Protocol Amendment 4

Study ID: 207636

A prospective epidemiological study of women between 24-27 weeks of pregnancy to describe pregnancy outcomes and events of interest in the mother and neonate, as well as determine incidence in infants of RSV LRTI and RSV hospitalization

Date of Document: 29-May-2020

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207636 (EPI-RSV-008 BOD)
Protocol Amendment 4 Final

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

eTrack study number and Abbreviated Title	207636 (EPI-RSV-008 BOD)
Date of protocol	Final Version 1: 11 July 2017
Date of Amendment	Amendment 1 Final: 12 February 2018 Amendment 2 Final: 03 July 2018 Amendment 3 Final: 18 February 2019 ***Amendment 4 Final: 29 May 2020***
Title	A prospective epidemiological study of pregnancy outcomes and of events of interest in pregnant women, neonates and infants (PEPNI)
Detailed Title	A prospective epidemiological study of women between 24-27 weeks of pregnancy to describe pregnancy outcomes and events of interest in the mother and neonate, as well as determine incidence in infants of RSV LRTI and RSV hospitalization.
Coordinating author	PPD
Contributing authors	• PPD, Clinical & Epidemiological Project Lead • PPD, Lead Epidemiologist • PPD, Expert Biostatistician, PPD PPD Lead ***Biostatistician*** • PPD, PPD, Study Delivery Leads • PPD, Clinical Read-Out Team Leader • PPD, ***Clinical Laboratory Sciences Study Manager, Business & Decision Life Sciences Contractor for GSK Biologicals*** • PPD, Safety Physician • PPD, Oversight Data Manager

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Authors who contributed to previous versions of the protocol:	• PPD PPD Clinical & Epidemiological Project Leads • PPD, Epidemiologists • PPD, PPD, Study Delivery Leads • PPD, Clinical Research and Development Lead • PPD, Clinical Research and Development Lead • PPD, Lead Epi Statistician • PPD, Study statistician • PPD (Aixial for GSK Biologicals), Clinical Trial Supply manager • PPD ***, Clinical Trial Supply manager*** • PPD, Safety Physician • PPD, Clinical Read-Out Team Leader • PPD (Business & Decision Life Sciences for GSK Biologicals), Clinical Laboratory Sciences Study Manager • PPD, Safety Physician • PPD, Oversight Data Manager • PPD, Study Data Manager (Tata Consultancy Services for GSK Biologicals) • PPD, Regulatory Affairs Representative

GSK Biologicals' Protocol DS v15.0

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Protocol Amendment 4 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207636 (EPI-RSV-008 BOD)
Date of Amendment	***Amendment 4 Final: 29 May 2020***
Detailed Title	A prospective epidemiological study of women between 24-27 weeks of pregnancy to describe pregnancy outcomes and events of interest in the mother and neonate, as well as determine incidence in infants of RSV LRTI and RSV hospitalization.
Sponsor signatory	Ouzama Henry, Clinical & Epidemiological Project Lead
Signature	
Date	

Protocol Amendment 4 Rationale

Amendment number:	Amendment 4

Rationale/background for changes:

This amendment outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The primary purpose of the amendment is to protect the subject's welfare, and as far as possible ensure the potential benefit to the subject and promote data integrity. Several additional modifications and clarifications have also been made.

Changes are outlined below.

- Globally:
  - Intervals between study visits/contacts/observations: the window for the first infant subject visit has been extended from 0-10 to 0-21 days to provide site personnel with additional time to obtain and document post-delivery/birth informed consent (where this is required).
  - References to Gestational Age Range at maternal Visits 2, 3 and 4 have been removed as their inclusion was only intended as a guide and was not intended to further restrict allowed intervals between study visits.
- Synopsis, Section 3.3, Tertiary Objectives, and Section 11.1.3, Tertiary Endpoints, have been updated to indicate that the incidence of LRTIs/ Severe LRTIs (using alternative case definitions) will also be evaluated.
- Synopsis and Section 11.1.3, Tertiary Endpoints, has been updated to clarify that further exploratory characterization of immune responses to RSV and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood) includes, for example, levels of RSV-B neutralizing antibodies.
- The List of Abbreviations has been updated to include a reference to COVID-19.
- Section 2.3, Overall Benefit: Risk Conclusion has been updated.
- Section 4, Figure 1: A note has been added to indicate that COVID-19 cases identified within the surveillance framework of the study will be captured to the eCRF.
- Section 5.4, Table 4, Alternative LRTI/Severe LRTI Case Definitions, has been added. All subsequent Table numbers therefore increase by one.
- Section 8.2.1, Study procedures during special circumstances, has been added.
- Section 8.3, Table 5 and Table 6, List of study procedures for maternal subjects, and List of study procedures for neonates/infants, have been clarified to indicate that COVID-19 cases are considered clinically significant events and will be recorded as such in the eCRF.

