exposed clusters).

(Amended 5 May 2020)

9.2.7.3. Biological sample handling and analysis

9.2.7.3.1. Biological samples

All enrolled subjects admitted to the hospital are expected to have routine laboratory tests performed according to good medical practice and routine practice (see Section 9.2.7.5), including, but not limited, to:

- All hospitalised children: haemoglobin concentration or full blood count
- Malaria suspects: Access to diagnosis of malaria using RDT and/or microscopy according to routine practice will be ensured for all children clinically suspected of malaria during active surveillance and at all the health care facilities.
- Meningitis suspects: CSF examination (and blood culture if feasible) according to routine practice (first line testing).
- Neurological diseases such as seizures, encephalitis, Acute Disseminated Encephalo-Myelitis (ADEM), Guillain Barre syndrome suspected: require neurological investigations (e.g. magnetic resonance imaging if available), eventually CSF analysis and other laboratory testing according to routine practice.
- Some AESI (such as diabetes mellitus, renal failure, hepatic failure, severe thrombocytopenia with bleeding) require laboratory testing for case management.

For all hospitalised children suspected of having an AESI or meningitis, a sample of approximately 5 mL of whole blood will be collected; a sample of at least 500 µL of CSF would be ideally collected for all cases of a suspected neurological AESI (seizures, encephalitis, ADEM, Guillain Barre syndrome suspected) or meningitis, when a CSF sample is taken as part of routine practice.

Full details for obtaining, storing and shipment of biological samples are provided in the Study Procedures Manual (SPM) accompanying this protocol.

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Collected samples will be used for protocol mandated research. In addition, these samples may be used to perform research related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be invited to give another specific consent to allow GSK or a contracted partner to use the samples for future research including development of tests and their quality assurance. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing, in the context of the study, will be done in line with the consent of the individual subject's parent(s)/LAR(s).

Refer also to the Investigator Agreement (Annex 9), that notes that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit/contact), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

9.2.7.3.2. Laboratory assays

Any biological sample evaluation will be limited to the scope of this study and only related to assessment of study endpoints; it could include, for example, serology or deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) for infectious diseases or confirmatory tests for autoimmune diseases.

For all required biological sample evaluations, details of assay type, assay method, test kit/manufacturer and laboratory used, as applicable for the test conducted, will be recorded.

GSK will ensure that all consumables and reagents are available to perform first line routine testing for all diseases under investigation, according to good medical practice and routine practice. In case second line confirmatory testing is required (for instance PCR for meningitis or antibody testing for auto-immune AESI), samples will be sent to a qualified referral second line laboratory in South Africa (Clinical Laboratory Services [CLS]).

9.2.7.4. Management of AESI, other AE leading to hospitalisation or death, meningitis cases, malaria episodes, abscess at injection site and foot positional deformations

Children showing defined signs and symptoms during a follow-up visit will be referred to a health care facility for further assessment if in need of investigation and care.

9.2.7.4.1. Case ascertainment for meningitis

Meningitis case identification

At the site level, a suspected meningitis case, based on clinical symptoms and/or signs is defined as [adapted from WHO, 2003]:

A child with sudden onset of fever (> 38.0 °C rectal or 37.5 °C axillary) and one or more of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign such as bulging fontanelle in children under one year of age.

Meningitis case characterisation

Further characterisation of a suspected meningitis case will imply performing a lumbar puncture for examination of CSF (and blood culture if feasible) and etiological (bacterial, viral, protozoal or fungal) search with a two-step laboratory approach.

Lumbar puncture will be performed according to routine medical practice. The diagnosis of bacterial meningitis will first be made on site, based on CSF macroscopic and microscopic examinations and blood culture if feasible (first line laboratory results). CSF tests will include selective culture for *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenza* type b; latex agglutination tests for detection of bacterial antigens (*Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenza* type b), Gram stain, white blood cell counts and cell differentiation and biochemistry testing (protein and glucose). Cryptococcal infection will be diagnosed using Indian ink, for HIV-positive children and those with unknown HIV-status, if feasible.

In addition, an external laboratory based in South Africa (CLS) is contracted to harmonize laboratory procedures, to provide Quality Assessment and Quality Control and to train laboratory technicians in all sites. If needed, GSK will supplement reagents and consumables to ensure that all diagnostic procedures can be conducted according to protocol.

Based on these first examinations, the diagnosis of bacterial meningitis will be made by the physicians in charge of the children, with support from RAFT upon request from the investigators. Job Aids for medical staff and training on standardized diagnosis are put in place in EPI-MAL-002 to improve the sensitivity and specificity of the case diagnosis for all meningitis. Decisions to start treatment of children with suspected meningitis will be based on the medical routine practice, and should not be delayed by the second line laboratory investigations.

All collected CSF samples, regardless of first line testing outcome, will be shipped to a referral second line laboratory based in South Africa (CLS; unique for all sites) for identification of bacterial, viral, protozoal and fungal meningitis using molecular testing such as PCR.

Final meningitis case ascertainment

For the purpose of this study, a panel of experts will be set up and a charter will be defined. As much as possible, the same experts will be involved in the case ascertainment process for studies EPI-MAL-002 and EPI-MAL-003, using the same rules and charter.

A specific subgroup of two experts will perform case ascertainment following strictly the definitions for meningitis as described in Section 9.2.5.3. The two experts will independently review all meningitis cases. They will use all available medical information (including the first line and second line laboratory results) and classify the meningitis cases according to the case definitions. They will also be provided with all the data available in the eCRF (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination and any other relevant information identified in patient medical records). If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification (strictly following the case definitions) will be used for the statistical analyses.

Additional follow-up of meningitis cases

After hospital discharge, meningitis cases will be followed up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

9.2.7.4.2. Case ascertainment for AESI

In the event of diagnosis of a disease specified as an AESI during routine care, case ascertainment will result in a diagnosis reaching the highest level of case definition at the hospital possible (see Table 3 and Annex 5). As part of good medical practice, study clinical staff will ensure appropriate diagnostic testing and adequate care to enrolled, hospitalised children diagnosed with a disease specified as an AESI as per National guidance (see Section 9.2.7.5). As diagnosis of these events may be challenging, the investigators and site physicians will be supported by specialized health care professionals, if required (see Section 9.2.7.6).

In addition, a panel of experts in the different fields will perform ascertainment of AESI with an uncertain diagnosis and outcome after review by the GSK safety physician. These cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. Two selected experts will independently review the cases. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (Annex 5). Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification (strictly following the case definitions) will be used for the statistical analyses.

Children diagnosed with an AESI, will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

9.2.7.4.3. Children suspected of having a serious adverse event (SAE)

As part of good medical practice enrolled children presenting at health facilities (outpatient and inpatient) with signs and symptoms of SAEs (see Section 11), are expected to receive appropriate diagnostic testing and care by clinical staff following standard care in the country (see Section 9.2.7.5).

9.2.7.4.4. Case ascertainment for other AE leading to hospitalisation or death

Other AE leading to hospitalisation or death with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the external panel of experts. These cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. Two selected experts will independently review the cases. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination and any other relevant information identified in patient medical records) and classify the cases. Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification will be used for the statistical analyses.

9.2.7.4.5. Case ascertainment for malaria

Enrolled children presenting at health facilities (outpatient and inpatient) with signs and symptoms of malaria will receive malaria testing (RDT and/or microscopy) as part of standard care in the country (see Section 9.2.7.5). As part of good medical practice the clinical staff will ensure that all subjects diagnosed with malaria will receive adequate care following national guidelines.

GSK will consider the following definition for cerebral malaria cases: severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age), and, if malaria with seizure: coma persisting for > 30 min after the seizure (see Section 9.2.5.5 [WHO, 2015(***b***)]). It should be noted that these coma scores are not specific for malaria and other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis) should be excluded. Therefore each severe malaria case will be reviewed by GSK medical staff according to standard procedure for signal detection. In addition, a panel of experts will perform case ascertainment. The same procedures will be followed as for meningitis and AESI. Two selected experts will independently review all cerebral malaria cases and severe malaria cases with an uncertain diagnosis and outcome after review by the GSK safety physician. These last cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. They will be provided with all

available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.5.5). Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification will be used for the statistical analyses.

Children diagnosed with cerebral malaria will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

9.2.7.4.6. Children with abscess at injection site

Enrolled children presenting at health facilities (outpatient and inpatient) with abscess at the injection site following routine vaccination will receive appropriate care as part of good medical practice (see Section 9.2.7.5).

9.2.7.4.7. Children with foot positional deformations

As part of good medical practice it is expected that enrolled children presenting at health facilities (outpatient and inpatient) with foot positional deformations will be referred to hospital for medical diagnosis and provision of appropriate care following standard practice in the country (see Section 9.2.7.5).

9.2.7.5. Package for standard of care

Any child participating in active surveillance presenting at primary health care level should have access to basic care that can be dispensed at this level, including:

- Consultation, Essential Medicines, RDT and any laboratory test available, if needed for diagnosis.
- Treatment for common diseases including malaria.

At the hospital level, any child enrolled in the study should have access to care and treatment as available, including:

- Admission and emergency care, diagnostic testing including laboratory and radiological examinations, treatment and care until discharge.
- For protocol-defined AESI and meningitis: diagnostic testing according to the algorithms (see medical Job Aid) and treatment required until the end of the study.

9.2.7.6. Capacity building

- As diagnosis of AESI, or meningitis in the study sites may be challenging, training will be conducted and diagnosis will be supported by specialised health care professionals:
  - The Agence de Médecine Préventive (AMP, http://amp-vaccinology.org) will provide intensive training for the study staff, community health workers and health care professionals working at all health care facilities in the study area on diagnosis of AESI, meningitis, and on pharmacovigilance. Appropriate training packages and educational material will be developed. The community health workers involved in active surveillance will be trained to recognize clinical symptoms, using simplified visual aids (non-medical Job Aid). Health care professionals will be trained using medical Job Aid, developed to facilitate diagnosis using decision-making algorithms.
  - In addition, all sites will have access to online continued medical education, training packages (including training on AESI, meningitis, HIV and hemoglobinopathies) and a telemedicine system established by RAFT (Réseau en Afrique Francophone pour la Télémédecine, Geneva; http://raft.globalhealthforum.net). The latter will allow the investigators to discuss cases with their colleagues and with medical experts.

  In EPI-MAL-002, health care staff (including EPI staff) and study staff will be trained in pharmacovigilance procedures. This training will also be provided to any new health care and study staff hired during the course of that study or for study EPI-MAL-003 using the same materials.

- Laboratory support

  GSK will ensure that all first line laboratory diagnostic procedures can be conducted according to routine practice by complementing reagents and consumables where needed. Specifically, if necessary, lumbar puncture kits and malaria RDT will be provided to the sites to facilitate adherence to the routine procedures required for diagnosis of meningitis and malaria. In addition, an external laboratory, CLS, is contracted to provide Quality Assessment & Control and training for laboratory technicians.

  CLS will perform PCR and serology testing on CSF and serum samples in order to complement the diagnosis done by the first line laboratory.

  (Amended 5 May 2020)

9.2.8. Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Active safety follow-up through home visits may be made by a telephone call or other means of virtual contact. It is acknowledged that the systematic measurement of body temperature may not be performed.***
- ***For children diagnosed with AESI, meningitis or cerebral malaria, the check-up at the hospital at 1 month, 6 months and 1 year after hospital discharge may be replaced by a telephone call or other means of virtual contact.***
- ***A retrospective data collection of medical events may be implemented at any of the health care facilities.***

  (Amended 5 May 2020)

9.3. Variables

Endpoints are aligned in EPI-MAL-002 and EPI-MAL-003.

9.3.1. Co-primary endpoints

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of AESI (see Section 9.2.5.1 for definition).
- Occurrence of other AE leading to hospitalisation or death (see Sections 9.2.5.2 and 9.2.5.8 for definitions).
- Occurrence of aetiology-confirmed meningitis (see Section 9.2.5.3 for case definition).

9.3.2. Secondary endpoints

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of probable meningitis (final classification) (see Section 9.2.5.3 for case definition).
- Occurrence of clinically suspected meningitis (final classification) (see Section 9.2.5.3 for case definition).
- Occurrence of meningitis cases identified at site level (first line laboratory) (see Section 9.2.5.3 for case definition).
- Occurrence of hospitalisation (including those attributed to an AESI, other AE, meningitis, or malaria) or death.

- Occurrence of febrile convulsions during the 7-day period (Days 0-6) and 1-month period (Days 0-29) following administration of routine EPI vaccines (see Section 9.2.5.4 for case definition).
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following any routine vaccination and foot positional deformation (see Section 9.2.6 for case definitions).
- Occurrence of episodes of malaria using RDT and/or microscopy
  - Any malaria (including *P. falciparum* malaria) (see Section 9.2.5.5 for case definition).
  - Severe malaria (including *P. falciparum* malaria) (see Section 9.2.5.5 for case definition).
  - Cerebral malaria (see Section 9.2.5.5 for case definition).
- Occurrence of anaemia (see Section 9.2.5.6 for case definitions) at hospital entry among hospitalised children.
- Occurrence of hospitalisation
  - All causes and hospitalisations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria (see Section 9.2.5.7 for case definitions).
- Occurrence of death
  - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death) (see Section 9.2.5.8 for case definitions).
  - AE attributed deaths (see Section 9.2.5.8 for case definitions).

9.3.3. Patient characteristics and potential confounding variables

9.3.3.1. Recorded in EPI-MAL-002 and EPI-MAL-003

For all enrolled subjects, socio-demographic characteristics, data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated) will be recorded in the eCRF. Information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals will also be recorded. Data on vaccination, more specifically, dates and doses of EPI vaccine administration, as well as data on medical history including co-morbidities (e.g. chronic diseases, such as known HIV infection), or diagnosed congenital

diseases, such as known hemoglobinopathies, will also be collected. In case of hospitalisation, type of health care facility will be collected.

For children enrolled in enhanced hospitalisation surveillance or hospitalised children in active surveillance, additional information on co-morbidities will be captured such as malnutrition, chronic diseases, known HIV infection status, known hemoglobinopathies.

Of note, the vaccine history will be ascertained for all enrolled subjects through the following channels: individual vaccination cards, vaccination registers at the health care facilities and vaccination data collected during study area census rounds. If any of the sources described here above confirm vaccination, it will be assumed that vaccination has taken place for the analysis.

9.3.3.2. Recorded in EPI-MAL-005

Malaria transmission intensity (MTI) data will be collected through EPI-MAL-005 (see Section 9.4.3 for more detail). Rainfall and humidity, where available, will be collected at the study area level. Bednet use, seasonal malaria chemoprevention and other malaria control measures will also be collected at the HDSS or equivalent surveillance system (population) and individual level (which will be summarized at centre level).

The *P. falciparum* parasite prevalence will be measured as a way to characterise the MTI. The *P. falciparum* parasite prevalence will be computed as the proportion of subjects infected with *P. falciparum* parasitaemia divided by the total number of subjects tested, and will be estimated through annual cross sectional surveys (study start, every 12 months, and study end) during malaria peak transmission, in subjects at least 6 months and less than 10 years of age at the time of survey. These estimates will be calculated for each year and for each site separately.

9.4. Data Sources

9.4.1. Health Demographic Surveillance System (or equivalent surveillance system)

Each HDSS or equivalent surveillance system site maintains a demographic database which is updated on a regular basis to include births, deaths, immigrations and emigrations. Data regarding vaccinations is also included in the study site database. This information is obtained through census rounds (at least once a year) and constantly updated in between the rounds with the help of key-informants living in the community. Cause of deaths is established by trained fieldworkers using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] for children who died at home. From this database, the listing of children at the beginning of the study will provide the study site with a basis for recruitment of children <18 months old for active surveillance and for the total number of children < 5 years of age recorded at least once a year during the study duration. During the study, further newborns may be identified by one of several possible mechanisms (depending on the site): by subsequent HDSS or equivalent surveillance system updates, by existing community-based informers who report new births/deaths/other events to the study sites between censuses, at the time of first EPI

vaccination (e.g. BCG vaccination or first DTP/HepB/Hib vaccination), or at birth (if born at a health care facility).

If a site is not part of the INDEPTH network, or does not have an equivalent surveillance system in place, the INDEPTH procedures for demographic census and for verbal autopsy might be implemented to ensure consistency across study sites.

9.4.2. Active surveillance and enhanced hospitalisation surveillance of study EPI-MAL-002

Subjects enrolled in active surveillance will have data collected during home visits, outpatient visits and hospitalisations at all health care facilities, while subjects enrolled in enhanced hospitalisation surveillance will have data collected during hospitalisation only (see also study procedures in Section 9.2.7).

The surveillance system should be embedded into all health care facilities (including community health care services and potential mobile teams) of the study area.

The first level of screening will be done at the community level during follow-up visits by study community health workers who will be trained to recognise signs and symptoms of AESI and meningitis. Any subject presenting with specific signs or symptoms, as described by the Job Aid tool, will be referred to the health care facility (usually primary care facility) where the public health care staff will perform clinical assessment according to routine practice (see Section 9.2.7.5). If a suspected AESI, meningitis or severe malaria, including cerebral malaria, case is detected at the primary health care facility level, the subject will be referred to a higher level health care facility (hospital) to confirm the diagnosis based on the highest level of diagnostic certainty available (see Annex 5). If another event is detected at the primary health care facility level, the study participant might be referred to a higher level health care facility according to the routine practice. In the case of a seriously sick child, this child will be referred directly to the hospital by the community health worker.

Training on AESI and meningitis diagnosis, HIV and hemoglobinopathies will be provided and support will be available from specialised health care professionals to confirm diagnosis (see SPM for details) (see Section 9.2.7.6).

The surveillance system will also be implemented in the study area at each health care level within the HDSS or equivalent surveillance system catchment area. Health care workers will record all outpatient visits (referral and non-referral) of subjects enrolled in the active surveillance up to the end of the active follow-up) on a register allowing for the collection of basic data (e.g. date of visit, clinical diagnoses and rapid testing confirmation, referral or treatment). In case appropriate registers are not available in the facilities, study registers should be developed. At enrolment, subjects participating in active surveillance will be given study specific stickers with the subject's study number. The stickers can be used on the health care facility's registers if no other system is in place to indicate a subject's visit and facilitate identification of data from enrolled subjects from the facility's register. The recorded data will be collected retrospectively on a regular basis and encoded in the eCRF.

Every day, study staff will perform a round at hospitals and other health care facilities (with hospitalisation facility) to see all newly hospitalised children that could be eligible for the study. Parents/LARs of eligible children not yet enrolled into the study should be asked if they would agree to their child's participation and signed or witnessed and thumbprinted informed consent shall be obtained.

The monthly total number of hospitalised children < 5 years of age will be recorded in the logbook monthly for the study duration, for the purpose of the aggregated data analysis.

All enrolled hospitalised children will have their diagnosis recorded with main symptoms and results from routinely performed confirmatory tests. In the case of AESI and meningitis, additional information should be recorded according to clinical and laboratory standard of diagnosis (see Annex 5). Study staff will complete the eCRF containing all relevant information for each enrolled subject, to include an International Classification of Diseases (ICD) code allocated by a physician. All enrolled hospitalised subjects diagnosed with suspected AESI or meningitis will have a sample of approximately 5 mL of whole blood taken; in the case of neurological AESI or meningitis requiring a CSF sample according to routine practice, where possible, an additional aliquot will be reserved (for details refer to Section 9.2.7.3.1). Admitted subjects are expected to receive care by hospital staff following National guidance. As part of good medical practice, the clinical staff will ensure that sick subjects admitted to hospital will receive adequate care provided by health care facilities (see Section 9.2.7.5).

AESI, other AE leading to hospitalisation or death, meningitis, or malaria will be recorded in the eCRF. Data entry is described in Section 9.6.

The investigator will assess the maximum intensity (mild, moderate, severe) that occurred over the duration of the event for all AESI, other AE leading to hospitalisation or death, meningitis, or malaria reported during the study. The assessment will be based on the investigator's clinical judgement.

9.4.3. Study EPI-MAL-005

The RTS,S/AS01$_E$ vaccine is expected to be introduced through national immunisation systems, and will lead to a reduction in the incidence of *P. falciparum* malaria in vaccinated subjects in EPI-MAL-003 when compared to baseline rates recorded in EPI-MAL-002. Annual fluctuations in malaria incidence occur as a result of changes in transmission intensity, which may be caused by changes in environmental factors such as rainfall or changes in usage of other malaria control interventions (use of bednets for example). Therefore, by taking into account these variations in MTI and malaria control intervention coverage, more accurate estimations of the vaccine impact on malaria disease using RDT and/or microscopy during EPI-MAL-003 will be possible.

In EPI-MAL-005, the following parameters will be assessed: estimates of *P. falciparum* parasite prevalence and of the use of malaria control interventions at community level, changes in environmental factors such as rainfall, changes in health care seeking behaviour, within-site geographical heterogeneity in MTI and individual malaria

prevention measures and risk factors for clinical malaria. Compliance with DTP-based, measles and RTS,S/AS01$_E$ vaccines will also be collected.

EPI-MAL-005 started in Q4 2014 and is planned to run in parallel with EPI-MAL-002 and EPI-MAL-003, in similar if not identical settings. Its primary objectives are to estimate the annual parasite prevalence and record malaria control measures, providing information on potential confounding factors relevant to interpreting EPI-MAL-002/003 outcome measures.