- Sections 8.5.8, 8.6.2, 8.6.7 have been modified to reference the collection of COVID-19 case information.
- Section 8.6.5.2 has been modified to clarify that RTI surveillance in infants cannot begin before additional consent for the infant's participation (where required) has been supplied.
- Section 8.7, Reporting COVID-19 cases, has been added.
- Section 11.3 has been modified to introduce definitions for the Enrolled set, and to clarify definitions for the Exposed, and Per Protocol sets for analysis.
- Section 11.6, 11.7, and 11.8 have been modified for consistency with the changes in Section 11.3.
- Section 11.11.1, Statistical considerations for interim analysis, has been modified to indicate that an interim analysis for RSV LRTIs may be performed if deemed necessary.
- Section 14 has been updated to include a reference to the WHO Guidance for surveillance of COVID-19.
- Additional editorial clarifications have been made and typographic errors have been corrected.
- A detailed summary of changes (including deletions) appears in APPENDIX E.

Protocol Amendment 4 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 acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the 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	207636 (EPI-RSV-008 BOD)
Date of Amendment	***Amendment 4 Final: 29 May 2020***
Detailed Title	A prospective epidemiological study of women between 24-27 weeks of pregnancy to describe pregnancy outcomes and events of interest in the mother and neonate, as well as determine incidence in infants of RSV LRTI and RSV hospitalization.
Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals

Rue de l'institut 89,1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Study Contact for Reporting of a Serious Adverse Event (SAE)

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 9.4.

SYNOPSIS

Detailed Title

A prospective epidemiological study of women between 24-27 weeks of pregnancy to describe pregnancy outcomes and events of interest in the mother and neonate, as well as determine incidence in infants of RSV LRTI and RSV hospitalization.

Objectives (Amended 29-MAY-2020)

Primary

In healthy pregnant women with uncomplicated pregnancies:

- To determine the frequencies of pregnancy outcomes.
- To determine the frequencies of pregnancy related events of interest from enrollment (Visit 1) through 42 days after delivery (Visit 6).

(Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.)

In all neonates live-born to women enrolled in the study:

- To determine the frequencies of neonatal events of interest.

Neonatal events of interest occur within the first 28 days after birth but may only be detected later, and are to be reported throughout the study.

Secondary

In healthy pregnant women with uncomplicated pregnancies

- To determine frequencies of pregnancy related events of interest according to GAIA levels of diagnostic certainty (where these are specified) from enrollment (Visit 1) through 42 days after delivery (Visit 6). (Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.)
- To describe the distribution of RSV-A antibody titers in maternal blood at delivery.

In all neonates live-born to women enrolled in the study:

- To determine frequencies of neonatal events of interest according to GAIA levels of diagnostic certainty (where these are specified). Neonatal events of interest occur within the first 28 days after birth (but may only be detected later and are to be reported throughout the study).
- To describe the distribution of RSV-A antibody titers in cord blood at delivery.

In all neonates/infants live-born to women enrolled in the study, from birth through 1 year of age:

- To determine the incidence of all, of severe, and of very severe RSV-lower respiratory tract illnesses (LRTIs).
- To determine the incidence of RSV hospitalization.

Tertiary

- To describe co-infections of RSV-LRTI with other respiratory viruses in infants.
- To estimate the association of RSV-LRTI in neonates/infants and the level of RSV neutralizing antibodies in cord blood.
- ***To determine the incidence of LRTIs/ Severe LRTIs (using alternative case definitions)***
- To determine risk factors for pregnancy-related and neonatal events of interest
- If deemed necessary, to further characterize the immune responses to RSV and other infections in maternal subjects and infants (based on maternal serum and cord blood).

Rationale for the study and study design

Maternal immunization aims to prevent diseases in neonates and infants via transplacental antibody transfer from the mother to the fetus following vaccination of the pregnant woman. Several marketed vaccines are already recommended for and routinely administered to pregnant women, including influenza, tetanus, and Tdap vaccines (CDC 2013a, CDC 2013b). There are also a number of maternal vaccines in development that aim to protect neonates and infants from pathogens in addition to respiratory syncytial virus (RSV). GlaxoSmithKline (GSK) is developing an investigational vaccine for use in pregnant women against RSV disease. Of note this vaccine is developed solely for immunization in pregnancy.