It may happen that subjects enrolled in EPI-MAL-002 are also enrolled in EPI-MAL-005. Cases of malaria detected only during the annual home visits planned for EPI-MAL-005 will not be included in the analysis of EPI-MAL-002. However, if the cases of malaria are detected during an EPI-MAL-005 home visit that coincides with a home visit scheduled in EPI-MAL-002, the events will be captured in EPI-MAL-002.

9.5. Study size

The study targets enrolling 15,000 children per group (i.e. 6-12 weeks group or 5-17 months group; with about 10,000 children of 15,000 in each group enrolled where the RTS,S/AS01$_E$ vaccine will be implemented), for a total of 30,000 children with ~~at~~ about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented.

Burkina Faso sites are planned to early terminate any study activities by Q2 2019. As a consequence, the data from those sites will be presented in the progress reports up to Q4 2019, but none of those data will be part of the statistical analyses for the interim and final reports. There will be a full follow-up of about 10000 and not 15,000 children.

The co-primary objectives will estimate the incidence of AESI and meningitis. The precision of the estimate is related to the incidence and the period at-risk of these events following any dose (or equal point in time for 5-17 months group), with a censoring of the follow-up time when the subject receives the next dose. For some of the AESI the incidence could be very rare (around 1/100,000 person-years [PY]) and the period at-risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis.

Table 6 provides an estimation of the 95% CIs based on:

- A sample of 10,000 children per group (either 10,000 in the 6-12 weeks group, or 10,000 in the 5-17 months group) where the RTS,S/AS01$_E$ vaccine will be implemented;
- Different numbers of detected events (for the less frequent events): 1, 3 or 5 events;
- Different risk periods following dose administration (with censoring to one month for the two first doses).
- A follow-up corresponding to the risk period after the virtual dose 4.

For example, the 95% CI around an observed incidence of 25.2 per 100,000 PY (corresponding to 1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], based on 10,000 subjects) will be [0.6, 140.2]. Other assumptions are displayed in Table 6.

Table 6 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events following dose administration based on 10,000 subjects, different numbers of detected events, and different risk periods

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
Events in different at-risk periods following dose administration (per age group)					
1	2 weeks	1538.46	65.0	1.6	362.2
1	6 weeks	3974.36	25.2	0.6	140.2
1	3 months	6666.67	15.0	0.4	83.6
1	6 months	11666.67	8.6	0.2	47.8
1	12 months	21666.67	4.6	0.1	25.7
3	2 weeks	1538.46	195.0	40.2	569.9
3	6 weeks	3974.36	75.5	15.6	220.6
3	3 months	6666.67	45.0	9.3	131.5
3	6 months	11666.67	25.7	5.3	75.1
3	12 months	21666.67	13.8	2.9	40.5
5	2 weeks	1538.46	325.0	105.5	758.4
5	6 weeks	3974.36	125.8	40.8	293.6
5	3 months	6666.67	75.0	24.4	175.0
5	6 months	11666.67	42.9	13.9	100.0
5	12 months	21666.67	23.1	7.5	53.9

Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990].

In addition, these incidences will be estimated, using the data collected for both active and enhanced hospitalisation surveillances, for all children less than 5 years of age during the study. Table 7 provides an estimation of the 95% CIs for the surveillances for all children less than 5 years of age based on:

- A birth cohort of 11,500 children;
- A follow-up of 2 years (for the enhanced hospitalisation surveillance, before the start of the EPI-MAL-003 study);
- Different numbers of detected events (for the less frequent events).

For example, the 95% CI around the observed incidence of 21.7 per 100,000 PY (25 events detected) will be [14.1, 32.1]. Other assumptions are displayed in Table 7.

Table 7 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events among all children less than 5 years of age based on 11,500 birth cohort, and different numbers of detected events

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
Events in all children < 5 years during a follow-up of 2 years					
1	2 years	115000	0.9	0.0	4.8
5	2 years	115000	4.3	1.4	10.1
25	2 years	115000	21.7	14.1	32.1
50	2 years	115000	43.5	32.3	57.3

Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990].

9.6. Data management

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

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

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

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the clinical study report is complete and approved by all parties.

9.7. Data analysis

All analyses will be specified in detail in the supporting document, the Statistical Analysis Plan (SAP).

Analyses will be based on about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Descriptive statistics will be computed by age group, study site and overall, as well as by type of surveillance.

Moreover, descriptive analysis of safety endpoints will be computed for specific sub-populations such as children with hemoglobinopathy and HIV-positive children.

Burkina Faso sites are planned to early terminate any study activities by Q2 2019. As a consequence, a description of data from those sites will be presented in the progress reports up to Q4 2019, but none of these data will be part of the statistical analyses for the interim and final reports. There will be a full follow-up of about 10000 and not 15,000 children.

9.7.1. Total cohort

The Total cohort will include all subjects enrolled in the study. All the information for these subjects will be collected in the eCRF (after receiving signed or witnessed and thumb printed informed consent).

9.7.2. According-to-protocol (ATP) cohort

The ATP cohort will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study).

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

All analyses will be conducted on the ATP cohort, unless otherwise detailed. The analyses will be done also on the Total cohort only if there are more than 5% of eliminated subjects; except for the demography where all the tables will be performed for both cohorts.

9.7.3. Derived and transformed data

Age at time of enrolment in the study will be computed as the difference between the date of enrolment (date of ICF) and the date of birth. The age will be expressed in months or in years.

For each AESI, the Time-to-Onset will be defined as the difference between the AESI onset date and the immunisation date of the most recently administered vaccine (when applicable) or the date 1 week prior to the most recent visit between the 3 first study visits. This second possibility is applicable for the 5-17 months group of children as they do not follow study visits according the EPI DTP/HepB/Hib vaccine administration schedule, in order to mimic study procedures in the subsequent EPI-MAL-003 study. Time-to-Onset will be expressed in days.

For all enrolled subjects, the vaccine history will be summarized. As detailed in Section 9.3.3.1, vaccine history will be collected from different sources. If any of the sources confirm vaccination, it will be assumed that vaccination has taken place.

9.7.4. 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 study report.

9.7.4.1. Sequence of analyses

Progress reports including listings and statistical tables for description of AESI, other AE leading to hospitalisation or death, meningitis and malaria, including severe malaria and cerebral malaria, will be produced every 6 months. Of note, data from Burkina Faso sites were part of the previous progress reports and will also be part of the progress reports planned up to Q4 2019.

An interim analysis will be performed when the RTS,S/AS01$_E$ vaccine will be implemented in most of the study sites. This interim analysis will be done with clean data* collected on a sub-group of subjects from sites where the vaccine will be implemented having 6 months of follow-up following the administration of dose 3 of DTP/HepB/Hib vaccine (6-12 weeks group), or 6 months after V3 (5-17 months group); corresponding to V5.

Of note, further details will be provided in the SAP.

* Some data may change after the interim analysis as access to the eCRF will still be granted to sites and investigators throughout the follow-up period, until study conclusion.

Final analysis will be carried out on clean data collected on study conclusion.

9.7.5. Analysis of co-primary objectives

9.7.5.1. Analysis population

The population will include the subjects from the active surveillance of the EPI-MAL-002 study.

A secondary population will include the subjects from the active and enhanced hospitalisation surveillance of the EPI-MAL-002 study, computing incidence for all children < 5 years.

9.7.5.2. Statistical approach

9.7.5.2.1. Incidence of AESI, and other AE leading to hospitalisation or death

The incidence rate of each AESI and other AE leading to hospitalisation or death will be calculated by dividing the number of subjects reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable. The at-risk period will follow any dose, with a censoring of subjects when they receive the following dose. The minimum at-risk period for the analyses is 2 weeks. All AESI expected to occur between 0 day and 13 days following

dose administration (see Table 3) will be analysed with an at-risk period of 2 weeks. The at-risk period of 6 weeks will be used for AESI expecting to occur between 14 days and 6 weeks. Finally, at-risk periods of 3 months, and 6 months will be for the AESI expected to occur between 6 weeks and 3 months, and between 3 months and 6 months, respectively. For other AE leading to hospitalisation or death the at-risk period for the analyses will be defined with the support of the GSK safety physicians and the panel of experts. In addition, the distribution of the Time-to-Onset of events after vaccination will be described, and additional at-risk periods will be considered based on the results as sensitivity analyses.

The person-time for an event of interest (e.g. juvenile chronic arthritis) will be calculated as the time between the reference date (date of first administration of DTP/HepB/Hib vaccine or date of first virtual vaccination, corresponding to the week before first visit) and the end of the at-risk period or the earliest of the followings:

- Date of first diagnosis of event of interest (e.g. first episode of juvenile chronic arthritis).
- Date of end of study period.
- Date of enrolment in EPI-MAL-003 (when applicable).
- Date when child reaches 5 years.
- Date of last contact (Lost-to follow-up).
- Date of death.

Each AESI will be grouped as follows after case ascertainment for both confirmed and non-confirmed cases (see Section 9.2.7.4.2):

- Nerves and central nervous system: ADEM, encephalitis, Guillain-Barre Syndrome, HHE, generalised convulsive seizure.
- Hepato-, gastrointestinal and renal system: intussusception, hepatic failure or renal insufficiency.
- Skin and mucous membrane, bone and joints system: juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease.
- Systemic diseases and haematology: diabetes mellitus type I, thrombocytopenia, anaphylaxis.

The incidence following DTP/HepB/Hib vaccine or virtual vaccination using at-risk period described above will be estimated for the 6-12 weeks group and 5-17 months group.

Meningitis will not be grouped with other AESI and will be considered as a single endpoint (see case definition in Section 9.2.5.3).

Incidence rates of these composite endpoints will be calculated as described for individual AE leading to hospitalisation or death /AESI; in case of multiple cases in a subject, only the first event will be considered in this analysis.

All other AE leading to hospitalisation or death will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary and presented by System Organ Class (SOC) and Preferred Term (PT).

Incidence following DTP/HepB/Hib vaccine or virtual vaccination will be computed for active surveillance only.

In addition, the incidence will be estimated for all children < 5 years. In such case, the person-time denominators for each rate will be reflective of the entire community population in the age group of interest. Each child will contribute person-time until the relevant age (at study end or at 5 years, whichever occurs first).

9.7.5.2.2. Incidence rate of aetiology-confirmed meningitis

Incidence rate (and 95% CI) of aetiology-confirmed meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for an AE.

Of note, the at-risk period of 12 months will be used for meningitis. This assumption is based on meningitis cases reported in MALARIA-055. In addition, the distribution of the Time-to-Onset of events after vaccination will be described, and additional at-risk periods will be considered based on the results as sensitivity analyses.

9.7.6. Analysis of secondary safety objectives

9.7.6.1. Analysis population

The same population as for the co-primary objectives (see Section 9.7.5.1) will be used.

9.7.6.2. Statistical approach

- The incidence rate (and 95% CI) of probable meningitis, the incidence rate (and 95% CI) of aetiology-confirmed and/or probable meningitis and the incidence rate (and 95% CI) of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for aetiology-confirmed meningitis (described in Section 9.7.5.2.2).

  (Amended 5 May 2020)

  For all suspected meningitis at the site level (based on first line laboratory results), a monthly listing report will be checked by the monitoring and GSK safety teams and every 6 months the number of cases of meningitis as well as the cumulative number of cases will be tabulated in the Progress Report.

- The incidence rate (and 95% CI) of cerebral malaria will be estimated with the same approach as for an AE as described in Section 9.7.5.2.
- Exposure determinants and potential risk factors for AESI and meningitis will be evaluated by means of univariate and multivariable Poisson regression models only for the incidence following DTP/HepB/Hib vaccine or virtual vaccination.

  Adjusted covariates are described in Section 9.3.3:

  – Study site.
  – Demographic parameters such as age at reference date.
  – Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drugs exposure, toxic agent exposure.
  – Comorbidity factors such as premature birth, history of trauma.
  – Health care seeking behaviour and distance to health care facilities.
  – Type of health care facility.
  – Neighbourhood of residence (urban/rural area).
  – Total number of outpatient visits per centre.

  The following strategy for covariate selection will be applied:

  Covariates occurring in less than 5% of the subjects (percentage will be computed over subjects both in 6-12 weeks and 5-17 months group) will not be included in the model.

  Of note, models will be run if a minimum number of cases of AESI or meningitis are observed (at least 10 cases in total).

  Some predefined clinical relevant covariates might be forced into the models and will be listed in the SAP with the rationale (e.g. prior knowledge from literature).

  Covariates selection will be done using statistical significance. Confounders will be included in the multivariable models if univariate p-value will be less than 20%.

  Co-linearity (i.e. correlation among predictor covariates) will be assessed on the full model including forced-in covariate and the other selected with the variance inflation factor (level of 10% [Hair, 1995]). If it is necessary to drop a variable due to co-linearity, the decision will be made on order of clinical importance.

  Then the selected set of covariates will be entered in the final model without transformations.
- Descriptive analysis of the causes of hospitalisation (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria) in children < 5 years will consist in computing the number of cases, person-time and incidence (with 95% CI). In the same way, descriptive analysis of causes of death classified by MedDRA will be done overall and by gender.

- Incidence rate (and 95% CI) of febrile convulsions will be estimated with the same approach as for an AE. Of note, two at-risk periods will be considered: 0-6 and 7-29 days.
- Surveillance indicator analysis

  The analysis done on AESI and other AE leading to hospitalisation or death will also be conducted on the incidence of foot positional deformations as a birth defect (negative control) and abscess at the injection site following routine vaccination (positive control).

  The incidence rate of the negative control should not increase after the vaccination, while the increase of incidence rate of the positive control after vaccination is expected.

9.7.7. Analysis for other secondary objectives

These analyses will be performed only on children enrolled in the active surveillance for each group (6-12 weeks and 5-17 months).

9.7.7.1. Analysis population

The main analysis on the other endpoints (i.e. malaria, anaemia, hospitalisation and death) will be performed at one year post last dose in order to anticipate further comparisons to be done with the EPI-MAL-003 study (i.e. indirect, total and overall effects computation):

- one year after the third dose (before 12 months of age) of DTP/HepB/Hib vaccine or virtual vaccination evaluated from third dose.

Additional analyses will be performed on the other endpoints:

- One year after the visit mimicking the 4th dose (i.e. Month 32) evaluated from the 3rd dose (before 12 months of age) of DTP/HepB/Hib vaccine or virtual vaccination;
- Two years after the 3rd dose of DTP/HepB/Hib vaccine or virtual vaccination evaluated from 3rd dose of DTP/HepB/Hib vaccine or virtual vaccination;
- Two years after the visit mimicking the 4th dose (i.e. Month 44) evaluated from the 1st dose of DTP/HepB/Hib vaccine or virtual vaccination;
- Two years after the visit mimicking the 4th dose (i.e. Month 44) evaluated from the 3rd dose of DTP/HepB/Hib vaccine or virtual vaccination.

9.7.7.2. Statistical approach

Incidence rates for each event will be calculated by dividing the number of cases by person-time as defined in Table 8. Of note, for cerebral malaria, incidence following DTP/HepB/Hib vaccine or virtual vaccination will be derived and Time-to-Onset will be computed (see Section 9.7.5.2.1).

For analyses using detailed information from the eCRF, children whose parents do not consent for them to take part in the active surveillance groups will not be included in the denominator.

Table 8 Incidence rate and prevalence calculations for other objectives (children enrolled in active surveillance)

Endpoints	Numerator	Denominator
Any malaria	# cases of any malaria Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children
Any *P. falciparum* malaria	# cases of any malaria due to *P. falciparum* Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children
Severe malaria	# cases of severe malaria Source: Hospitalisations	Person-years contribution of enrolled children
Severe *P. falciparum* malaria	# cases of severe malaria due to *P. falciparum* Source: Hospitalisations	Person-years contribution of enrolled children
Cerebral malaria	# cases of cerebral malaria Source: Hospitalisations	Person-years contribution of enrolled children
Anaemia in hospitalised children	# cases of anaemia Source: Hospitalisations	Number of enrolled children
Death – all cause	# deaths (due to any cause) Source: Scheduled home visits; outpatient visits and hospitalisations at all health care facilities; completion visit; HDSS or equivalent surveillance system register	Person-years contribution of enrolled children
Malaria attributed deaths	# deaths with malaria listed as a contributing cause Source: Scheduled home visits; outpatient visits and hospitalisations at all health care facilities; completion visit; HDSS or equivalent surveillance system register	Person-years contribution of enrolled children
Hospitalisation - all cause	# of children hospitalised during study period Source: Hospitalisations	Person-years contribution of enrolled children
Malaria attributed hospitalisations	# of children hospitalised during study period where malaria is listed as the primary diagnosis Source: Hospitalisations	Person-years contribution of enrolled children

Incidence rates will be adjusted by means of Poisson regression models (the dependent variable will be the number of events). The details are given in Section 9.7.9.

Univariate and multivariable models will be conducted. Those adjusted covariates are described in Section 9.3.3:

- Study site.
- Demographic parameters such as age at reference date.

- Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drugs exposure, toxic agent exposure.
- Use of malaria control measures such as bednets, indoor residual spraying, seasonal malaria chemoprevention.
- Comorbidity factors such as premature birth, history of trauma.
- Health care seeking behaviour and distance to health care facilities.
- Type of health care facility.
- Neighbourhood of residence (urban/rural area).
- Total number of outpatient visits per centre.
- Seasonal MTI (i.e. parasite prevalence) estimated in study EPI-MAL-005 on the vaccine ineligible group (see Annex 3 for definition).
- Other centre level covariates estimated in study EPI-MAL-005 per year: malaria control intervention use, bednet use and health care seeking behaviour.

The same strategy as described in Section 9.7.6.2 will be used for covariates selection to be included in the multivariable model.

9.7.8. Statistical considerations

All the statistical calculations will be done in SAS 9.2 or higher.

Unless specified otherwise, all the statistical tests will be two-sided at alpha level of 0.05.

9.7.8.1. Handling of missing data

A worst case allocation will be done for suspected events (i.e. suspected AESI, suspected malaria) for which confirmation of the outcome is not available. In such case a sensitivity analysis will be done considering these unresolved events as confirmed.

For the determinants included in multivariable models, a complete cases analysis will be performed as primary analysis (i.e. missing data will not be substituted).

As sensitivity analysis, for analysis of risk factors of the co-primary endpoint only, a precise diagnosis of missing pattern will be done to describe the kind of missing data (i.e. missing at random, missing completely at random and missing not at random). Considering the diagnosis an appropriate method of imputation will be conducted and will only concern the covariates forced in the models. The strategy will be the following:

- For continuous covariates, a multiple imputation [Rubin, 1987] method will be applied to handle missing value if missing at random mechanism is confirmed. Indeed, as noted by Sterne et al [Sterne, 2009], multiple imputations may give misleading results in case data are missing not at random.

- For categorical covariates, missing indicator method will be done (i.e. a specific category of missing value will be created).

Of note, if the "complete cases" analysis contains 90% of the subjects, no imputation will be done. In the case that for a single covariate more than 50% of values are missing, the covariate will not be included in the model.

The method of imputation will be detailed in the SAP.

9.7.8.2. Descriptive statistics

Frequency tables including number of cases and percentages will be generated for categorical variables.

Mean, standard error, median and range will be provided for continuous variables.

9.7.9. Statistical models

Poisson regression will be conducted using the SAS GENMOD procedure. The dependent variable is the number of events (Y). The model will include the study site as a fixed effect, the log-transformed total person-time (PY) as an offset and the risk factors.

Main model: $\ln(Y)= \beta_0 + \beta_1 X_1 +\ldots+ \beta_k X_k+ \ln (PY)$

The coefficients β_1 and β_i are the coefficients associated to study sites and the covariates, respectively. The risk ratio of covariates will be derived as the exponential of their associated coefficient and their 95% Wald CI.

The SAS code is:

```
PROC GENMOD data=<filename> ;
 CLASS X1 Xk;
 MODEL Y= X1 Xk / OFFSET=Ln_PY DIST=poisson LINK=log ;
RUN;
```

For each model, the following assumptions will be checked in order to interpret the results obtained from the Poisson regression: the outcome variable follows a Poisson distribution and does not have an excessive number of zeros. The deviance will measure the adequacy of the model. If the scaled deviance is closed to one, the regression model is adequate. Otherwise, the validity of the model is questionable. In particular, value greater than 1 indicates over dispersion.

In case of over dispersion, corrective measures will include the introduction of a dispersion parameter with respect to the Poisson model. This will be done by adding the option DSCALE and examining the fit statistics. If over dispersion is still a problem, another alternative approach considering a negative binomial distribution model will be discussed considering scientific inputs.

This last method will be detailed further in the SAP. Of note, the same procedure PROC GENMOD will be adapted by specifying option DIST=negbin in the model statement:

```
PROC GENMOD data=<filename> ;
 CLASS X1 Xk;
 MODEL Y= X1 Xk / OFFSET=Ln_PY DIST=negbin LINK=log ;
RUN;
```

9.7.10. Statistical analyses during special circumstances

Special circumstances (see section 9.2.8) may have an impact on the proposed analysis plan. Any changes in the analysis plan will be further described in the SAP.
(Amended 5 May 2020)

9.8. Quality Control

9.8.1. Monitoring by GSK Biologicals

Monitoring visits by a GSK Site Monitor or delegate are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP or other applicable guidelines 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 study).

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

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV GSK understands verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

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

For eCRF, the monitor will freeze the screen after she/he estimates that data are authentic, accurate and complete.

In accordance with applicable regulations, GCP or other applicable guidelines, and GSK procedures, GSK Site Monitors or delegates will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and

documentation of data items for which the eCRF/CRF entries will serve as the source document.

GSK Site Monitors or delegates will monitor the study to verify that, amongst others, the:

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

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

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

9.8.2. Archiving of data at study sites

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic for studies with an eCRF); however, caution needs to be exercised before such action is taken. The investigator 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 investigator 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 investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by International Conference on Harmonisation (ICH) GCP or other applicable guidelines any institutional requirements or applicable laws or regulations, or GSK standards/procedures.

The investigator/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 investigator leaves the site.

9.8.3. Audits

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

9.9. Limitations of the research methods

The Protocol Amendment 4 was taking into account a follow-up of children up to the age of 5 years, with baseline events collected for each subject in the active surveillance over 44 months (mimicking 24 months of active follow-up after the 4th dose of RTS,S/AS01$_E$ in EPI-MAL-003). The study will enrol children in the two age groups in which the Phase III study MALARIA-055 was conducted (6-12 weeks at first dose and 5-17 months at first dose) to collect background data in both age groups. However, in the post-implementation safety study EPI-MAL-003, only the 5-17 months age group will be kept.

The Protocol Amendment 5 described the sample size reduction from 40,000 to 30,000 with at least 20,000 children to be enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. There was a resultant reduction in the size of the two study groups to 15,000 subjects each (with at least 10,000 children in sites where the vaccine will be implemented).

At the start of this study, some uncertainties remained regarding the recommendations for use of RTS,S/AS01$_E$ in SSA, and what will be the vaccine uptake at the start of the vaccine programme implementation. Therefore, one or several amendments were needed during the course of the study. Participating countries have been identified because they have active HDSS or equivalent surveillance system sites and are representing moderate/high transmission of malaria. Other sites in SSA settings with moderate-to-high transmission of malaria, from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented (see Section 9.2), were added to the already defined study sites. The transition from EPI-MAL-002 (pre-implementation) to EPI-MAL-003 (post-implementation) is expected to occur in the study sites from Kenya and Ghana. The possible switch from a subject enrolled to EPI-MAL-002 to EPI-MAL-003 (if eligible) will be detailed in the EPI-MAL-003 protocol. GSK acknowledges that, in addition, the study start of EPI-MAL-003 might vary according to vaccination schedule and timing of vaccine implementation in each country.

In terms of study design, to better take into account the potential vaccine scenarios and to perform the study most close to routine medical practice, a cohort design allowing to prospectively collect standardized information seems to be the most suitable approach. Collecting data at a large population level (population size estimated at 30,000 subjects) is challenging from an operational perspective in SSA countries. To base the studies on existing HDSS or equivalent surveillance system offers the opportunity to benefit from

existing research and health care structures, in a population that is already part of a demographic and health indicators survey, and thus likely to be willing to participate in additional research. The selected study sites vary with regards to MTI (from moderate to high), which covers the same malaria disease spectrum than recommended by SAGE/MPAC. Pre-implementation of the active and enhanced hospitalisation surveillance efforts will allow collecting data in a well-characterised population and better understanding fluctuations over time in the community of AESI, other AE leading to hospitalisation or death, meningitis, any and severe malaria, including cerebral malaria.

This pre-implementation study will target enrolling 30,000 children eligible for vaccination in an active surveillance with at least 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented: approximately 15,000 children in the 6-12 weeks group (with at least 10,000 children enrolled in sites where the vaccine will be implemented; to collect background data in this age group) and approximately 15,000 children in the 5-17 months group (with at least 10,000 children enrolled in sites where the vaccine will be implemented; to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group). To ensure a study duration compatible with the anticipated implementation of the RTS,S/AS01$_E$ vaccine in 2018, the children in the 5-17 months group will be recruited either from a subgroup corresponding to a catch-up, 5 to <18 months of age at time of their first encounter with study staff, or from a subgroup during the first visit for administration of DTP/HepB/Hib vaccine.

GSK acknowledges that this sample size is not appropriate to detect an increase of some rare adverse events or very rare adverse events following vaccination with RTS,S/AS01$_E$ (i.e. with incidence of 1/100,000 PY). To address safety research with rare outcomes, most epidemiological studies are based on existing disease-specific registries or large healthcare databases such as insurance claim databases, which do not exist in SSA at the time being. Thus, the limitation in the ability to detect increases in very rare events is partly related to the fact that the vaccine will be implemented only in SSA.

All efforts will be made to reinforce the detection and standardize diagnosis of AESI, meningitis and severe malaria (including cerebral malaria). The enhanced hospitalisation surveillance should help to identify additional cases of AESI, other AE leading to hospitalisation or death, meningitis and severe malaria (including cerebral malaria) occurring in children living in the study area but not enrolled in the active surveillance.

The surveillance is planned such that cases (AESI, other AE leading to hospitalisation or death, meningitis, any and severe malaria, including cerebral malaria) are likely to be identified. Training of physicians and field staff will start before this study. All efforts will be made to ensure an optimal standardized way of collecting data across the different sites. Progress reports every 6 months will help in monitoring the participation rate and the trends in event detection. An interim analysis will be performed when the RTS,S/AS01$_E$ vaccine will be implemented in most of the study sites, in order to get first results of background incidence (before implementation of RTS,S/AS01$_E$ vaccine), and to get information about feasibility/ capability to acquire data for EPI-MAL-003 according to the planned timelines. This interim analysis will be done with clean data collected on a sub-group of subjects having 6 months of follow-up following the administration of

dose 3 of DTP/HepB/Hib vaccine (6-12 weeks group), or 6 months after V3 (5-17 months group); corresponding to V5. The interim analysis will concern primary safety endpoints and the main impact endpoints (at 6 months post last dose for the purpose of this interim).

Detecting the occurrence of AESI, other AE leading to hospitalisation or death, and meningitis cases are the primary objectives of this study. AESI and meningitis cases require specific diagnostic methods and such data may not be routinely collected in the study settings, potentially leading to underreporting. Therefore, specific training and monitoring of the field teams (community health workers, health care facilities staff, physicians and hospital staff) will be provided. The reinforcement of the pharmacovigilance practices and clinical and laboratory data collection most close to routine medical practice is a key component of this study. All procedures will be performed in line with the current national guideline recommendations in each of the participating countries. Improvement in surveillance over time may increase sensitivity in detecting those events and this potential bias will be taken into account when analysing data collected over time. Surveillance quality indicators will be utilised to help detect trends in changes in surveillance capacity.

Longitudinal detection of events such as meningitis might also be difficult to interpret because of the changing meningitis disease epidemiology. The study will take place in countries of the "meningitis belt", which is affected yearly by bacterial meningitis epidemics (mostly meningococcal meningitis). This zone comprises 22 countries from Senegal in the West to Ethiopia in the East. During 1993-2012, nearly one million suspected meningitis cases were reported; 80% of epidemics were caused by *Neisseria meningitidis* serogroup A. Despite successful introduction of a meningococcal A conjugate vaccine in the African meningitis belt since 2010 [Novak, 2012], meningococcal meningitis outbreaks may occur in some study sites during the EPI-MAL-002 study period, due to other *Neisseria meningitidis* serogroups, or if the study site is in a region/country which has not yet introduced the vaccine. Therefore, the interpretation of meningitis incidence rates should take into account the epidemiological context of each site. As for AESI, all efforts will be made to standardize meningitis diagnosis and reach an optimal proportion of laboratory confirmed cases to establish the aetiology. The case ascertainment process to classify meningitis cases will be based on additional laboratory testing (mainly based on molecular detection methods such as PCR) and the review of individual data by external experts.

Because surveillance will be conducted in study areas covering mainly rural areas, children severely ill might die before being transported to hospital. In the event of death, the cause of death will be systematically documented through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital. However, ascertaining the cause of death remains a concern considering the limitation of the verbal autopsy methods in the field, this is why all-cause mortality is an important endpoint to consider in this study.

* If a site is not part of the INDEPTH network, or does not have an equivalent surveillance system in place, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

All efforts will be made to standardize data collection during EPI-MAL-002. However, due to the long duration of this study, changes in diagnostic procedures, implementation of malaria control measures such as seasonal malaria chemoprevention [WHO, 2012], and changes in treatment measures will have to be considered during the analyses of the safety and malaria data. Potential confounders will be collected at individual level during EPI-MAL-002, and at community level during EPI-MAL-005. Some subjects might also leave the study area during the study period but this is regularly documented through demographic census (scheduled at least once a year during the study periods).

To assess the vaccine effectiveness, the follow-up of an unvaccinated group during the EPI-MAL-003 study (post-implementation) is planned. However, there is an uncertainty about the recruitment of a sufficiently large unvaccinated group after the vaccine implementation of the RTS,S/AS01$_E$ in those countries. The decision to collect information related to any malaria cases has been taken because the vaccine uptake may be very high and the number of unvaccinated children in EPI-MAL-003 may be too low to reliably estimate the direct vaccine effect. In this instance, the unvaccinated comparison group may have to be derived from EPI-MAL-002 only (estimations of the overall and total vaccine effects).

In summary, the data collection and result interpretation of the EPI-MAL-002 are key components to the success of the EPI-MAL-003 post-implementation study. This protocol has been written knowing that one or several amendments may be needed when more details about WHO recommendations and national policies on vaccine use will be known. The interpretation of the results will take into account the limitations described above.
(Amended 5 May 2020)

10. PROTECTION OF HUMAN SUBJECTS

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

The study will be conducted in accordance with the ICH Guideline for GCP, Guidelines for Good Pharmacoepidemiology Practices (GPP) [ISPE, 2015], other applicable guidelines, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

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

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site

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

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

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

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

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

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

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

11. MANAGEMENT AND REPORTING OF SERIOUS ADVERSE EVENTS RELATED TO STUDY PROCEDURE

The present study is performed prior to the introduction of the RTS,S/AS01$_E$ vaccine in the population. Therefore, there will be no management of AESI or other AE related to the use of the RTS,S/AS01$_E$ vaccine, but only reports of SAE related to study procedure. In addition to standard medical case management procedures, blood sampling is expected to be performed in case of a suspected AESI or meningitis. Serious adverse events (SAEs) related to this study procedure will therefore be collected.

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

Note: Any untoward medical occurrence, which in the view of the investigator is suspected to be related to a *GSK licenced vaccine/product, is to be reported to GSK Biologicals spontaneously via the local GSK Biologicals Named Safety Contact (see contact details in the Prescribing Information sheet).*

Any AESI or other AE occurring after standard EPI vaccination and recognised as being related to vaccination should be reported to National Health authorities following national reporting systems for the reporting of AE as part of routine practice.

11.1. Safety definition

11.1.1. Definition of a serious adverse event

For the purpose of this study, a serious adverse event (SAE) is defined as any untoward medical occurrence in a subject temporally associated with a study procedure 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 adverse event should be considered serious.

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

d. Results in disability/incapacity, or

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

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.

11.2. Detecting and recording serious adverse events

11.2.1. Time period for detecting and recording serious adverse events

In order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. blood sampling in case of a suspected AESI or meningitis) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

11.2.2. Evaluation of serious adverse events

11.2.2.1. Assessment of intensity

The investigator will assess the maximum intensity that occurred over the duration of the event for all SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each SAE recorded in the SAE screens should be assigned to one of the following categories:

1 (mild)	=	A SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	A SAE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	A SAE which prevents normal, everyday activities (in a young child, such a SAE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.

11.2.2.2. Assessment of outcomes

Outcome of any SAE reported during the entire study will be assessed as:

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

11.3. Reporting of serious adverse events

11.3.1. Prompt reporting of serious adverse events to GSK Biologicals

SAEs that occur in the time period defined in Section 11.2.1 will be reported promptly to GSK within the timeframes described in Table 9 once the investigator determines that the event meets the protocol definition of a SAE.

Table 9 Timeframes for submitting SAEs related to blood sampling in case of a suspected AESI or meningitis to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs related to blood sampling in case of a suspected AESI or meningitis	24 hours*	SAE screen	24 hours*	SAE screen

* Timeframe allowed after receipt or awareness of the information.

Study related SAEs will also be reported to PATH Research Ethics Committee (PATH REC) in accordance with PATH REC policy.

11.3.2. Contact information for reporting serious adverse events to GSK Biologicals

Study Contact for Reporting SAEs
See Sponsor Information Sheet for contact details
Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: Email: RIX.CT-Safety-Vac@gsk.com GSK Biologicals Clinical Safety & Pharmacovigilance Fax: +32 2 656 51 16 or +32 2 656 80 09

11.3.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the SAE screens of the eCRF WITHIN 24 HOURS. The SAE screens will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the SAE screens should still be completed within 24 hours. Once additional information is received, the SAE screens in the eCRF should be updated WITHIN 24 HOURS.

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

11.3.3.1. Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a SAE Report Form and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the SAE screens in the eCRF within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

11.3.3.2. Updating of SAE information after removal of write access to the subject's eCRF

When additional SAE information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 9.

11.4. Follow-up of serious adverse events

All events 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 study.

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 Site Monitor.

GSK Biologicals may request that the investigator performs or arranges for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the event. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

To comply with Guidelines for GPP or other applicable guidelines administrative obligations relating to data collection, archiving data, audits, confidentiality and publications must be fulfilled.

Study information from this protocol will be posted on public registers (e.g., GSK Clinical Study Register, clinicaltrials.gov, Pan African Clinical Trials Registry) and the European Union Post-Authorisation Studies (EU PAS) register before the start of the study, as applicable.

Progress reports will be written and submitted every six months from study start. An interim report will be written with the data collected on all subjects after 6 months of follow-up following the administration of dose 3 of DTP/HepB/Hib vaccine (6-12 weeks group), or 6 months after V3 (5-17 months group); corresponding to V5. A final study report will be written and submitted.

For the three studies a Safety Post Approval Program Partnership Committee has been created and will ensure preparation and review of manuscripts resulting from the studies. This Committee is composed of local Principal Investigators with GSK and PATH representation. This Committee acts as the main governance body for the studies. (Charter is available upon request.)

A manuscript will be submitted to a peer reviewed journal for publication within the policy defined timelines. In addition, study information will be posted to the GSK Clinical Study Register.

13. REFERENCES

Absoud M, Lim MJ, Chong WK, et al. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. Mult Scler 2012;19(1):76-86.

Al Qudah Z, Abukwaik W, Patel H, et al. Encephalitis after vaccination in United States. A Report from the CDC/FDA Vaccine Adverse Event Reporting System. [1990–2010]. Neurology April 24, 2012; 78(Meeting Abstracts 1): P03.151.

Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology 2009;72(3):232-239.

Bar-Meir M, Haklai Z, Dor M. Kawasaki disease in Israel. Pediatr Infect Dis J 2011;30(7):589-92.

Begg S, Vos T, Barker B ,et al. 2007. The burden of disease and injury in Australia 2003. Cat. no. PHE 82. Canberra: Australian Institute of Health and Welfare.

Bohlke K, Davis RL, Marcy SM. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics 2003;112;815-820.

Buettcher M, Heininger U, Braun M, et al; Brighton Collaboration HHE Working Group. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2007;25(31):5875-81.

Carlin JB, Macartney KK, Katherine J, et al. intussusception risk and disease prevention associated with rotavirus vaccines in Australia's national immunization program. Clin Infect Dis 2013;57(10):1427-34.

Chen Y, Ma F, Zhang J, et al. Population incidence of Guillain-Barré syndrome in parts of China: three large populations in Jiangsu province, 2008-2010. Eur J Neurol 2014;21(1):124-9.

Decker WW, Campbell RL, Manivannan V, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. J Allergy Clin Immunol 2008;122:1161-1165.

Demirbilek H, Ozbek MN, Baran RT. Incidence of type 1 diabetes mellitus in Turkish children from the southeastern region of the country: a regional report. J Clin Res Pediatr Endocrinol 2013;5(2):98-103.

El-Ziny MA, Salem NA, El-Hawary AK, Chalaby NM, Elsharkawy AA. Epidemiology of childhood type 1 diabetes mellitus in Nile Delta, northern Egypt - a retrospective study. J Clin Res Pediatr Endocrinol 2014;6(1):9-15.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. EMA/813938/2011. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 23 November 2015.

European Medicines Agency. First malaria vaccine receives positive scientific opinion from EMA. 24 July 2015(a). http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/07/WC500190447.pdf. Accessed 23 November 2015.

European Medicines Agency. Mosquirix H-W-2300. 23/07/2015(b). http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000395.jsp&mid. Accessed 23 November 2015.

Ehrmann Feldman D, Bernatsky S, Houde M. The incidence of juvenile rheumatoid arthritis in Quebec: a population data-based study. Pediatr Rheumatol Online J 2009;7:20.

Galler A, Stange T, Muller G, et al. Incidence of childhood diabetes in children aged less than 15 years and its clinical and metabolic characteristics at the time of diagnosis: data from the Childhood Diabetes Registry of Saxony, Germany. Horm Res Paediatr 2010;74(4):285-291.

Gardner-Medwin JM, Dolezalova P, Cummins C, et al. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002;360:1197.

Gutierrez Brito M, Thompson A, Girgenti D, et al. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in Mexico. Rev Panam Salud Publica 2013;33(6):414-21.

Habeb AM, Al-Magamsi MS, Halabi S, Eid IM, Shalaby S, Bakoush O. High incidence of childhood type 1 diabetes in Al-Madinah, North West Saudi Arabia (2004-2009). Pediatr Diabetes 2011;12(8):676-81.

Hair JF Jr, Anderson RE, Tatham RL, Black WC (1995). Multivariate Data Analysis (3rd ed). New York: Macmillan.

Holman RC, Belay ED, Christensen KY, et al. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J 2010; 29:483-488.

Howlett WP, Vedeler CA, Nyland H, et al. Guillain-Barré syndrome in northern Tanzania: a comparison of epidemiological and clinical findings with western Norway. Acta Neurol Scand 1996;93(1):44-9.

Hua W, Izurieta HS, Slade B, et al. Kawasaki disease after vaccination: reports to the vaccine adverse event reporting system 1990-2007. Pediatr Infect Dis J 2009;28(11):943-7.

INDEPTH Network. http://www.indepth-network.org/. Accessed 23 November 2015.

INDEPTH Network. INDEPTH Standardized Verbal Autopsy questionnaire (Revised August 2003). http://www.indepth-network.org/index.php?option=com_content&task=view&id=1831. Accessed 23 November 2015.

International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). Rev 3 (June 2015). http://www.pharmacoepi.org/resources/guidelines_08027.cfm; 2015. Accessed 14 June 2017.

Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. J Paediatr Child Health 2005;41:475-478.

Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. Autoimmun Rev 2014;13(3):215-24.

Karvonen M, Viik-Kajander M, Moltchanova E, et al. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care 2000;23:1516–1526.

Ketelslegers IA, Catsman-Berrevoets CE, Neuteboom RF, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. J Neurol 2012;259(9):1929-35.

Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurology 2011;77(12):1143-8.

Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998;339:1787-802.

Loughlin J, Mast TC, Doherty MC, Wang FT, Wong J, Seeger JD. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. Pediatr Infect Dis J 2012;31(3):292-296.

Malaria Vaccine Funders Group. Malaria Vaccine Technology Roadmap. 2013. http://www.who.int/immunization/topics/malaria/vaccine_roadmap/en/. Last accessed: 23 November 2015.

Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2007-2008 nationwide survey. J Epidemiol 2010;20:302.

Novak RT, Kambou JL, Diomandé FV, et al. Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data. Lancet Infect Dis. 2012;12(10):757-764.

Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr 2007;166(5):405-412.

Rosillon D, Buyse H, Friedland LR, et al. Risk of Intussusception After Rotavirus Vaccination: Meta-analysis of Postlicensure Studies. Pediatr Infect Dis J 2015;34(7):763-768.

Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333(24):1600-7.

Rubin DB. Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc. 1987. http://onlinelibrary.wiley.com/doi/10.1002/9780470316696.fmatter/pdf.

Sáez-Llorens X, Guevara JN. Intussusception and rotavirus vaccines: what is the background risk? Pediatr Infect Dis J 2004;23(4):363-5.

Sejvar JJ, Baughman AL, Wise M, et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 2011;36(2):123-33.

Sella T, Shoshan A, Goren I, et al. A retrospective study of the incidence of diagnosed Type 1 diabetes among children and adolescents in a large health organization in Israel, 2000-2008. Diabet Med 2011;28(1):48-53.

Skordis N, Efstathiou E, Kyriakides TC, et al. Epidemiology of type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century. Hormones (Athens) 2012;11(1):86-93.

Steketee RW, Campbell CC. Impact of national malaria control scale-up programmes in Africa: magnitude and attribution of effects. Malar J 2010;9:299.

Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

Stoltzfus RJ, Dreyfuss ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington DC, ILSI PRESS; 1993 http://www.who.int/nutrition/publications/micronutrients/guidelines_for_Iron_supplementation.pdf. Accessed 23 November 2015.

Sutor AH, Harms A, Kaufmehl K. Acute immune thrombocytopenia (ITP) in childhood: Retrospective and prospective survey in Germany. Semin Thromb Hemost 2001;27:253-267.

Swai AB, Lutale JL, McLarty DG. Prospective study of incidence of juvenile diabetes mellitus over 10 years in Dar es Salaam, Tanzania. BMJ 1993; 306(6892):1570-1572.

Tate JE, Simonsen L, Viboud C, et al. Trends in intussusception hospitalizations among US infants, 1993-2004: implications for monitoring the safety of the new rotavirus vaccination program. Pediatrics 2008;121(5):e1125-32.

Tenembaum S, Chitnis T, Ness J, et al. International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology 2007;68(16 Suppl 2):S23-36.

The RTS,S Clinical Trials Partnership. First results of a phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365(20):1863-75.

The RTS,S Clinical Trials Partnership. A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. N Engl J Med 2012;367(24):2284-95.

The RTS,S Clinical Trials Partnership. Efficacy and Safety of the RTS,S/AS01 Malaria Vaccine during 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites. PLOS Med. 2014;11(7):e1001685. doi: 10.1371/journal.pmed.1001685.

The RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8.

The Uppsala Monitoring Centre, 2011: Glossary of terms used in Pharmacovigilance. http://clinicalsafetygeek.com/wp-content/uploads/2013/10/PV-Terms.pdf. Accessed 06 September 2017.

Tseng HF, Sy LS, Liu IL, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine 2013;31(22):2578-2583.

Ulm K. Simple method to calculate the confidence interval of a standardized mortality ratio (smr). Am J Epidemiol 1990;131(2):373-375.

United Nations. Sex differentials in childhood mortality, New York, 2011. http://www.un.org/esa/population/publications/SexDifChildMort/SexDifferentialsChildhoodMortality.pdf. Accessed 24 October 2016.

Vanlander A, Hoppenbrouwers K. Anaphylaxis after vaccination of children: Review of literature and recommendations for vaccination in child and school health services in Belgium. Vaccine 2014;32(26):3147-3154.

VanLandingham M, Hanigan W, Vedanarayanan V, Fratkin J. An uncommon illness with a rare presentation: neurosurgical management of ADEM with tumefactive demyelination in children. Childs Nerv Syst 2010;26(5):655-661.

Vora NM, Holman RC, Mehal JM, et al. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. Neurology 2014;82(5):443-51.

WHO case definition, 2003. WHO Coordinated Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) Surveillance Network: Tier 1 Meningitis Surveillance. http://apps.who.int/nuvi/surveillance/IB-VPD_Case_Defs.pdf. Accessed 23 November 2015.

WHO. Global malaria programme. WHO policy recommendation: Seasonal malaria chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. March 2012. http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf. Accessed 23 November 2015.

WHO World Malaria Report 2012. http://www.who.int/malaria/publications/world_malaria_report_2012/report/en/. Accessed 23 November 2015.

WHO Definition. Programmes and projects. 2012. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/S.AfricaDraftGuidelines.pdf. Accessed 23 November 2015.

WHO. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2015 - conclusions and recommendations. Weekly epidemiological record. 2015(a);50(90):681-700. http://www.who.int/wer/2015/wer9050.pdf?ua=1. Accessed July 2017.

WHO. Guidelines for the treatment of malaria. 3rd Edition. 2015***(b)***. http://www.who.int/malaria/publications/atoz/9789241549127/en/. Accessed 23 November 2015.

WHO. Summary of Key Points – Malaria Vaccine: WHO Position Paper January 2016(a). http://www.who.int/immunization/policy/position_papers/malaria_pp_jan_2016_presentation.pdf?ua=1. Last accessed 31 August 2016.

WHO. Malaria vaccine: WHO position paper – January 2016. Weekly Epidemiological Record 2016(b);91(4):33-52.

WHO. Ghana, Kenya and Malawi to take part in the WHO malaria vaccine pilot programme. April 2017. http://www.afro.who.int/news/ghana-kenya-and-malawi-take-part-who-malaria-vaccine-pilot-programme. Last accessed 11 October 2017.

Xiong CH, Yan Y, Liao Z, et al. Epidemiological characteristics of acute disseminated encephalomyelitis in Nanchang, China: a retrospective study. BMC Public Health 2014;14:111.

Annex 1 LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	List of stand-alone documents
2.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	List of principal and coordinating investigators
3.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	Glossary of terms
4.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	Trademarks
5.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	Case definitions for protocol-defined adverse events of special interest (AESI) and surveillance indicators
6.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	Study specific guidance document
7.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	Amendments to the protocol
8.	115055 (EPI-MALARIA-002 VS AME)	***4 May2020***	Protocol amendment 5 sponsor signatory approval
9.	115055 (EPI-MALARIA-002 VS AME)	***5 May 2020***	Protocol amendment 5 investigator agreement

(Amended 5 May 2020)

Annex 2 LIST OF PRINCIPAL AND COORDINATING INVESTIGATORS

Contact details and list of all investigators available upon request.

Annex 3 GLOSSARY OF TERMS

Active surveillance:	Screening for AESI and other diseases during study follow-up visits at the community level.
Adverse event of special interest (AESI):	A predefined list of adverse events that have historically been associated with vaccines other than RTS,S/AS01$_E$, or may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines.
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.
Cohort event monitoring:	A prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time [The Uppsala Monitoring Centre, 2011].
Cohort study:	A form of epidemiology study where subjects in a study population are classified according to their exposure status/disease and followed over time (prospective / retrospective) to ascertain the outcome(s) (disease).
DTP/HepB/Hib	This refers to Diphtheria, Tetanus, and Pertussis (DTP), or DTP-Hepatitis B (DTP-HepB tetravalent) or DTP-HepB-Haemophilus influenza type b (Hib) (DTP-HepB-Hib pentavalent) vaccines.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enhanced hospitalisation surveillance:	Case detection during hospitalisation through monitoring of medical records and registries.
Epidemiology study:	An observational study or an interventional study without administration of medicinal product(s) as described in a research protocol.

eTrack:	GSK's tracking tool for clinical/epidemiology studies.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Section 9.7.2 for details on criteria for evaluability).
Exposed clusters	Study sites where the RTS,S/AS01$_E$ vaccine will be implemented at the beginning of the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.
Job Aids Tool:	Tool to help health care professionals detect signs and symptoms of AESI and to provide guidelines for diagnosis based on case definition.
Hospitalisation:	Subjects requiring overnight stay in a health care facility.
National EPI:	Routine vaccination programmes, administered by the national EPI system in place, usually given at 6, 10 and 14 weeks of age (e.g. DTP/HepB/Hib vaccines. NOTE: in some countries the EPI schedule may differ by a few weeks).
Pharmacovigilance:	Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs) [WHO Definition, 2012].
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, study design, or scientific integrity of the study.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Serious Adverse Event:	For the purpose of this study, a SAE is defined as any untoward medical occurrence in a subject temporally associated with a study procedure that: a. results in death; b. is life-threatening; c. requires hospitalisation or prolongation of existing hospitalisation; d. results in disability/incapacity; Medical or scientific judgment 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. A full definition of the events that constitute SAEs can be found in Section 11.1.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical/ epidemiology studies at one or more investigational sites.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical/ epidemiology study, or a person about whom some medical information has been recorded in a database.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Surveillance:	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.

Unexposed clusters	Study sites where the RTS,S/AS01$_E$ vaccine will not be implemented in the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.
Vaccine ineligible	Vaccine ineligible is defined as those subjects that on the basis of age would be ineligible for RTS,S/AS01$_E$ vaccination, regardless of vaccine availability at the time of assessment. The age will depend on the label for RTS,S/AS01$_E$ vaccination in the country.

Annex 4 TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademarks of the GlaxoSmithKline group of companies	Generic description
Mosquirix™	*Plasmodium falciparum* and hepatitis B vaccine (recombinant, adjuvanted)
Rotarix®	Live attenuated human rotavirus vaccine
Pediarix®	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus combined vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
RotaTeq® (Merck & CO., Inc.)	Live, oral, pentavalent rotavirus vaccine

Annex 5 CASE DEFINITIONS FOR PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST (AESI) AND SURVEILLANCE INDICATORS

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Nerves and Central Nervous System		
ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)	**LEVEL 1** • Diffuse or multifocal demyelination revealed on histopathological sampling **OR** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus **AND** • On MRI: diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences **AND** • Monophasic character of the illness (absence of relapse within a minimum of 3 months of symptomatic nadir) **LEVEL 2** • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) **AND** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness)	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry) • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus **AND** • On MRI: Diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences **AND** • Follow up insufficient to confirm a monophasic nature of the illness (absence of relapse within a minimum of three months after the clinical nadir). **LEVEL 3** • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) **AND** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	Exclusion criteria for all levels of diagnostic certitude • Authentication of an acute infection or of a differential diagnosis is compatible with the clinical picture • Relapse of the illness at any moment after a minimum period of three months of clinical improvement after the nadir of clinical symptoms. • MRI images or histopathology in the clinical diagnosis is compatible with the case definition with the diagnosis of ADEM. **In Summary** ADEM can be confirmed if: • The clinical diagnosis is compatible with the case definition. • All differentials diagnoses have been excluded • The CSF exam supports the diagnosis of ADEM. NB: Plan for diagnostic confirmation by a neurologist (and MRI if possible). Generally the illness completely resolves in a few months. The diagnosis must be confirmed by a clinical examination performed 3 months after the nadir of the clinical symptoms.	
ENCEPHALITIS	**LEVEL 1** • Demonstration of acute inflammation of the central nervous system parenchyma (+/- the meninges) on histopathology **LEVEL 2** • Signs of encephalopathy (depressed level of consciousness, somnolence , acute personality change for more than 24 hours) **AND** *One or more of the following signs:* • Absent or diminished reflexes to external stimuli (such as a loud noise or painful stimuli) • Absent or markedly diminished eye contact • Inadequate or absent response to an external stimuli • Seizures with loss of consciousness **OR**	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, more often focal) • Sensory abnormalities • Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) • Cerebellar dysfunction, such as ataxia, dysmetria, cerebellar nystagmus **AND** *Two or more of the following signs:* • Fever (≥ 37.5°C) • CSF: Pleocytosis – >15 leukocytes/ mm3 in a child 2 months of age or younger – >5 leukocytes/ mm3 in a child 2 months of age or older • EEG signs compatible with an encephalitis • Cerebral imagery compatible with an encephalitis. **LEVEL 3** • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) **AND** *One or more of the following signs:* • Absent or diminished response to external stimuli (such as a loud noise, painful stimuli) • Absent or markedly diminished eye contact • Inconsistent or absent response to an external stimuli • Seizures with associated loss of consciousness	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	OR Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) • Cerebellar impairment, such as ataxia, dysmetria, cerebellar nystagmus **AND** *One of the following signs:* • Fever (≥ 37.5°C) • CSF: Pleocytosis – >15 leukocytes/ mm3 in a child 2 months of age or younger – >5 leukocytes/ mm3 in a child 2 months of age or older • EEG signs compatible with an encephalitis • Cerebral imagery compatible with an encephalitis **Evaluation Criteria** • Exclude the presence of all diseases (cancer, toxic-metabolic encephalopathy, vascular problems, trauma, meningitis etc.) **In Summary** The diagnosis of encephalitis is confirmed if: • The clinical diagnosis is is compatible with the case definition. **AND** • The CSF analysis is compatible with an encephalitis picture. **AND** • The differential diagnoses (especially meningitis) have been excluded.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
GUILLAIN BARRÉ SYNDROME	**LEVEL 1** • Bilateral weakness (symmetric) with flaccid extremities (usually of all 4 limbs) **AND** • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities **AND** • Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase **AND** • Electromyography: Electrophysiological signs the clinical diagnosis is compatible with the case definition with GBS **AND** • Albuminocytologic dissociation: hyperproteinorachia (elevation of CSF protein) and normal CSF white cell count [< 50 cells/µl] **AND** • Absence of plausible differential diagnosis (to explain the motor weakness) **LEVEL 2** • Bilateral AND flaccid weakness of the extremities **AND** • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities **AND** • Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau **AND** • CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value) **OR** • If CSF not collected or results not available, electrophysiologic studies consistent with GBS **AND** • Absence of identified alternative diagnosis for weakness **LEVEL 3** • Bilateral AND flaccid weakness of the extremities	Sejvar JJ, Kohl KS, Gidudu J, et al. The Brighton Collaboration Guillain-Barré Syndrome Working Group. Guillain-Barré Syndrome and Fisher Syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. Vaccine. 2011; 29(3): 599–612.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities **AND** • Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase **AND** • Absence of plausible differential diagnosis (to explain the motor weakness) **In Summary** The diagnosis of Guillain-Barre Syndrome can be confirmed if: • The clinical diagnosis is compatible with the case definition • The poliovirus is not isolated from the stool • The CSF examination is compatible with GBS: Hyperproteinorachia (elevation of CSF protein), absence of pleocytosis. • There is diagnostic confirmation by a neurologist.	
GENERALIZED *CONVULSIVE* SEIZURE	**LEVEL 1** • Witnessed sudden loss of consciousness **AND** • Generalized tonic, clonic, tonic-clonic or atonic motor manifestations **LEVEL 2** • Reported sudden loss of consciousness **AND** • Generalized tonic, clonic, tonic-clonic or atonic motor manifestations **LEVEL 3** • Reported sudden loss of consciousness **AND** • Other generalized motor manifestations **In Summary** The diagnosis of generalized seizure can be confirmed if: • The clinical diagnosis is compatible with the case definition. • The history of present illness evokes seizure activity	Bonhoeffer J, Menkes J, Gold MS, et al; The Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22:557-562.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• The etiological work up is negative: (i.e. febrile seizure ***that does not fit GCS definition,*** acute intoxication, trauma, severe malaria etc. have all been excluded) **(Amended 5 May 2020)**	
HYPOTONIC HYPORESPONSIVE EPISODE (HHE)	**LEVEL 1** • Hypotonia (muscular weakness) **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Pallor or cyanosis **LEVEL 2** • Indeterminate muscle tone **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Pallor or cyanosis **OR** • Hypotonia (muscular weakness) **AND** • Reduction or absence of response to sensory or verbal stimuli **OR** • Indeterminate skin color **LEVEL 3** • Normal muscle tone **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Pallor or cyanosis **OR** • Hypotonia (muscular weakness) **AND** • Indeterminate response to sensory or verbal stimuli **AND** • Palor or cyanosis.	Bonhoeffer J, et al. Brighton Collaboration HHE Working Group. Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004; 22(5-6): 563–568.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Hepato-Gastrointestinal and Renal System		
HEPATIC FAILURE	**Major criteria** • Total serum bilirubin ≥1.5 times the upper limit of normal (ULN) **OR** • Elevation of the serum transaminases (ALT ***or*** AST ≥ 3 times the upper limit of normal (ULN)) **(Amended 5 May 2020)** **AND** • Coagulopathy unresponsive to vitamin K (prothrombin time (PT) ≥ 15 seconds or INR ≥1.5). **In Summary** The diagnosis of hepatic insufficiency can be confirmed if: • The diagnosis can be considered if the major criteria are present and confirmed on at least two blood draws. • The etiologies of the most frequent causes of jaundice and alterations of liver function tests and the non-hepatic encephalopathies are excluded: viral hepatitis, malaria, sickle cell anemia, exposure to toxins and medicines. NB: In case of fortuitous discovery of a perturbation in the hepatic panel without clinical manifestations, it is recommended to do a follow up hepatic panel.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012;30(33): 5038–5058.
INTUSSUSCEPTION	**I) Definition of criteria** DIAGNOSTIC CRITERIA • Surgical criteria – Demonstration of intussusception during exploratory surgery • Imaging criteria – Demonstration of intussusception via non-barium or aircontrast enema; – Demonstration via ultrasound of an intra-abdominal mass with specific characteristics – target (or doughnut) sign on transverse images and pseudokidney or sandwich sign on longitudinal images – the reduction of these signs by hydrostatic enema is also confirmed by ultrasound. **Major criteria** • Symptoms and signs of intestinal obstruction: – History of vomiting bile	Bines JE, Kohl K, Forster J, et al and the Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22:569–574.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND – Clinical examination shows acute abdominal distention and abnormal or absent bowel sounds **OR** – Radiological examination (plain abdominal X-ray) shows air-fluid levels and loops of distended small bowel. • Signs of intussusception, ≥ 1 following signs: – Abdominal mass – Rectal mass – Rectal prolapse – Plain abdominal X-ray shows a soft tissue mass – Abdominal ultrasound shows a soft tissue mass – Abdominal CT shows a soft tissue mass • Evidence of vascular compromise or venous congestion: – Anal bleeding **OR** – Currant jelly stools" **OR** – Blood detected during rectal examination **Minor criteria** • Predisposing factors: aged < 1 year, male • Abdominal pain • Lethargy • Pallor • Hypovolemic shock • Plain abdominal X-ray showing an abnormal and unspecific distribution of air in the intestines. **II) Diagnostic certainty levels** **LEVEL 1** • Surgical criteria: The demonstration of invagination of the intestine at surgery; **AND/OR** • Radiologic criteria:	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	The demonstration of invagination of the intestine by either air or liquid contrast enema; **OR** The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on postreduction ultrasound; **AND/OR** • Autopsy criteria: The demonstration of invagination of the intestine. **LEVEL 2** • Clinical criteria: Two major criteria or One major criterion and three minor criteria. **LEVEL 3** • Clinical criteria: Four or more minor criteria.	
RENAL INSUFFICIENCY	**Major criteria** Creatinine ≥ 1.5 times the upper limit of normal (ULN) or 1.5 times the patient's initial value. **Minor criteria** Urine production <0.5 ml/kg/hour **In Summary** Renal insufficiency can be confirmed if: • The major criteria is present and confirmed (at least two blood draws) • The etiological diagnosis has been carried out.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012; 30(33): 5038–5058.
Skin and Mucous Membranes & Bones and Joints		
HENOCH SCHÖNLEIN PURPURA	**I) Definition of criteria** **MAJOR CRITERIA** • Purpura (mandatory criterion) Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, not related to thrombocytopenia • Abdominal pain Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding • Histopathology Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit • Arthritis or arthralgias	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion. • Renal involvement Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample. Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick. **MINOR CRITERIA** • Other diagnoses unlikely (exclude meningitis) **II) Diagnostic certainty levels** **LEVEL 1** • Purpura or petechiae (mandatory) with lower limb predominance **AND ≥ 1 following criteria** • Abdominal pain • Histopathology • Arthritis or arthralgias • Renal involvement **AND** • Absence of thrombocytopenia **LEVEL 2** • Purpura or petechiae (mandatory) with lower limb predominance **AND** • Absence of thrombocytopenia.	
JUVENILE CHRONIC ARTHRITIS	Juvenile Chronic Arthritis is defined by an evolution of symptoms of at least three months. The clinical examination often reveals a child with growth retardation. The different clinical forms are the following: **1) Pauciarticular form (the most common form between 1 and 3 years of age).** Clinically this presents with: • Involvement of four or less joints • Symmetric involvement of the small joints • Tenosynovitis of the flexor tendons and erosive nodules (frequent) • Rheumatoid factor seronegativity	Medical websites resources: e.g. http://www.arthritis.co.za/jra.htm; http://emedicine.medscape.com/article/1007276-overview; http://www.med.univ-rennes1.fr/etud/pediatrie/arthrite_cique.hthronm

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	These signs can be associated with: • A positive anti-nuclear antibody (among 40 to 75% of children) • Uveitis **2) Polyarticular form** • Affects 5 or more joints • Rheumatoid factor IgM can be positive or negative • Hips, cervical spine, hands and feet are the joints the most often affected, followed by the knees, wrists and ankles. • Among the patients seronegative for the rheumatoid factor, an association of fever, hepatosplenomegaly and symmetrical arthritis has been described. **3) Systemic form** • Accompanied by a fever up to 39.5°C during at least two weeks • A typical rash on the trunk and thighs can be seen • Frequent involvement of the wrists, knees, ankles as well as the temporomandibular joint, and the hands. • The illness typically lasts between 2 and 5 years before complete resolution **In Summary** The diagnosis of Juvenile Chronic Arthritis (JCA) can be confirmed if: • The clinical diagnosis responds to the case definition • The biological panel shows signs of chronic inflammation • The most frequent differential diagnoses are excluded If necessary, the diagnosis should be confirmed by a specialist. The symptoms must last at least 3 months before concluding JCA. A confirmation of the diagnosis requires a follow up visit 3 months after the beginning of the illness.	

<table>
<tr><th>Body system/ AESI</th><th>Diagnosis/Level of Diagnostic Certainty</th><th>References</th></tr>
<tr><td>STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)</td><td>Symptoms start by a feeling of malaise, fever, headache, cough and conjunctivitis. Then the macular eruption appears, rapidly transforming into confluent bullae over one to three days. Nails and eyebrows can be lost due to epidermal involvement.
The diagnosis of Stevens-Johnson syndrome becomes evident with the appearance of cutaneous lesions, the rapid and expansive progression of symptoms, which include two mucosal sites.
<table>
<tr><th>Diagnosis</th><th>Lesion morphology</th><th>Body surface area detachment</th></tr>
<tr><td>SJS</td><td>Maculae, bullae, atypical target lesions</td><td>≤10%</td></tr>
<tr><td>SJS-TEN overlap</td><td>Maculae, bullae, atypical target lesions</td><td>10-30%</td></tr>
<tr><td>TEN with spots</td><td>Maculae, bullae, atypical target lesions</td><td>≥30%</td></tr>
</table>
In Summary
The diagnosis of STEVENS-JOHNSON SYNDROME (SJS) can be confirmed if:
• The clinical diagnosis responds to the case definition
• The etiological research indicates exposure to a triggering element (medication, immunization, toxin, febrile state, virus)
• In case of doubt, consultation of a specialist is necessary.</td><td>Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993; 129:92-6.</td></tr>
<tr><td>KAWASAKI DISEASE</td><td>I) DEFINITION OF CRITERIA
Major criteria
• Fever ≥ 5 days
• Clinical criteria:
Signs of mucocutaneous inflammation:
– Polymorphic exanthem
– Non-exudative bilateral conjunctivitis
– Involvement of the lips and oral cavity: erythema, cracked lips, “strawberry red” tongue, diffuse inflammation of the oral and pharyngeal mucosa
– Involvement of the hands and feet: erythema of the palms and/or soles, oedema of the hands and/or the feet. Hand and/or foot periungual peeling skin (week 2-3 of disease course)</td><td>Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110(17):2747-71.</td></tr>
</table>

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	– Usually unilateral neck lymphadenopathy (≥ 1.5 cm) **Minor criteria** • Erythrocyte sedimentation rate ≥ 40 mm/h or CRP ≥ 3 mg/dL • Echocardiogram showing coronary artery or heart involvement **II) Diagnostic certainty levels** **LEVEL 1** • Fever ≥ 5 days **AND** • ≥ 4 clinical criteria: **AND** • Other diagnoses unlikely after clinical examination and laboratory tests **LEVEL 2** • Fever ≥ 5 days **AND** • < 4 clinical criteria: **AND** • Erythrocyte sedimentation rate ≥ 40 mm/h OR CRP ≥ 3 mg/dL **AND** • Other diagnoses unlikely after clinical examination and laboratory tests **LEVEL 3** • Fever ≥ 5 days **AND** • < 4 clinical criteria: **AND** • Normal erythrocyte sedimentation rate OR normal CRP **AND** • Coronary artery or heart involvement **AND** • Other diagnoses unlikely after clinical examination and laboratory tests.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Cardiovascular system and blood disorders		
ANAPHYLAXIS	**For all levels of diagnostic certainty** • Sudden onset AND • Rapid progression of signs and symptoms AND • Involving multiple (≥ 2) organ systems, as follows: **LEVEL 1** • ≥1 major dermatological criterion **AND** • ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion **LEVEL 2** • ≥1 major cardiovascular AND ≥1 major respiratory criterion **OR** • ≥1 major cardiovascular OR respiratory criterion **AND** • ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) **OR** • ≥1 major dermatologic AND ≥1 minor cardiovascular AND/OR minor respiratory criterion **LEVEL 3** • ≥1 minor cardiovascular OR respiratory criterion **AND** • ≥1 minor criterion from each of ≥2 different systems/categories **In Summary** The diagnosis can be confirmed if: • The clinical diagnosis is compatible with the case definition (at least 2 major signs/criteria) • Symptom onset occurred after a short period of time (a few minutes to hours) after exposure to a food item, an insect sting, a vaccination, or contact with a product allergen (such as peanuts) • If the child reports a known allergy, one major sign/criteria following exposure to a known allergen is sufficient for a diagnosis of anaphylaxis.	Rüggeberg JU, Gold MS, Bayas JM et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-5684.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
DIABETES MELLITUS TYPE 1	• Serum fasting glucose ≥ 7 mmol/L (> 126 mg/dL) **OR** • Postprandial serum glucose ≥11.1 mmol/L (≥ 200 mg/dL) 2 hours after ingesting 1.75 g/kg (max.75g) of glucose (oral glucose tolerance test) **OR** • A1C Hemoglobin ≥ 6.5% AND Hyperglycemia **AND** • No other cause of hyperglycemia **In Summary** The diagnosis of type 1 diabetes mellitus can be confirmed when a confirmed hyperglycemia responds to the case definition.	WHO Definition and Diagnosis of diabetes mellitus and intermediate hyperglycaemia, 2006 and http://www.nlm.nih.gov/medlineplus/encyclopedia.html
THROMBOCYTOPENIA	**LEVEL 1** • Platelet concentration < to 150 x 10^6/mL **AND** – Confirmation par blood smear **OR** – Clinical signs of spontaneous bleeding (i.e. non traumatic)* **LEVEL 2** • Platelet concentration < to 150 x 10^6/mL. **Spontaneous bleeding (i.e. non traumatic), includes purpura (i.e. petechiae, purpura sensu stricto, ecchymoses) exudative hemmorhage, hematomas, hematemesis, occult bleeding par rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding, conjunctival bleeding, intracranial bleeding.* **In Summary** The diagnosis of thrombocytopenia can be confirmed if: • It corresponds to the level 1 of diagnostic certainty case definition • An etiological investigation was carried out.	Wise RP, Bonhoeffer J, Beeler J, et al. Brighton Collaboration Thrombocytopenia Working Group. Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5717-5724.
Surveillance indicators		
Injection Site Abscess **Abscess of infectious *a*etiology**	**LEVEL 1** • Spontaneous or surgical drainage of the mass contents **AND** • Microbiologic confirmation (Gram stain, culture or other exam) of the presence of bacteria with or without altered polynuclear neutrophils in the aspirated/drained fluid.	Kohl K, et al. The Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Abscess at injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	LEVEL 2 In situations where microbiologic confirmation (Gram stain, culture or other examination) was not performed, or was performed after the start of antibiotic therapy, or was not ordered at all. • Spontaneous or surgical drainage of the purulent fluid from the mass contents **OR** • Mass collection diagnosed by an imaging technique or the mass is fluctuant. **AND** • Signs of localized inflammation including at least one of the following aspects: erythema, pain on light palpation, and warmth to the touch at the injection site. **AND** • Resolution of symptoms after antibiotic therapy	Vaccine. 2007; 25(31): 5821–5838.
Injection Site Abscess **Sterile abscess**	**LEVEL 1** • Spontaneous or surgical drainage of the mass contents **AND** • Drainage liquid obtained before the beginning of antibiotic therapy and no infectious pathogen found on examination (Gram stain, culture or other examination) **LEVEL 2** In situations where microbiologic confirmation (Gram stain, culture or other examination) was not performed, or was performed after the start of antibiotic therapy, or was not ordered at all. • Non purulent fluid is spontaneous or surgically drained from the mass **OR** • A collection of material, such as fluid, is diagnosed by imagery or there is fluctuance on palpation. **AND** • Absence of signs of local inflammation: erythema, pain on light palpation, warmth to the touch at the injection site **OR** • No improvement following a course of an antibiotic treatment. **In Summary** An injection site abscess is confirmed by a clinical diagnosis responding to the case definition.	Kohl K, et al. The Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Abscess at injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31): 5821–5838.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Foot positional deformations	• Metatarsus adductus characterised by medial deviation (adduction) of the forefoot while the hindfoot remains in a normal position, thus forming a "C" shape, or concavity of the medial aspect of the foot OR • Positional calcaneovalgus feet characterised by hyperdorsiflexion of the foot with the abduction of the forefoot, which often results in the forefoot resting on the anterior surface of the lower leg OR • Clubfoot characterised by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward.	

Annex 6 STUDY SPECIFIC GUIDANCE DOCUMENT

Screening tool for assessing serious delays in developmental milestones and/or physical disabilities in children from 3 months to 36 months of age

If the caregiver responds negatively to 2 or more questions, the child should be referred to a medical consultation for further investigations according to routine medical practice. All questions are to be responded by YES or NO.

A. Screening questions for caregiver of children aged 3-4 months

A1	Does your baby smile to familiar people?
A2	Has your baby begun to make sounds?
A3	Does your baby follow moving people or objects with eyes?
A4	Does your baby hold his head unsupported?
A5	Does your baby bring his hands to his mouth?

B. Screening questions for caregiver of children aged 5-9 months

B1	Does your baby grasp objects with both hands?
B2	Can your baby sit with support?
B3	Does your baby respond to sounds by making sounds?
B4	Does your baby know familiar faces and know if someone is a stranger?

C. Screening questions for caregiver of children aged 10-15 months

C1	Does your baby sit without support?
C2	Does your baby crawl on hands and knees?
C3	Does your baby take steps holding on to furniture, walls, etc?
C4	Does your baby try to imitate words and sounds and respond to simple requests?
C5	Does your baby show fear in some situations?

D. Screening questions for caregiver of children aged 16-21 months

D1	Does your child point to things?
D2	Does your child say several single words?
D3	Does your child walk without any help?
D4	Does your child use 4-10 different words?

E. Screening questions for caregiver of children aged 22-28 months

E1	Does your child copy others, especially adults and older children?
E2	Does your child say short sentences?
E3	Does your child follow simple instructions?
E4	Does your child run?
E5	Does your child scribble or draw?
E6	Does your child enjoy simple stories or songs?

F. Screening questions for caregiver of children aged 29-36 months

F1	Does your child walk, run, climb, and kick a ball easily?
F2	Does your child talk using 2 to 3 short sentences?
F3	Can your child say his name or age?
F4	Does your child understand what “two” means?
F5	Does your child feed himself?

Annex 7 AMENDMENTS TO THE PROTOCOL

GlaxoSmithKline Biologicals **Vaccine Value & Health Science (VVHS)** Protocol Amendment 1	
eTrack study number and Abbreviated Title	115055 (EPI-MALARIA 002 VS AME)
Amendment number:	Amendment 1
Amendment date:	22 October 2013
Co-ordinating author:	PPD (Contract Scientific Writer for GSK Biologicals)

Rationale/background for changes:

- In order to improve pharmacovigilance across projects in Africa, a cross-project review of Periodic Safety Update Reports (PSUR) was conducted and four diseases were identified: Intussusception, Kawasaki diseases, Henoch-Schonlein Purpura and Hypotonic Hyporesponsive Episode (HHE). This amendment serves to classify them as adverse events of specific interest (AESI) thereby ensuring diagnosis according to well defined case definitions.
- Meningitis of any etiology has been identified as a potential risk for RTS,S/AS01 in the Phase III trial Malaria-055. Therefore meningitis of any etiology has become an AESI for RTS,S/AS01 and will be closely monitored in clinical and epidemiological studies. Bacterial meningitis has been added as an AESI in addition to aseptic meningitis currently included as an AESI in this study.
- When a lumbar puncture is to be performed for evaluation of a neurological AESI an additional cerebrospinal fluid (CSF) sample will be taken for storage for potential further evaluation.

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

1. List of Abbreviations: AEFI, CSF, DNA, HHE, PCR, PSUR added;
2. Trademarks: Rotarix® trademark added;
3. Section 5.3.1. Protocol-defined diseases specified as adverse events of specific interest (AESI): addition of text on Bacterial Meningitis, Intussusception, Kawasaki diseases, Henoch-Schonlein Purpura and Hypotonic Hyporesponsive Episode [HHE];
4. Section 5.3.3 Case definition for malaria disease: more detailed definition for severe malaria disease added;
5. Section 5.4.2 Surveillance of adverse events: text added on collection of cerebrospinal fluid sample when neurological AESI are observed;
6. Section 5.4.3 Package for standard of care: small edits;

7. Section 5.7.1.11 Recording of cases of NC/NT-SAE, suspected AESI, malaria disease, abscess at injection site and foot positional deformations: new text on collection of cerebrospinal fluid sample when neurological AESI are observed;
8. Section 5.8.1 Biological samples: new text on collection of cerebrospinal fluid sample when neurological AESI are observed;
9. Section 5.8.2 Laboratory assays: small edits;
10. Section 10 References: Agnandji, Bines, Buettcher, Gardner-Medwin, Holman, Nakamura, Newburger and WHO 2013 references added;
11. Appendix A - CASE DEFINITIONS FOR PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIFIC INTEREST (AESI): new text added to table particularly for aseptic meningitis, bacterial meningitis, Henoch Schönlein purpura, intussusception, hypotonic hyporesponsive episode, and Kawasaki disease;
12. Appendix D - STUDY ACTIVITIES FLOWCHART DURING HOSPITALISATION: HOSPITALISED GROUP: small edits;
13. Appendix F - POTENTIAL FUTURE TESTING OF STORED SAMPLES: small edit.

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 2

eTrack study number and Abbreviated Title	115055 (EPI-MALARIA 002 VS AME)
Amendment number:	Amendment 2
Amendment date:	03 June 2014
Co-ordinating author:	PPD (Keyrus Biopharma consultant for GSK Biologicals)

Rationale/background for changes:

- The EPI-MAL-002 protocol will serve to collect baseline information necessary to prepare the PASS study EPI-MAL-003 that will start with the implementation of the RTS,S/AS01$_E$ vaccine in Sub-Saharan Africa.
- Although EPI-MAL-002 is not a targeted safety study the protocol has been formatted as a "PASS protocol", proposed by the new EMA pharmacovigilance guidance [European Medicines Agency, 2012], and is therefore in alignment with EPI-MAL-003.
- The EPI-MAL-003 protocol has been extensively reviewed within GSK Biologicals and with external regulatory agencies. For clarity, consistency and comparability in the objectives, endpoints and methodologies, text has been aligned in EPI-MAL-002 with the EPI-MAL-003 protocol.

The following table summarises significant changes made in Protocol amendment 2 (using the EMA "PASS protocol" template) compared to Protocol Amendment 1 (that used GSK protocol template INS-BIO-EPI-1000 v13.2), by Section number. Amended text has been included in *bold italics* and deleted text in strikethrough for study Title, Objectives and Endpoints.

Protocol Amendment 2: PASS Protocol Section	Amendment 1 Protocol Section (GSK template V13.2)	Summary of Changes
1. PROTOCOL INFORMATION	Title page	Revised
2. OPINION HOLDER	Title page	No change
3. RESPONSIBLE PARTIES	-	New section

Protocol Amendment 2: PASS Protocol Section	**Amendment 1 Protocol Section (GSK template V13.2)**	**Summary of Changes**
4. ABSTRACT	**SYNOPSIS**	
Title	**Detailed Title**	A~~n interventional epidemiology,~~ cohort event monitoring study to define ***the*** incidence ~~rates~~ of diseases specified as ***protocol-defined potential*** adverse events of specific interest (AESI) and ~~any other non-communicable and non-traumatic~~ serious adverse events (~~NC/NT-~~SAE) in infants and children in Africa prior to implementation of the RTS,S/AS01$_E$ candidate vaccine.
Rationale and background	**Rationale for the study**	Reworded to provide clarity in background and rationale in relation to the primary aims of the study.
Research question and objectives	**Objectives**	**Co-primary objectives:** ~~• To estimate the incidence of protocol-defined diseases specified as adverse events of specific interest (AESI) among children <3 years of age, prior to implementation of the RTS,S/AS01 candidate vaccine, overall, by body system and by each AESI.~~ ~~• To estimate the incidence of any other non-communicable and non-traumatic serious adverse event (NC/NT-SAE), with the exception of malnutrition, that requires hospitalisation among children <3 years of age.~~ • ***To estimate the incidence of protocol-defined potential adverse events of special interest (AESI), and other serious adverse events (SAE) leading to hospitalisation or death, in children <3 years of age, prior to implementation of RTS,S/AS01$_E$.*** • ***To estimate the incidence of confirmed meningitis (any aetiology), in children <3 years of age, prior to implementation of RTS,S/AS01$_E$.***
		Secondary objectives: ~~• To estimate the incidence of protocol-defined diseases specified as adverse events of specific interest (AESI) among children <3 years of age following immunisation, prior to implementation of the RTS,S/AS01 candidate vaccine, overall, by body system and by each AESI.~~ ~~• To assess if risk factors or health conditions can be associated with protocol-defined diseases specified as AESI, or any other NC/NT-SAE, among children <3 years of age.~~ ~~• To monitor serious morbidity, defined as requiring hospital admission, among children <3 years of age.~~ ~~• To estimate the prevalence of anaemia among hospitalised children <3 years of age prior to RTS,S/AS01 implementation.~~

Protocol Amendment 2: PASS Protocol Section	Amendment 1 Protocol Section (GSK template V13.2)	Summary of Changes
		~~• To monitor mortality by cause of death among children <3 years.~~ ~~• To estimate the incidence of confirmed malaria disease as diagnosed in health facilities among children <3 years of age, prior to implementation of the RTS,S/AS01 candidate vaccine.~~ ~~• To estimate the prevalence of serious disabilities (developmental retardation or chronic physical impairment) among children <3 years of age.~~ ***In children <3 years of age living in a geographically limited area with a health and demographic surveillance system (HDSS) in place, prior to implementation of RTS,S/AS01$_E$:*** • ***To monitor trends over time of meningitis (confirmed and suspected)*** • ***To estimate the incidence of meningitis (confirmed and suspected)*** • ***To estimate the incidence of febrile convulsion*** • ***To explore the association between determinants and the incidence of protocol-defined potential AESIs*** • ***To estimate the incidence of anaemia among hospitalised children*** • ***To estimate the incidence of episodes of malaria (including P. falciparum malaria) clinically diagnosed in health care facilities (uncomplicated and severe disease)*** • ***To describe the causes of hospitalisation (including protocol-defined potential AESI and malaria) and death*** • ***To monitor mortality by cause of death.***
Study design	**Study design**	Reworded
Population, including the setting and study population	-	Summary of information provided in Section 9.2 of protocol amendment 2.

Protocol Amendment 2: PASS Protocol Section	Amendment 1 Protocol Section (GSK template V13.2)	Summary of Changes
Variables	**Endpoints**	**Co-primary endpoints** In children <3 years old***, prior to implementation of RTS,S/AS01$_E$***: • Occurrence of protocol-defined ~~adverse event of specific interest (~~AESI~~)~~***:*** – ***Acute Disseminated Encephalo-Myelitis (ADEM), encephalitis, Guillain Barre Syndrome, Henoch-Schonlein purpura, juvenile chronic arthritis, diabetes mellitus Type I, thrombocytopenia, Kawasaki disease, intussusception*** – ***Anaphylaxis, Stephen-Johnson syndrome/toxic epidermal necrolysis*** – ***Hepatic or renal insufficiency*** – ***General convulsive seizure or hypotonic-hyporesponsive episode.*** • ~~Occurrence of any other non-communicable and non-traumatic serious adverse event (NC/NT-SAE) that requires hospitalisation~~ • ***Occurrence of serious adverse events leading to hospitalisation and death*** • ***Occurrence of confirmed meningitis (any aetiology).*** **Secondary endpoints** **In *children <3 years old, prior to implementation of RTS,S/AS01$_E$:*** • ***Occurrence of confirmed and suspected meningitis*** • ***Occurrence of febrile convulsions*** • ~~Demographic (age, gender, etc) and standard immunisations type and date administered.~~ • ~~Occurrence of risk factors in cases diagnosed with protocol-defined diseases specified as AESI, or any other NC/NT-SAE, that requires hospitalisation.~~ • ~~Occurrence of any serious adverse event that requires hospitalisation.~~ • Occurrence of anaemia ~~(see case definition section 5.3.3)~~ among hospitalised children; • Occurrence of ~~confirmed~~ ***clinical episodes of*** malaria ~~diseases as diagnosed in primary health facilities (subjects enrolled in EPI and Non-EPI schedule groups) and hospital (any enrolled subject).~~ – ***Uncomplicated and severe malaria (including P. falciparum malaria).***

Protocol Amendment 2: PASS Protocol Section	Amendment 1 Protocol Section (GSK template V13.2)	Summary of Changes
		• ~~Occurrence of developmental retardation or chronic physical impairment.~~ • ***Occurrence of hospitalisations*** – ***All causes and hospitalisations for malaria (including P. falciparum malaria).*** • Occurrence ~~and cause~~ of deaths ~~as defined by hospital diagnosis or verbal autopsy~~ – ***All causes and malaria attributed deaths (including P. falciparum malaria attributed death).*** • ***Occurrence of two events used as surveillance quality indicators: abscess at injection site and foot positional deformation.***
Data sources	-	Summary of information provided in Section 9.4 of protocol amendment 2.
Study size	**Number of subjects**	Reworded
Data analysis	-	Summary of information provided in Section 9.7 of protocol amendment 2.
Milestones	-	Summary of Section 6 of protocol amendment 2.
5. AMENDMENTS AND UPDATES	-	New section
6. MILESTONES	-	New section
7. BACKGROUND AND RATIONALE	**1. INTRODUCTION** **1.1 Background** **1.2 Rationale for the study**	Reworded and information/references updated.
8. RESEARCH QUESTION AND OBJECTIVES	**2. OBJECTIVES**	See Section 4. ABSTRACT/ Research question and objectives
9. RESEARCH METHODS	**3. Study design overview** **4. Study population** **5. Conduct of the study** **7. Data Evaluation: Criteria for Evaluation of Objectives** **8. Administrative matters**	Restructured and reworded sections.
10. PROTECTION OF HUMAN SUBJECTS	**5.1 Regulatory and ethical considerations, including the informed consent process**	Reworded.

Protocol Amendment 2: PASS Protocol Section	Amendment 1 Protocol Section (GSK template V13.2)	Summary of Changes
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	**6. SERIOUS ADVERSE EVENTS**	Reworded.
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	**8.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication**	Reworded.
13. REFERENCES	**10. REFERENCES**	Updated.
ANNEX 1 LIST OF STAND-ALONE DOCUMENTS	**-**	New Annex.
ANNEX 2 LIST OF PRINCIPAL AND COORDINATING INVESTIGATORS	**-**	New Annex.
ANNEX 3 GLOSSARY OF TERMS	**GLOSSARY OF TERMS**	Updated.
ANNEX 4 TRADEMARKS	**TRADEMARKS**	No change.
ANNEX 5 CASE DEFINITIONS FOR MENINGITIS	**-**	Meningitis case definitions separated from ANNEX 6. Case definitions revised.
ANNEX 6 CASE DEFINITIONS FOR PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIFIC INTEREST (AESI)	**Appendix A**	Case definitions revised.
ANNEX 7 DIAGNOSTIC TESTS FOR AESI	**-**	New ANNEX.
ANNEX 8 STUDY ACTIVITY FLOWCHART – PASSIVE SURVEILLANCE IN HEALTH CARE FACILITIES	**Appendix C**	No change.
ANNEX 9 STUDY SPECIFIC GUIDANCE DOCUMENT	**Appendix E**	No change.
ANNEX 10 POTENTIAL FUTURE TESTING OF STORED SAMPLES	**Appendix F**	No change.
ANNEX 11 AMENDMENTS TO THE PROTOCOL	**Appendix G**	Updated.

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment *3 &* 4

eTrack study number and Abbreviated Title	115055 (EPI-MALARIA 002 VS AME)
Amendment number:	***Amendment 3 &*** Amendment 4, Final
Amendment date:	***19 March 2015 &*** 11 December 2015
Co-ordinating author:	PPD (Keyrus Biopharma consultant for GSK Biologicals)

Rationale/background for changes:

Protocol Amendment 3 was published for inclusion in the RTS,S/AS01$_E$ Risk Management Plan (July 2015) knowing that the SAGE/MPAC recommendations were not yet issued.

This Protocol Amendment 4 describes changes to the protocol provided in Amendment 3 and includes the SAGE/MPAC recommendations. It will be submitted by the study investigators for review and approval by their local ECs before implementation.

Amendment 4 has been prepared for the following reasons:

- The background section has been updated with data about cerebral malaria from a post-hoc analysis of the Phase III study MALARIA-055.
- Additional secondary objectives have been added for estimation of probable meningitis and for estimation of the incidence of cerebral malaria using RDT and/or microscopy.
- The design and the analysis have been modified to take into account implementation of a 4th dose of RTS,S/AS01$_E$. In addition, the follow-up period after the last dose has been extended to correspond to the follow-up period of the children enrolled in EPI-MAL-003 (i.e. 24 months after the 4th dose of RTS,S/AS01$_E$). Indeed, home visits at 12 months and 24 months after the last RTS,S/AS01$_E$ dose will help to capture protocol-defined diseases that may have long risk window periods and that may not have been identified if the subject did not visit a health care facility, and to monitor the occurrence of malaria episodes for evaluation of vaccine effect. The age of the study population has been adapted accordingly (< 5 years).
- The section about sites participating to the study was updated following SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01$_E$ in 3–5 distinct settings in SSA restricted to moderate-to-high transmission of malaria.
- The activities related to home visits to detect malaria cases, including training of community health workers for systematic measurement of body temperature of all children, and availability of malaria tests have been clarified for alignment with the EPI-MAL-003 protocol.

- It has been clarified that cases of malaria only detected during the annual visits planned for EPI-MAL-005 will not be included in the analysis of EPI-MAL-002. However, if the cases of malaria are detected during an EPI-MAL-005 home visit that coincides with a home visit scheduled in EPI-MAL-002, the events will be captured in EPI-MAL-002.
- The case definitions for malaria have been revised, according to the 3rd edition of the WHO guidelines for the treatment of malaria (2015). In addition, a case definition for cerebral malaria has been added.
- Case ascertainment by the external panel of experts has been clarified.
- It has been clarified that severe/cerebral malaria cases and other AE leading to hospitalisation or death will be reviewed by the external panel of experts.
- The incidence of other AE leading to hospitalisation or death, meningitis and malaria morbidity and mortality will be monitored in sub-populations of children with hemoglobinopathies and HIV-positive children.
- The section about analysis of co-primary objectives has been revised to mention that additional at risk periods will be considered based on results as sensitivity analyses.
- The section about analysis of secondary objectives has been revised for clarification of potential variables that may be considered for models, in line with information collected in eCRF, and for estimation of the incidence of cerebral malaria.
- It has been clarified that an interim analysis will be performed with the data collected on all subjects after 6 months of follow-up following the administration of dose 3 of DTP/HepB/Hib vaccine (6-12 weeks group), or 6 months after V3 (5-17 months group).
- The section about handling of missing data has been revised.
- It has been clarified that data about seasonal malaria chemoprevention will be collected.

Other changes were made for simplification, clarification or consistency.

Amended text has been included in *bold italics* and deleted text in strikethrough.

Booster dose of RTS,S/AS01$_E$ has been replaced by 4th dose of RTS,S/AS01$_E$ throughout the document.

The age of 3 years has been replaced by the age of 5 years throughout the document.

Section 1 Title page

Research question and objectives:

- To estimate the incidence of adverse events of special interest, and of other adverse events leading to hospitalisation or death, in children ~~< 3 years of age~~, prior to implementation of RTS,S/AS01$_E$.
- To estimate the incidence of aetiology-confirmed meningitis, in children ~~<3 years of age~~, prior to implementation of RTS,S/AS01$_E$.

Countries of study: Reworded text – three countries selected (Burkina Faso, Ghana, and Kenya) and other countries in Sub-Saharan Africa might be added.

Authors: PPD added, Path representative is now PPD, PPD PPD (Clinical Laboratory Services) added and authors who did not work on amendment removed.

List of abbreviations: Added QS-21 ***Stimulon*** plus clarified meaning of abbreviation**,** ***Haemoglobin, MPAC, and SAGE***

Section 4 Abstract: Rationale and background: Reworded following positive opinion for the RTS,S/AS01E vaccine from European Medicines Agency and recommendations from WHO's SAGE and the MPAC.

Section 4 Abstract and Section 8: Research question and objectives

Co-primary objectives

- To estimate the incidence of AESI[4], and of other AE leading to hospitalisation or death, in children ~~<3 years of age~~, prior to implementation of RTS,S/AS01$_E$.
- To estimate the incidence of aetiology-confirmed meningitis, in children ~~<3 years of age~~, prior to implementation of RTS,S/AS01$_E$.

Secondary objectives

In children ~~<3 years of age~~ living in a geographically limited area with a health and demographic surveillance system (HDSS) in place, prior to implementation of RTS,S/AS01$_E$:

- ***To estimate the incidence of probable meningitis (final classification).***
- To estimate the incidence of any ~~malaria and severe~~ malaria (including *P. falciparum* malaria) ~~diagnosed by~~ ***using*** rapid diagnostic test (RDT) and/or microscopy.

[4] Acute disseminated encephalomyelitis, encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode, ~~***general***~~ ***generalised*** convulsive seizure.
Intussusception, hepatic failure, renal insufficiency.
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease.
Diabetes mellitus type I, thrombocytopenia, anaphylaxis.

- ***To estimate the incidence of severe malaria (including P. falciparum malaria) using RDT and/or microscopy.***
- ***To estimate the incidence of cerebral malaria using RDT and/or microscopy.***

Section 4 Abstract: Study design: Reworded with information on active surveillance.

Section 4 Abstract: Population, including the setting and study population: Age of children and number of sites in different countries clarified.

Section 4 Abstract: Variables, Section 9.3.1 Co-primary endpoints, and Section 9.3.2 Secondary endpoints

Co-primary endpoints

In children ~~<3 years old,~~ included in active or enhanced hospitalisation surveillance, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of AESI.

Secondary endpoints

In children ~~<3 years old,~~ included in active or enhanced hospitalisation surveillance, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of probable meningitis (final classification).

In children ~~<3 years old,~~ included in active surveillance, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of episodes of malaria ~~diagnosed by~~ ***using*** RDT and/or microscopy
  - ***Any malaria*** ~~and severe malaria~~ ***(including P. falciparum malaria).***
  - ***Severe malaria (including P. falciparum malaria).***
  - ***Cerebral malaria.***
- Occurrence of hospitalisation
  - All causes and hospitalisations for ~~severe~~ malaria (including *P. falciparum* malaria).

Section 4 Abstract: Data sources: new wording on subjects actively participating in other trials.

Section 4 Abstract: Study size: Reworded.

Section 4 Abstract: Milestones: Updated with current dates / planned dates.

Section 7.1 Background: Updated after EMA positive opinion for the RTS,S/AS01$_E$ vaccine, and recommendations about RTS,S/AS01$_E$ issued by WHO's SAGE and MPAC. The study protocol has been adapted to take into account implementation of a 4th dose of RTS,S/AS01$_E$ 18 months after the 3rd dose.

Section 7.2. Safety results of the clinical development of RTS,S/AS01$_E$: Updated with details of 4th vaccine dose and new text describing key safety e.g. cerebral malaria results from the Phase III MALARIA-055 study.

Section 7.3 Efficacy results of the clinical development of RTS,S/AS01$_E$:Updated with details of 4th vaccine dose.

Section 7.4. Rationale for the study: EPI-MAL-002 was re-classified as a pre-implementation study rather than pre-authorisation study; EPI-MAL-003 was re-classified as a post-implementation study rather than post-authorisation study.

Section 8.2 Secondary Objectives: Same edits are shown above for Section 1 Abstract: Secondary objectives.

Section 9.1. Study design: New text describes usual dosing schedule for DTP/HepB/Hib vaccine, further details of the follow-up period and potential early study conclusion visit for EPI-MAL-002 subjects who meet eligibility criteria for EPI-MAL-003 study. Updates to the footnotes for Figure 1, for children in the 6-12 weeks age group and 5-17 months age group.

Section 9.1.1 Rationale for the study design: Edits to the 1st paragraph on target population and new text on analyses for any malaria, severe malaria and cerebral malaria by plasmodium species. In active surveillance sub-section: more details on home based visits in relation to vaccine doses.

Section 9.2. Setting: New details on use of INDEPTH procedures for demographic census and SAGE/MPAC pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria.

Section 9.2.1. Study population: Updates specifying a Safety Post Approval Program Partnership Committee meeting involving study site investigators in main text and Table 2 footnote. Table 2 updated with latest estimates. Low malaria transmissions sites not pursued. Potential addition of moderate-to-high malaria transmission sites, or increased enrolment at current sites.

Section 9.2.1.1. Participant recruitment: Details of dosing schedule for DTP/HepB/Hib vaccine.

Section 9.2.4 Elimination criteria during the study: Text deleted.

Section 9.2.4 Study period: Details of active surveillance for each subject and the potential early study conclusion for subjects enrolled in EPI-MAL-002 if they meet the eligibility criteria for EPI-MAL-003 study enrolment.

Section 9.2.5.1 Case definition: AESI: In Table 3, per 100,000/year, and /100,000 per year has been replaced by /100,000 PY.

Section 9.2.5.2 Case definition: Hospitalisations for an AE other than an AESI, meningitis or severe malaria (including cerebral malaria): Added text on meningitis and severe malaria.

Section 9.2.5.5 Case definition: Malaria: Updated text for severe falciparum malaria, and new text for severe vivax malaria and cerebral malaria.

Section 9.2.5.7 Hospitalisation case definition: Small update.

Section 9.2.5.8 Deaths: INDEPTH procedures for verbal autopsy will be implemented to ensure consistency across study sites.

Section 9.2.6.2 Case definition for foot positional deformations: Small update.

Section 9.2.7.1 Study procedures for active surveillance: Updates concerning study visits.

Section 9.2.7.1 .4 Collect demographic data: Small update.

Section 9.2.7.1.5 Health history: Record brief medical history and physical exam at Visit 1.

Section 9.2.7.1.6 Check and record vaccinations: Small update.

Section 9.2.7.1.7 Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards: Rewritten.

Section 9.2.7.1.9 Physical examination, record of signs and symptoms, record any serious delay in developmental milestones or physical disability: New text describing role of community workers.

Section 9.2.7.1.10 Refer sick children or children with disabilities to outpatient clinic or hospital: Reworded.

Section 9.2.7.1.11 Record cases of death: INDEPTH procedures for verbal autopsy will be implemented.

Section 9.2.7.1.12 Study conclusion: Small update.

Section 9.2.7.1.13 Outline of study procedures: Table and footnotes 1, 5 and 6 updated.

Section 9.2.7.2.1 Informed consent (for subjects not enrolled previously, i.e. for previous hospitalisation or for active surveillance): Small update.

Section 9.2.7.2.3 Assign subject study number (for subjects not enrolled previously): Reworded.

Section 9.2.7.2.7 Health history: Reworded.

Section 9.2.7.2.8 Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards: Rewritten.

Section 9.2.7.2.9 Record standard vaccinations: Small update.

Section 9.2.7.2.11 Record haemoglobin measurement: Small update.

Section 9.2.7.2.13 Record cases of suspected AESI, other AE leading to hospitalisation or death, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations: New wording on children diagnosed with meningitis, cerebral malaria or with an AESI.

Section 9.2.7.2.15 Study conclusion: Small update.

Section 9.2.7.2.16 Outline of study procedures: Table 5 updates.

Section 9.2.7.3.1 Biological samples: Small updates.

Section 9.2.7.3.2 Laboratory assays: New paragraph on consumables and reagents being provided to perform first line routine testing for all diseases under investigation.

Section 9.2.7.4.1 Case ascertainment for meningitis: Meningitis case characterization: Small update.

Final meningitis case ascertainment: Details on panel of experts.

Additional follow-up of meningitis cases: Small update.

Section 9.2.7.4.2 Case ascertainment for AESI: Doubtful diagnosis and outcome changed to uncertain diagnosis and outcome, and other updates concerning GSK safety physician review and external expert review.

Section 9.2.7.4.4 Case ascertainment for other AE leading to hospitalisation or death: Doubtful diagnosis and outcome changed to uncertain diagnosis and outcome, and other updates concerning GSK safety physician review and external expert review.

Section 9.2.7.4.5 Case ascertainment for malaria: Definition for cerebral malaria cases added together with details of GSK safety physician review and review by two selected experts.

Section 9.2.7.6 Capacity building: Details of training packages for site staff.

Section 9.3.3.1 *Recorded in* EPI-MAL-002 and EPI-MAL-003: Reworded.

Section 9.3.3.2 *Recorded in* EPI-MAL-005: Reworded.

Section 9.4.1 Health Demographic Surveillance System: Small updates.

Section 9.4.2 Active surveillance and *enhanced hospitalisation surveillance of study EPI-MAL-002:* New first paragraph plus other updates.

Section 9.4.3 ~~Malaria Transmission Intensity~~ Study EPI-MAL-005: Details of enrolling subjects in EPI-MAL-002 and EPI-MAL-005 studies plus other small updates.

Section 9.5 Study size: Updated text.

Section 9.7 Data analysis: Text on descriptive analysis of safety endpoints.

Section 9.7.4.1 Sequence of analyses: Details of interim analysis added.

Section 9.7.5.1 Analysis population: Small update.

Section 9.7.5.2.1 Incidence of AESI, and other AE leading to hospitalisation or death: Small updates.

Section 9.7.5.2.2 Incidence rate of aetiology-confirmed meningitis: Small updates.

Section 9.7.6.2 Statistical approach: Updates to text.

Section 9.7.7 Analysis for other secondary objectives: Small updates.

Section 9.7.7.1 Analysis population: New text on Main and Complementary analyses.

Section 9.7.7.2 Statistical approach: Updates including updates to Table 8.

Section 9.7.8.1 Handling of missing data: Details of a sensitivity analysis added.

Section 9.8.2 Archiving of data at study sites: Small update.

Section 9.9 Limitations of the research methods: Updates included length of follow-up, malaria transmission intensity for sites and the interim analysis.

Section 10.1 Regulatory and ethical considerations, including the informed consent process: Small update.

Section 12 Plans for disseminating and communicating study results: Details on the interim report added.

Section 13 References: Added both European Medicines Agency references plus, Rubin, Sterne, The RTS,S Clinical Trials Partnership, WHO - Global malaria programme, WHO - Management of severe malaria, and WHO - Background brief: malaria vaccine RTS,S/AS01 references, removed the GlaxoSmithKline study report reference, and made updates to other references e.g. updating date last accessed.

Annex 4 TRADEMARKS

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Stimulon® (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)	***Triterpene glycoside immune enhancer***

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 5

eTrack study number and Abbreviated Title	115055 (EPI-MALARIA 002 VS AME)
Amendment number:	Amendment 5
Amendment date:	11 October 2017
Co-ordinating authors:	PPD (GSK Biologicals) PPD ***, Lead Scientific Writer (GSK Biologicals)***

Rationale/background for changes:

Protocol Amendment 5 describes the sample size reduction from 40,000 to 30,000 with a resultant reduction in the size of the two study groups to 15,000 subjects each.

Amendment 5 has been prepared for the following reasons:

- In order to have a synergy with the WHO pilot implementation, the study size was reduced from 40,000 to 30,000 children in active surveillance with at least 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Among the 30,000 children, approximately 15,000 children (with at least 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 6-12 weeks group (to collect background data in this age group) and approximately 15,000 children (with at least 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 5-17 months group (to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group). Study size updates involved multiple sections, e.g. Section 9.1 Study Design and Section 9.5 Study size.
- For multiple sections: the number of countries and number of study sites has been updated following the WHO announcement that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP.
- For multiple sections: estimation of the mortality rate, overall and by gender, has been added.
- For multiple sections: the informed consent process has been clarified “signed or witnessed and thumbprinted ICF”.
- For multiple sections: “or equivalent surveillance system” has been added after HDSS; and the term “study site(s)” or “study area” has been added.
- For multiple sections: the replacement strategy has been updated.
- For multiple sections: the duration of the recruitment period has been removed, as it could/can not be respected in all sites due to logistical constraints.
- For multiple sections: it was clarified that census rounds are scheduled at least once a year during the study periods instead of twice a year.

- The milestones in Section 6 have been updated.
- New sub-sections on “Severe malaria including cerebral malaria” and “Overall mortality by gender” have been added to Section 7.2 Safety results of the clinical development of RTS,S/AS01$_E$.
- The wording of “secondary objectives” on “describe the causes of hospitalisation” and “estimate the incidence of cerebral malaria” has been changed, and the secondary objective “To describe the causes of death, overall and by gender” has been added in Section 8.2 and in the corresponding part of Section 4 Abstract.
- The opening paragraph of Section 8.2 Secondary Objectives and of the corresponding part of Section 4 Abstract has been updated.
- The wording of the last two “study variables” / “study endpoints” on “Occurrence of hospitalisations” and “Occurrence of death” has been modified in Section 9.3.2 and in the corresponding part of Section 4 Abstract.
- In Section 9.2.1 Study population: the text on “Estimated annual birth cohorts by study site” (Table 2) has been removed, with removal of planned number of sites in selected countries.
- Section 9.2.5.3 Meningitis has been edited, including addition of a new opening paragraph, addition of “turbid macroscopic aspect” as a sign of CSF abnormality, and clarification that clinically suspected meningitis cases included subjects with no CSF sample available and no alternative diagnosis.
- For consistency between the way the objectives and the endpoints are presented, and to avoid repeating several endpoints, the two sub-sections in Section 9.3.2 Secondary endpoints: "In children included in active or enhanced hospitalisation surveillance, prior to implementation of RTS,S/AS01$_E$" and “In children included in active surveillance, prior to implementation of RTS,S/AS01$_E$” have been replaced by one sub-section: “In children living in the study area, prior to implementation of RTS,S/AS01$_E$”, followed by all the secondary endpoints.
- In Section 9.4.3 Study EPI-MAL-005 “changes in environmental factors such as rainfall” has been added to the parameters assessed in EPI-MAL-005.
- Section 9.5 Study size has been updated as shown in bullet 1 above with greater detail on the estimates of observed incidence of events following dose administration based on either: 15,000 subjects, 10,000 subjects, the estimated birth cohort of 11,500 subjects and an estimated birth cohort of 17,250 children in Tables 6-9.
- Section 9.7.6 Analysis of secondary safety objectives has been updated, including analysis of cerebral malaria of the causes of death, overall and by gender.
- Finally, changes in study personnel have been included on the protocol cover page.

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

1. **Cover page - Countries of study:** The number of countries and number of study sites has been updated following the WHO announcement that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through ~~WHO-coordinated pilot implementation programme~~ ***the MVIP***.

2. **Cover page - Authors:** PPD has been added as coordinating author. PPD, PPD, PPD, PPD ***and*** PPD have been added as main authors. PPD, PPD, PPD ***, and*** PPD have been added as other GSK contributing authors. Names of chair and co-chairs of the Safety Post Approval Program Partnership Committee have been removed as they change every year. Other non-GSK Biologicals partners have been updated as follows: PATH (represented by PPD, Seattle, United States of America) and Quintiles (represented by PPD, Project Manager). Training activities have been transferred from AMP Services to AMP Regional Office for Africa due to bankruptcy of AMP Services. Therefore ~~Agence de Médecine Préventive (AMP) (represented by PPD, Paris, France)~~ has been replaced by ***Agence de Médecine Préventive (AMP) Regional Office for Africa (represented by Dr.*** PPD PPD ***, Abidjan, Ivory Coast)***. Considering EpiConcept ***did not update their IT standard as required per IT audit and conditional to the contract signature,*** was not performant and didn't solve technical issues in due time, GSK study team has decided to early terminate the collaboration with EpiConcept. Parexel has been selected to provide similar services. Therefore ~~EpiConcept (represented by PPD PPD Paris, France)~~ has been replaced by ***Parexel (represented by*** PPD ***, Senior Project Manager)***.

3. **Section 2 Opinion Holder:** ~~**Copyright**~~ **© 2012-2017 GSK group of companies or its licensor.** ~~**of the GlaxoSmithKline group of companies. All rights reserved. Unauthorised copying or use of this information is prohibited.**~~

4. **List of Abbreviations**: ***CLS, DTP, DTP-HepB, MTI, MVIP, PT, RMP and SOC*** abbreviations have been added. ~~Hb~~ and ~~NRA~~ abbreviations have been removed.

5. **Section 3 Responsible Parties:** Names and titles of PPD ***, Senior Epidemiology Lead – Malaria*** and PPD ***, Epidemiology Lead – Malaria*** have been added. Name of PPD has been removed.

6. **Section 4 Abstract:** Names and titles of PPD ***, Senior Epidemiology Lead – Malaria*** and PPD ***, Epidemiology Lead – Malaria*** have been added. Name of PPD has been removed.

   Section 4 Abstract (continued): Edits for the "Rationale and background" section. Addition of the WHO announcement that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through a ~~WHO-coordinated pilot implementation programme~~ ***the MVIP***. Estimation of the mortality rate, overall and by gender, has been added.

   Section 4 Abstract (continued): Edits to opening paragraph of "Secondary objectives" and to bullet points:

In children living in ~~a geographically limited area with a health and demographic surveillance system (HDSS) in place~~ ***the study area***, prior to implementation of RTS,S/AS01$_E$:

- To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria)~~ and death~~.
- ***To describe the causes of death, overall and by gender.***
- To estimate the incidence of cerebral malaria ***(malaria diagnosed by*** ~~using~~ RDT and/or microscopy***)***.
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*])***, overall and by gender***.

Section 4 Abstract (continued): For the "Study design" section, new wording for bullet point 3 and edits for bullet point 5 which are provided below

– The study targets enrolling ~~40,000~~***30,000*** children in active surveillance***, with at least 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented***. Among the ~~40,000~~***30,000*** children, approximately ~~20,000~~***15,000*** children (***with at least 10,000 children in sites where the vaccine will be implemented***) will be enrolled in the 6-12 weeks group (to collect background data in this age group) ***and*** approximately ~~20,000~~***15,000*** children (***with at least 10,000 children in sites where the vaccine will be implemented***) will be enrolled in the 5-17 months group (to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group).

– The diseases under surveillance for safety include AESI, other AE leading to hospitalisation or death, and meningitis, and will be monitored among children enrolled in active surveillance and in enhanced hospitalisation surveillance. ***To estimate vaccine*** ~~For~~ impact, several measures of malaria burden will be monitored among children in the active surveillance. ***The mortality rate, overall and by gender, will also be estimated.***

Section 4 Abstract (continued): For the section on "Population, including the setting and study population", inclusion of "or equivalent surveillance system" after HDSS ~~and removal of text on specific sites in specific countries~~. In addition, the number of countries and number of study sites have been updated following the WHO announcement that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through ~~a WHO-coordinated pilot implementation programme~~ ***the MVIP***.

Section 4 Abstract (continued): For the "Variables" section, edits to opening paragraphs and to the bullet points as shown below:

Co-primary endpoints

In children ~~included in active or enhanced hospitalisation surveillance~~ ***living in the study area***, prior to implementation of RTS,S/AS01$_E$:

Secondary endpoints

In children ~~included in active or enhanced hospitalisation surveillance~~ ***living in the study area***, prior to implementation of RTS,S/AS01$_E$:

~~In children included in active surveillance, prior to implementation of RTS,S/AS01$_E$:~~

- Occurrence of hospitalisation
  - All causes and hospitalisations for ***any*** malaria (including *P. falciparum* malaria)**,** ***severe malaria (including P. falciparum malaria) and cerebral malaria***.
- Occurrence of death
  - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death).
    - ***AE attributed deaths.***

Section 4 Abstract (continued): Small edits for the "Data Sources" section.

Section 4 Abstract (continued): The "Study size" section was updated as shown below:

The ~~enrolment is fixed to~~ ***study targets enrolling*** ~~20,000~~***15,000*** children per group (i.e. 6-12 weeks group and 5-17 months group***; with at least 10,000 children of 15,000 in each group enrolled where the RTS,S/AS01$_E$ vaccine will be implemented***), for a total of ~~40,000~~***30,000*** children ***(at least 20,000 children enrolled where the vaccine will be implemented)***. For some of the AESI the incidence could be very rare (around 1/100,000 person years [PY]) and the period at-risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis. The 95% confidence interval (CI) around an observed incidence of ~~17.7~~***25.2*** per 100,000 PY (corresponding to 1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], based on ~~20,000~~ ***10,000*** subjects) will be [~~0.4~~***0.6,*** ~~98.8~~***140.2***].

Section 4 Abstract (continued): Small edits for the "Data analysis" section as shown below:

The incidence rate of aetiology-confirmed meningitis ***and of cerebral malaria*** will be computed with 95% CI using the same approach as described above.

Section 4 Abstract (continued): Small edits for the "Milestones" section as shown below:

The study started in Q4 2015, and is planned to end in ***Q2 2022*** ~~Q4 2020~~ (tentative date, depending on recruitment timelines).

7. **Section 5 Amendments and Updates:** Details for Protocol Amendment 4 added.
8. **Section 6 Milestones:** Planned dates for end of data collection and final report of study results have been updated.

End of data collection	***Q2 2022*** ~~Q4 2020~~**
Final report of study results	***Q4 2022*** ~~Q2 2021~~**

9. **Section 7.1 Background:** Small edits. Addition of the WHO announcement that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through ~~a WHO-coordinated pilot implementation programme~~ ***the MVIP***.

10. **Section 7.2 Safety results of the clinical development of RTS,S/AS01$_E$:** General text on SAEs reports moved up to the start of the section; new sub-section titles added; new sections on "Severe malaria including cerebral malaria" including Table 2 and "Overall mortality by gender" added; concluding summary updated; and other updates made to the text including updates to Table 1.
11. **Section 8.2 Secondary objectives:** Updates to text for opening paragraph and to bullet points as in the abstract.
12. **Section 9.1 Study design:** Updates to text on number of subjects recruited as for the abstract; modified paragraph on possible overlap between EPI-MAL-002 and EPI-MAL-003. Addition of sentence about estimation of mortality rate, overall and by gender.
13. **Section 9.1.1 Rationale for the study design:** Updates to text on number of subjects recruited as for the abstract; and other edits e.g. adding "or equivalent surveillance system" after HDSS. Addition of sentence about estimation of mortality rate, overall and by gender. Clarification of participant recruitment for enhanced hospitalisation surveillance.
14. **Section 9.2 Setting:** Edits including adding "or equivalent surveillance system" after HDSS or adding the term "study sites". Clarification that census rounds are scheduled at least ~~twice~~ ***once*** a year during the study periods. Addition of new information about countries and sites that have started, or will start, enrolment, following the WHO announcement in April 2017 that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through ~~a WHO-coordinated pilot implementation programme~~ ***the MVIP***. Replacement strategy updated.
15. **Section 9.2.1 Study population:** Updates to text on number of subjects recruited as for the abstract. Removal of text on "Estimated annual birth cohorts by study site" (Table 2) with removal of planned number of sites in selected countries.
16. **Section 9.2.1.1 Participant recruitment**: Edits including adding "or equivalent surveillance system" after HDSS or adding the term "study area". Figures for expected number of children recruited updated. Clarification that written or witnessed ***and*** thumbprinted informed consent must be obtained. Duration of the recruitment period removed, as it could/can not be respected in all sites due to logistical constraints. Clarification of participant recruitment for enhanced hospitalisation surveillance.
17. **Section 9.2.2 Inclusion criteria for enrolment:** Inclusion criteria of enrolment: Edits including adding "or equivalent surveillance system" after HDSS.
18. **Section 9.2.4 Study period**: First paragraph about enrolment period and last paragraph about overlap of study EPI-MAL-002 and study EPI-MAL-003 edited. Duration of the recruitment period removed, as it could/can not be respected in all sites due to logistical constraints.
19. **Section 9.2.5.1 AESI:** Minor edits.

20. **Section 9.2.5.2 Hospitalisations for an AE other an AESI, meningitis, *any malaria* or severe malaria (including cerebral malaria)**: Addition of "any malaria" to the sentence.
21. **Section 9.2.5.3 Meningitis:** Edits including adding new opening paragraph, adding "turbid macroscopic aspect" as a sign of CSF abnormality, and clarifying that clinically suspected meningitis cases included subjects with no CSF sample available and no alternative diagnosis.
22. **Section 9.2.5.8 Deaths:** Edits including new paragraph at end of section explaining that malaria-attributed deaths with an uncertain diagnosis and outcome after review by the GSK safety physician would be reviewed by an expert panel, to confirm primary/secondary cause of death.
23. **Section 9.2.7.1 Active surveillance:** Edits including adding "or equivalent surveillance system" after HDSS, including the term "study area", and text to clarify exactly which children would be recruited.
24. **Section 9.2.7.1.1 Informed consent:** Clarification that written or witnessed ***and*** thumbprinted informed consent must be obtained.
25. **Section 9.2.7.1.9 Physical examination, record of signs and symptoms, record any serious delay in developmental milestones or physical disability:** Minor edits.
26. **Section 9.2.7.1.11 Record cases of death:** Minor edits.
27. **Section 9.2.7.1.12. Study conclusion**: Last paragraph about overlap of study EPI-MAL-002 and study EPI-MAL-003 edited.
28. **Section 9.2.7.1.13 Outline of study procedures:** Minor edit.
29. **Section 9.2.7.2 Enhanced hospitalisation surveillance:** Minor edit.
30. **Section 9.2.7.2.1 Informed consent:** Clarification that written or witnessed ***and*** thumbprinted informed consent must be obtained.
31. **Section 9.2.7.2.3 Assign subject study number (for subjects not enrolled previously):** Second paragraph edited.
32. **Section 9.2.7.2.11 Record haemoglobin measurement:** Minor edit.
33. **Section 9.2.7.2.16 Outline of study procedures:** Edits to several rows of Table:

Provide study ID card (to all subjects not enrolled previously) and study-specific stickers (only to subjects ***identified before 1st DTP or aged 5 to*** <18 months not enrolled previously and enrolled before the active surveillance recruitment is terminated)	○	
For each diagnosis of an AESI~~, cerebral malaria~~ or meningitis, collect approx. 5 mL of whole blood and store serum [5]	●	
For each diagnosis of a neurological AESI~~, cerebral malaria~~ or meningitis, where a CSF sample has been taken as part of routine practice, store part of the CSF sample (minimum 500 µL)[5]	●	

34. **Section 9.2.7.3.1. Biological samples:** Small edits.
35. **Section 9.2.7.3.2. Laboratory assays:** Small edits including adding CLS abbreviation for Clinical Laboratory Services.

36. **Section 9.2.7.4.1. Case ascertainment for meningitis:** Edits for Meningitis case characterisation subsection.

37. **Section 9.2.7.4.3. Children suspected of having a serious adverse event (SAE):** New cross-reference to Section 11 added.

38. **Section 9.2.7.4.5. Case ascertainment for malaria:** Addition of the following paragraph: ***Children diagnosed with cerebral malaria will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.***

39. **Section 9.2.7.6. Capacity building:** Edits including using terms "study area", study ~~team~~ ***staff***, community ***health*** worker, and "routine practice" and adding new paragraph on laboratory tests performed by CLS.

40. **Section 9.3.1 Primary endpoints:** Edits to opening paragraph as shown below:

    In children ~~included in active or enhanced hospitalisation surveillance~~ ***living in the study area***, prior to implementation of RTS,S/AS01$_E$:

41. **Section 9.3.2 Secondary endpoints:** Edits to opening paragraphs and to the bullet points as shown below:

    In children ~~included in active or enhanced hospitalisation surveillance~~ ***living in the study area***, prior to implementation of RTS,S/AS01$_E$:

    ~~In children included in active surveillance, prior to implementation of RTS,S/AS01$_E$:~~

    - Occurrence of hospitalisation
      - All causes and hospitalisations for ***any*** malaria (including *P. falciparum* malaria) ***severe malaria (including P. falciparum malaria) and cerebral malaria*** (see ***and cerebral malaria*** (see Section 9.2.5.7 for case definitions).
    - Occurrence of death
      - ***AE attributed deaths (see Section 9.2.5.8 for case definitions).***

42. **Section 9.3.3.1. Recorded in EPI-MAL-002 and EPI-MAL-003:** Added "study area". Clarification that if any of the sources described here above confirm vaccination, it will be assumed that vaccination has taken place ***for the analysis***.

43. **Section 9.3.3.2. Recorded in EPI-MAL-005:** Added "or equivalent surveillance system" after HDSS and the terms "study area" and "malaria transmission intensity" (MTI).

44. **Section 9.4.1. Health Demographic Surveillance System (or equivalent surveillance system):** Clarification that census rounds are scheduled at least ~~twice~~ ***once*** a year during the study periods. Edits including adding "or equivalent surveillance system" after HDSS and the terms "study site / study sites". Last paragraph updated.

45. **Section 9.4.2. Active surveillance and enhanced hospitalisation surveillance of study EPI-MAL-002:** Added "or equivalent surveillance system" after HDSS.

Clarification that signed ***or witnessed and*** thumbprinted informed consent shall be obtained. Last paragraph updated.

46. **Section 9.4.3 Study EPI-MAL-005:** Addition of "changes in environmental factors such as rainfall" to the parameters assessed in EPI-MAL-005.
47. **Section 9.5 Study size:** Updates to this section as shown for Section 4 Abstract with greater detail on the estimates of observed incidence of events following dose administration based on either: 15,000 subjects, 10,000 subjects, the estimated birth cohort of 11,500 subjects and an estimated birth cohort of 17,250 children in Tables 6-9.
48. **Section 9.7 Data analysis:** Text updated with new sample size numbers.
49. **9.7.1 Total cohort:** Clarification that written ***or witnessed and*** thumbprinted informed consent must be obtained.
50. **Section 9.7.5.2.1 Incidence of AESI, and other AE leading to hospitalisation or death:** Two edits related to vaccination.
51. **Section 9.7.6.2 Statistical approach:** New bullet point added (bullet point 3 about incidence of cerebral malaria), new text added to bullet points 4 and 5, and one short paragraph on the categorisation of covariates removed.
52. **Section 9.7.7.1 Analysis population:** New text added to the first paragraph and further edits to put the emphasis on the main analysis and additional analyses rather than main and complementary analyses.
53. **Section 9.7.7.2 Statistical approach:** New wording for first paragraph and in Table 10 - new text for rows 8 and 9.
54. **Section 9.7.8.1 Handling of missing data:** New text for paragraph 3.
55. **Section 9.9 Limitations of the research methods:** Edits including new paragraph on the content of protocol amendment 5, updated paragraph about countries/sites and number of children to be enrolled, adding "or equivalent surveillance system" after HDSS, providing new figures for the number of subjects recruited, and including the term "study area(s)". Clarification that demographic census is scheduled at least ~~twice~~ ***once*** a year during the study periods. Duration of the recruitment period removed, as it could/can not be respected in all sites due to logistical constraints.
56. **Section 10.1 Regulatory and ethical considerations, including the informed consent process:** Clarification that written or witnessed ***and*** thumbprinted informed consent must be obtained.
57. **Section 11 Management and reporting of serious adverse events related to study procedures:** Minor edit.
58. **Section 11.3.3. Completion and transmission of SAE reports to GSK Biologicals:** New second paragraph added.
59. **Section 13 References:** ***Hair 1995, Rosillon 2015, Ulm 1990, United Nations 2011, WHO 2016(a), WHO 2016(b), WHO 2017*** references added. WHO, 2015(a), ISPE ***2015 and The Uppsala Monitoring Centre, 2011*** references updated. ~~Bines 2004~~ and ~~Newburger 2004~~ references removed.

60. **Annex 3 Glossary of Terms:** Added DTP/HepB/Hib.

61. **Annex 4 Trademarks:** Removed Stimulon® (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
    Triterpene glycoside immune enhancer

    Added: ***Mosquirix ™: Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)***

62. **Annex 6 Recruitment scheme ratio 1-1 (6-12 weeks group - 5-17 months group):** Figure removed, as the duration of the recruitment period could/can not be respected in all sites due to logistical constraints.

63. **Annex 7 Study specific guidance document:** Title updated: Screening tool for assessing serious delays in developmental milestones and/or physical disabilities in children ~~less than 3 years of age~~ ***from 3 months to 36 months of age***. Sentence updated: If the caregiver responds negatively to 2 or more questions, the child should be referred to a medical consultation for further investigations ***according to routine medical practice***.

GlaxoSmithKline Biologicals	
Vaccine Value & Health Science (VVHS)	
Protocol Amendment 6	
eTrack study number and Abbreviated Title	115055 (EPI-MALARIA 002 VS AME)
Amendment number:	Amendment 6
Amendment date:	06 July 2018
Co-ordinating authors:	PPD, Lead Scientific Writer (GSK Biologicals)

Rationale/background for changes:

Protocol Amendment 6 has been put in place to document that the EPI-MAL-002 study sites in Burkina Faso will early terminate the study and that sites in Malawi, one of the country where RTS,S/AS01$_E$ will be introduced through the MVIP will not take part in the study.

GSK, in agreement with WHO, decided to terminate the study EPI-MAL-002 in the two sites located in Burkina Faso, i.e. Nouna and Sapone. Briefly, it was previously decided that Burkina Faso sites would continue participating in EPI-MAL-002 until study end. However, given that the MVIP will not be conducted in this country, there is no scientific value to collect additional data (the EPI-MAL-002 data collected in Burkina Faso will neither be used for the before-after analyses, nor for the generation of EPI-MAL-002 indicators that inform any other analyses of the EPI-MAL-003 study). Therefore, the study EPI-MAL-002 in Burkina Faso sites has been early terminated and data collected and recorded to date in those sites will be reported in a descriptive way.

In order to align with the MVIP, the study sites for the GSK Phase IV studies have been selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented (Ghana, Kenya and Malawi). Considering the RTS,S/AS01E vaccine implementation date in Malawi currently planned in October 2018, the baseline data that might be collected in Malawi in the EPI-MAL-002 study would be too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment observed from sites in Kenya (Kombewa) and Ghana (Kintampo) and extending recruitment in Ghana (Navrongo), hence limiting the impact on the before/after comparison study power.

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

1. **Cover page - Countries of study:** Sites in sub-Saharan Africa (SSA) countries have been ~~or will be~~ selected for EPI-MAL-002 based on

   In order to align with the MVIP, the study sites for the GSK Phase IV studies have been, or will be, selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented ~~(i.e. two sites in Malawi are planned to be included in EPI-MAL-002 in addition to the already defined sites)~~. ***As a consequence,*** ~~The only exception is for~~ Burkina Faso sites, ***that*** ~~as they have~~ ***had*** already started EPI-MAL-002, ***early terminated the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance since 06 June 2018, with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI. All study activities are planned to be terminated by Q2 2019. A description of data from these sites will be presented in the progress reports up to Q4 2019, but none of these data will be part of the statistical analyses for the interim and final reports.*** ~~They will continue participating in EPI-MAL-002 until study end.~~

2. **Cover page - Authors:** PPD , ***Clinical and*** Epidemiology Scientist ~~(Keyrus Biopharma for~~ GSK Biological, PPD , GVCL CLS Clinical Read-out Manager Leader (GSK Biologicals), PPD ***, Local Delivery Lead (GSK Biologicals),*** PPD , ~~Senior Local Delivery Lead~~ ***Clinical Operations Head, Africa and Middle East*** (GSK Biologicals). Other non GSK Biologicals partners: ~~Quintiles~~ IQVIA (represented by PPD ~~-~~PPD PPD Project Manager)

3. **Section 2 Opinion Holder:** © 2012- ~~2017~~***2018*** GSK group of companies or its licensor.

4. **Section 4 Abstract-Study design:** The study targets enrolling 30,000 children in active surveillance, with ~~at least~~ ***about*** 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Among the 30,000 children, approximately 15,000 children (with ~~at least~~ ***about*** 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 6-12 weeks group (to collect background data in this age group) and approximately 15,000 children (with ~~at least~~ ***about*** 10,000 children in sites where the vaccine will be implemented)

5. Active surveillance will last 44 months for each subject (mimicking 24 months of active follow-up after the 4th dose of RTS,S/AS01$_E$ in EPI-MAL-003), ***except for subjects enrolled from Burkina Faso sites for whom their participation in the study has been early terminated.***

6. **Section 4 – Abstract: Population, including the setting and study population:** Sites in SSA countries have been ~~or will be~~ selected for EPI-MAL-002 based on the existence of a HDSS

7. In order to align with the MVIP, the study sites for the GSK Phase IV studies have been, or will be, selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented ~~(i.e. two sites in Malawi are planned to be included in EPI-MAL-002 in addition to the already defined sites)~~. ~~The only exception~~ ***As a consequence,*** Burkina Faso sites, ***that had already started*** EPI-MAL-002***, stopped the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance on 06 June 2018, with the exception of the follow-up check-ups at the***

hospital for children diagnosed with meningitis, cerebral malaria or with an AESI. All study activities are planned to be terminated by Q2 2019. A description of data from these sites will be presented in the progress reports up to Q4 2019, but none of these data will be part of the statistical analyses for the interim and final reports. ~~is for as they have .They will continue participating in EPI-MAL-002 until study end.~~

8. **Section 4 Abstract - Study size:** The study targets enrolling 15,000 children per group (i.e. 6-12 weeks group and 5-17 months group; with ~~at least~~ ***about*** 10,000 children of 15,000 in each group enrolled where the RTS,S/AS01$_E$ vaccine will be implemented), for a total of 30,000 children (~~at least~~ ***about*** 20,000 children enrolled where the vaccine will be implemented)

9. **Section 4 Abstract – Milestones:** The study started in Q4 2015, and is planned to end in ~~Q2~~ ***Q1*** 2022 ~~(tentative date, depending on recruitment timelines).~~ Progress reports will be generated every 6 months. An interim report is planned to be written by ~~Q4 2018~~ ***Q3 2019***(~~tentative date, depending on vaccine implementation timelines~~).

10. **Section 5 Amendments and Updates:** ***Final: 31 May 2012, Amendment 5 Final: 11 October 2017.*** The rationale for the protocol amendments 1, 2, 3, 4, 5 and ***6,*** and the summary of changes are provided in Annex 7

11. **Section 6 Milestones:**

Milestone	Planned date
Start of data collection	Q4 2015*
End of data collection	~~Q2~~ ***Q1*** 2022~~**~~
Study progress report	1 progress report every 6 months
Interim report	***Q3 2019***~~***~~
Final report of study results	***Q4 2022***~~**~~

*Actual date
~~**Tentative date, depending on recruitment timelines~~
~~***Tentative date, depending on vaccine implementation timelines~~

12. **Section 9.1 Study design - Active surveillance:** Approximately 30,000 children will be recruited within the collaborating study sites, and enrolled into active surveillance, with ~~at least~~ ***about*** 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Among these children, approximately 15,000 children will be enrolled in the 6-12 weeks group (with ~~at least~~ ***about*** 10,000 children in sites where the vaccine will be implemented) and approximately 15,000 children will be enrolled in the 5-17 months group (with ~~at least~~ ***about*** 10,000 children in sites where the vaccine will be implemented; see Section 9.2.1.1).

Enrolled children will be followed up through home visits for a total period of 44 months (see Figure 1 and Section 9.2.7.1) ***except for subjects enrolled from Burkina Faso sites for whom their participation in the study has been early terminated***.

13. **Section 9.1.1 Rationale for study design:** The active surveillance will include approximately 15,000 children in the 6-12 weeks group (with ~~at least~~ ***about*** 10,000 children where the RTS,S/AS01$_E$ vaccine will be implemented; to collect background data in this age group) and approximately 15,000 children in the 5-17

months group (with ~~at least~~ ***about*** 10,000 children where the RTS,S/AS01$_E$ vaccine will be implemented; to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group).

14. **Section 9.2 Setting:** For this reason, other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01$_E$ vaccine is planned to be implemented according to the MVIP, were~~/will be~~ added to the already defined study sites as described below.

    High malaria burden areas will be prioritized [WHO, 2017]. ~~In order to align with the MVIP, study sites that are participating or will participate in the GSK baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively).~~ ***GSK baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) being fully embedded in the MVIP, selection of the clusters that are/will participate in those studies depends on the cluster identification process led by the Ministries of Health according to WHO guidance. They*** have been, or will be, selected as follows:

- ***EPI-MAL-002 study sites:*** ~~In summary:~~ currently, a total of 5 sites (2 in Ghana [Kintampo, Navrongo], 1 in Kenya [Kombewa] and 2 in Burkina Faso [Sapone, Nouna]) ~~are enrolling~~ ***have enrolled*** study participants in the EPI-MAL-002 study.
  - ***Since*** sites have been, or will be, selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented~~. The only exception is for~~ Burkina Faso sites ***that*** ~~as they have already~~ started EPI-MAL-002 ***have early terminated the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance on 06 June 2016, with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI (see sections 9.2.7.4.1, 9.2.7.4.2 and 9.2.7.4.5). All study activities are planned to be terminated by Q2 2019. A description of data from these sites will be presented in the progress reports up to Q4 2019, but none of the data from these sites will be part of the statistical analyses for the interim and final reports.*** ~~They will continue participating in EPI-MAL-002 until study end. Their data will therefore not be included~~ (neither in the before/after comparison analyses of the EPI-MAL-002 and EPI-MAL-003 studies, nor in any other indicators planned to be generated by EPI-MAL-002 data to inform analyses of the EPI-MAL-003 study [e.g. background incidence of meningitis for study sample size and the exposure to other vaccines]). ***Burkina Faso sites*** will not be included in EPI-MAL-003 because the MVIP will not take place in the country. ~~Two new sites located in Malawi are planned to be included in EPI-MAL-002.~~

- Two sites in Malawi have fulfilled the criteria of the study feasibility assessment and ~~are~~ ***were*** planned to initiate the EPI-MAL-002 study in Q1-Q2 2018. ***Considering the RTS,S/AS01$_E$ vaccine implementation date in Malawi, currently planned in October 2018, the baseline data that might be collected in Malawi in the EPI-MAL-002 study would be too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size***

from Malawi sites by using the high recruitment observed from sites in Kenya (Kombewa) and Ghana (Kintampo) and extending recruitment in Ghana (Navrongo). ~~With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 should become exposed study sites/clusters in EPI-MAL-003. Selection of the unexposed study sites/clusters that will be included in the EPI-MAL-003 study is ongoing and is fully embedded in the MVIP. Study feasibility in all sites/clusters is assessed through a comprehensive scientific and operational study site assessment.~~

- ***EPI-MAL-003 study sites: as currently planned in the*** ~~Currently, as per~~ MVIP and ***according to*** WHO guidance, 4 study sites (corresponding to 4 clusters of the MVIP) in each of the 3 countries selected for the RTS,S/AS01$_E$ pilot implementation programme (12 study sites/clusters in total) are planned to be part of EPI-MAL-003: 2 of them should become exposed clusters and 2 of them should become unexposed clusters (see Annex 3 for definitions of exposed and unexposed clusters). ~~Phase IV vaccine evaluation being fully embedded in the MVIP, selection of the clusters that will be included in study EPI-MAL-002 and EPI-MAL-003 depends on the cluster identification process led by the Ministries of Health in collaboration with the WHO. As per~~ ***In order to allow the before-after comparison of study endpoints and according to*** WHO guidance, study sites from Ghana ***and*** Kenya ~~and Malawi~~ included in the EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters. ~~Selection of the unexposed study sites/clusters that will be included in the EPI-MAL-003 study is ongoing and is fully embedded in the MVIP.~~
- ***EPI-MAL-005 study sites: being an ancillary study to EPI-MAL-002 and EPI-MAL-003 studies, EPI-MAL-005 is/will be conducted in study sites conducting EPI-MAL-002 and/or EPI-MAL-003.***
- Of note***, all study sites*** ~~the clusters, once pre-identified by the Ministries of Health~~ are submitted to a comprehensive scientific and operational study site assessment conducted by GSK, which will determine study feasibility in those sites.

15. **Section 9.2.1 Study Population:** “at least” in the number of subjects replaced by “about”
16. **Section 9.2.4 Study period:** Recruitment for active surveillance is expected to be done until the enrolment target is reached. Enrolment in enhanced hospitalisation surveillance ***has been early terminated*** ~~will continue throughout the whole study period~~ for the sites where the RTS,S/AS01$_E$ vaccine will not be implemented.

Active surveillance will last 44 months for each subject (mimicking 24 months of active follow-up after the 4th dose of RTS,S/AS01$_E$ in EPI-MAL-003) ***except for subjects enrolled from Burkina Faso sites for whom their participation in the study was early terminated.***

17. **Section 9.2.7 Study procedures:** Notes added to clarify that although the study has been early terminated at the Burkina Faso sites, the 1, 6, and 12 months follow-up check-ups in case of an already diagnosed meningitis, cerebral malaria or AESI before the early termination should still be done.
18. **Section 9.5 Study size:** “at least” replaced with “about” and the following added and deleted respectively; ***Burkina Faso sites are planned to early terminate any study***

activities by Q2 2019. As a consequence, the data from those sites will be presented in the progress reports up to Q4 2019, but none of those data will be part of the statistical analyses for the interim and final reports. There will be a full follow-up of about 10000 and not 15,000 children.

~~Table 6 provides an estimation of the 95% CIs based on:~~

- ~~A sample of 15,000 children per group (either 15,000 in the 6-12 weeks group, or 15,000 in the 5-17 months group);~~
- ~~Different numbers of detected events (for the less frequent events): 1, 3 or 5 events;~~
- ~~Different risk periods following dose administration (with censoring to one month for the two first doses).~~
- ~~A follow-up corresponding to the risk period after the virtual dose 4.~~

~~**Table 6 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events following dose administration based on 15,000 subjects, different numbers of detected events, and different risk periods**~~

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
Events in different at-risk periods following dose administration (per age group)					
1	2 weeks	2307.69	43.3	1.1	241.4
1	6 weeks	5961.54	16.8	0.4	93.5
1	3 months	10000.00	10.0	0.3	55.7
1	6 months	17500.00	5.7	0.1	31.8
1	12 months	32500.00	3.1	0.1	17.1
3	2 weeks	2307.69	130.0	26.8	379.9
3	6 weeks	5961.54	50.3	10.4	147.1
3	3 months	10000.00	30.0	6.2	87.7
3	6 months	17500.00	17.1	3.5	50.1
3	12 months	32500.00	9.2	1.9	27.0
5	2 weeks	2307.69	216.7	70.4	505.6
5	6 weeks	5961.54	83.9	27.2	195.7
5	3 months	10000.00	50.0	16.2	116.7
5	6 months	17500.00	28.6	9.3	66.7
5	12 months	32500.00	15.4	5.0	35.9

~~Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm 1990].~~

~~Table 9 provides an estimation of the 95% CIs for the surveillances for all children less than 5 years of age based on:~~

- ~~A birth cohort of 17,250 children;~~
- ~~A follow-up of 2 years (for the enhanced hospitalisation surveillance, before the start of the EPI-MAL-003 study);~~
- ~~Different numbers of detected events (for the less frequent events).~~
- ~~Table 9 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events among all children less than 5 years of age based on 17,250 birth cohort, and different numbers of detected events~~

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
Events in all children < 5 years during a follow-up of 2 years					
1	2 years	172500	0.6	0.0	3.2
5	2 years	172500	2.9	0.9	6.8
25	2 years	172500	14.5	9.4	21.4
50	2 years	172500	29.0	21.5	38.2

~~Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990].~~

19. **Section 9.7 Data analysis:** Analyses will be based on ***about*** 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Descriptive statistics will be computed by age group, study site and overall, as well as by type of

surveillance. Moreover, descriptive analysis of safety endpoints will be computed for specific sub populations such as children with hemoglobinopathy and HIV-positive children. ***Burkina Faso sites are planned to early terminate any study activities by Q2 2019. As a consequence, a description of data from those sites will be presented in the progress reports up to Q4 2019, but none of these data will be part of the statistical analyses for the interim and final reports. There will be a full follow-up of about 10000 and not 15,000 children.***

20. **Section 9.7.4.1 Sequence of analyses:** ***Of note, data from Burkina Faso sites were part of the previous progress reports and will also be part of the progress reports planned up to Q4 2019.***

    This interim analysis will be done with clean data* collected on a sub-group of subjects ***from sites where the vaccine will be implemented***

21. **Section 9.9 Limitations of the study:** ~~This~~ ***The*** Protocol Amendment 5 describe***d*** ~~s~~ the sample size reduction from 40,000 to 30,000 with at least 20,000 children ***to be*** enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. There ~~is~~ ***was*** a resultant reduction in the size of the two study groups to 15,000 subjects each (with at least 10,000 children in sites where the vaccine will be implemented).

    Other sites in SSA settings with moderate-to-high transmission of malaria, from the 3 countries where the RTS,S/AS01$_{\boldsymbol{E}}$ vaccine will be implemented (see Section 9.2), were~~/will be~~ added to the already defined study sites. The transition from EPI-MAL-002 (pre-implementation) to EPI-MAL-003 (post-implementation) is expected to occur in the study sites from Kenya and Ghana ~~and Malawi.~~

GlaxoSmithKline Biologicals	
Vaccine Value & Health Science (VVHS)	
Protocol Amendment 7	
eTrack study number and Abbreviated Title	115055 (EPI-MALARIA 002 VS AME)
Amendment number:	7
Amendment date:	5 May 2020
Co-ordinating authors:	PPD, Lead Scientific Writer (GSK Biologicals)

Rationale/background for changes:

This protocol amendment 7 outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The purpose of the amendment is to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity.

The use of the alert system has been early terminated in Q4 2019 due to its complexity and alternatives have been put in place by the study sites.

1. **Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections.**
2. **Cover page - Authors:** PPD, ***Oversight*** Data ~~Management~~ ***Manager*** (GSK Biologicals), PPD, ***Epidemiology lead*** ~~Clinical and Epidemiology Scientist~~ (GSK Biologicals) PPD**,** Safety Physician (GSK Biologicals), PPD /Study Delivery Lead (GSK Biologicals), ~~Mobile Phone Alert System: Parexel (represented by~~ PPD ~~, Senior Project Manager)~~
3. **Section 2 Opinion Holder**: © 2012- ~~2018~~
4. **Section 5 Amendments and Updates**: ***Amendment 6 Final: 06 July 2018***. The rationale for the protocol amendments 1, 2, 3, 4, 5, 6 and *7*, and the summary of changes are provided in Annex 7
5. **Section 7 Rationale for the study**: The EPI-MAL-002 study started in Q4 2015 and will last for approximately 5 years (depending on recruitment timelines). EPI-MAL-003 ~~will start~~ ***started in Q1 2019*** when the vaccine ***became*** ~~becomes~~ available in the study sites that are exposed clusters after its implementation according to WHO guidelines in the framework of the MVIP (first vaccine introduction ***was*** foreseen in 2018, see section 9.2).
6. **Section 9.2 Setting**: – Since sites have been, or will be, selected from the 3 countries where the RTS,S/AS01E vaccine will be implemented, Burkina Faso sites that started EPI-MAL-002 have early terminated the follow-up activities in active surveillance and enrolment in enhanced hospitalisation surveillance on 06 June ~~2016~~***2018***, with the exception of the follow-up check-ups at the hospital for children

diagnosed with meningitis, cerebral malaria or with an AESI (see sections 9.2.7.4.1, 9.2.7.4.2 and 9.2.7.4.5).

~~7.~~ **Section 9.2.7.6 Capacity building:** ~~Use of time sensitive event device~~

~~An alert system using mobile phones will be developed in EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate time-sensitive events to study staff. The alert system will be implemented in order to closely monitor AESI, meningitis cases, and severe malaria, and to ensure that all the procedures and tests specified in the protocol are done for a proper diagnosis of the diseases while maintaining the safety of the patients. Mobile phone reporting logs will be cross-checked with hospital discharge logs and primary health care facility registries for process improvement.~~

~~In addition, GSK and Quintiles will also be made aware of the AESI, meningitis cases, and severe malaria cases, including cerebral malaria cases (they will not receive any patient's personally identifiable information via that system). The system should act as an alert system between the health care facilities and the principal investigator, but is not intended to replace the reporting through eCRF (as defined in Section 11).~~

8. **Section 9.2.7.1.13 Outline of study procedures**

Table 4 List of study procedures to be conducted at each visit, and study visit schedule (active surveillance)

Epoch	1										
Type of contact	Enrolment	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Visit days: 6-12 weeks group [6] (identified at first administration of DTP/HepB/Hib vaccine)		1 wk (±3 days) after 1st DTP/ HepB/ Hib dose	1 wk (±3 days) after 2nd DTP/ HepB/ Hib dose	1 wk (±3 days) after 3rd DTP/ HepB/ Hib dose	6 wks (±5 days) after 3rd DTP/ HepB/ Hib dose	6 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose	18 mths (±2 wks) after 3rd DTP/ HepB/ Hib dose	5 wks (±5 days) post V6	12 mths (±2 wks) post V6	24 mths (±2 wks) post V6	At 5 yrs of age or study end [7] (±2 *wks)*
Visit days: 5-17 mths group (identified at first administration of DTP/HepB/Hib vaccine)		At the age of 6 mths *(> 5 mths to < 7 mths)*	4 wks (±3 days) post V1	4 wks (±3 days) post V2	5 wks (±5 days) post V3	6 mths (±2 wks) post V3	18 mths (±2 wks) post V3	5 wks (±5 days) post V6	12 mths (±2 wks) post V6	24 mths (±2 wks) post V6	At 5 yrs of age or study end [7] *(*±2 *wks)*
Visit days: 5-17 mths group (catch-up, enrolled at 5 to <18 mths of age)		First contact with study staff or 1 wk later	4 wks (±3 days) post V1	4 wks (±3 days) post V2	5 wks (±5 days) post V3	6 mths (±2 wks) post V3	18 mths (±2 wks) post V3	5 wks (±5 days) post V6	12 mths (±2 wks) post V6	24 mths (±2 wks) post V6	At 5 yrs of age or study end [7](±2 *wks*)

9. **Section 9.2.7.2.16 Outline of study procedures**

Table 5 List of study procedures to be conducted in the event of hospitalisation

Epoch	1	
Type of contact	Hospitalisation Visit	Study Conclusion Visit (At 5 years of age or study end, whichever occurs first)[7] *(±2 wks)*

10. **Section 9.2.8 Study procedures during special circumstances:**

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Active safety follow-up through home visits may be made by a telephone call or other means of virtual contact. It is acknowledged that the systematic measurement of body temperature may not be performed.***
- ***For children diagnosed with AESI, meningitis or cerebral malaria, the check-up at the hospital at 1 month, 6 months and 1 year after hospital discharge may be replaced by a telephone call or other means of virtual contact.***
- ***A retrospective data collection of medical events may be implemented at any of the health care facilities.***

~~11.~~ **Section 9.7.6.2 Statistical approach:** ~~An alert system (see Section 9.4.2) will be implemented in order to closely monitor the meningitis cases~~

12. **Section 9.7.10 Statistical analyses during special circumstances:** ***Special circumstances (see section 9.2.8) may have an impact on the proposed analysis plan. Any changes in the analysis plan will be further described in the SAP.***

~~13.~~ **Section 9.9 Limitations of the research methods:** ~~The introduction of an alert system using mobile phones to ease communications between the health care staff and the study staff will allow facilitating the adherence to national recommendations for diagnosis during the study. However, meningitis cases based on clinical symptoms only, or suspected cases, can be expected~~

14. Annex 5 Case definitions for protocol-defined adverse events of special interest (AESI) and surveillance indicators

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
GENERALIZED CONVULSIVE SEIZURE	The etiological work up is negative: (i.e. febrile seizure ***that does not fit GCS definition,*** acute intoxication, trauma, severe malaria etc. have all been excluded)	
HEPATIC FAILURE	**Major criteria** **OR** • Elevation of the serum transaminases (ALT ***or*** AST ≥ 3 times the upper limit of normal (ULN))	.

Annex 8 PROTOCOL AMENDMENT 7 SPONSOR SIGNATORY APPROVAL

eTrack study number and Abbreviated Title	115055 (EPI-MALARIA-002 VS AME)
Date of protocol amendment	Amendment 7: 5 May 2020
Detailed Title	A prospective study to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of the RTS,S/AS01$_E$ candidate vaccine.
Sponsor signatory	François Roman, Clinical and Epidemiological Project Lead, DDW Vaccines
Signature	_____
Date	_____

Annex 9 PROTOCOL AMENDMENT 7 INVESTIGATOR AGREEMENT

I agree:

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

Hence I:

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

eTrack study number and Abbreviated Title	115055 (EPI-MALARIA-002 VS AME)
Date of protocol amendment	Amendment 7: 5 May 2020
Title	A prospective study to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of the RTS,S/AS01$_E$ candidate vaccine.

Investigator name _____

Signature _____

Date _____