Maternal immunization is implemented worldwide and has the potential to make a major contribution to reducing RSV lower respiratory tract illnesses (LRTI) and the burden of other diseases in infants globally. Therefore, it is imperative that clinical trials are conducted across different countries in different settings. GSK is proactively addressing potential challenges of conducting clinical trials in pregnant women in low- and middle income countries (LMIC).

Before conducting clinical trials it is important to understand the frequency of pregnancy outcomes and the maternal and neonatal events of interest (i.e. clinically significant events that may be considered adverse events if they occur after vaccination) in each setting where clinical trials may be conducted for better interpretation of safety data. Also, to ensure safety of the participating women, and to characterize the safety profile of the product, adverse events (AEs)

in pregnancy should be appropriately detected and managed. This study addresses gaps in understanding of anticipated rates of pregnancy outcomes as well as events of interest in pregnant women and neonates. Furthermore, this study will be conducted at potential sites for future maternal immunization trials and will help assure the capacity of sites to detect and manage clinically significant events of interest in pregnant women and their neonates.

Secondarily, the study will establish surveillance mechanisms for RSV associated illnesses in the neonate/infant (through the first 12 months of life. Whilst there is good documentation of the global burden of RSV disease, incidence of RSV-LRTI according to the World Health Organization (WHO) 2015 case definitions [Modjarrad, 2016] is limited in the literature, particularly in many LMIC settings. Hence, this study will also estimate the incidence of infant RSV-LRTI using WHO case definitions across geographically distinct locations to support incidence rate assumptions for planning of future efficacy trials.

To achieve these goals, GSK will be guided by the WHO recommendations on antenatal care for a positive pregnancy experience [WHO, 2016] and the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) case definitions [Bonhoeffer, 2016; Bauwens, 2016; Kochhar, 2017]. Standardization of surveillance methodology and case definitions (applicable to maternal immunization AEs) may support comparison of data across different countries [Jones, 2016].

This multi-country study will enroll pregnant women $\geq 24^{0/7}$ weeks and $\leq 27^{6/7}$ weeks gestational age (GA). Study procedures in this protocol are defined to ensure that maternal and neonatal events of interest are captured. They are not intended to replace procedures performed by local healthcare providers as part of standard care. Prenatal screening and care will be provided by local healthcare providers (in accordance with local standards).

Study design

- Type of design: Prospective, epidemiological, interventional (without administration of medicinal products as described in a research protocol), multi-country, cohort study.
- Study population: The study will be conducted in multiple countries, in pregnant women and their infants.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

Synopsis Table 1 Sampling schedule for maternal subjects

		Visit				
Sample	**Parameter(s) evaluated**	**1**	**2**	**3**	**4**	**Delivery**
Maternal **Blood**	Hematology/ biochemistry[1, 4]	x		x[3]		
	Antibody titer (RSV-A)					≤ 72 hours after delivery[5]
Cord Blood	Antibody titer (RSV-A)					x
Urine	Protein, glucose, RBC, WBC [2, 4]	x	x	x	x	

[1] To be performed preferentially by local healthcare providers, as per local practice. To be performed by the investigator/study staff ONLY if not done by the local healthcare provider within 2 weeks before the study visit.

[2] The investigator/site staff will perform a urine dipstick test using supplies provided by GSK.

[3] Hemoglobin only

[4] If results are abnormal, subjects will be referred per local standard of care.

[5] This sample may be collected from start of labor (e.g. when the mother arrives at the hospital to deliver and an intravenous line is inserted) through 72 hours after delivery.

Sampling schedule for neonates/ infants	Surveillance for RSV LRTI will be conducted in infants through the 12 month study period. During this 1-year post-birth surveillance period, for each RTI with suspicion of difficulty in breathing, or wheezing, or with parental concern, a nasal swab will be collected at a visit to assess potential RSV associated RTIs/LRTIs
Primary Completion Date (PCD)	42 days post-delivery/birth (i.e. Visit 6 for the mother and Visit 2-NB for the infant) or last visit of Epoch 2.
End of Study (EoS)	Last testing results released of samples collected up to Visit 4-NB (assays related to primary and secondary endpoints)
Duration of the study	Approximately 4.5 to 6 months for participating pregnant women; approximately 1 year for participating infants. • Epoch 001: Screening • Epoch 002: Primary starting at Visit 1 and ending 42 days post-delivery/birth (Visit 6 for the mothers and Visit 2-NB for the infants).* • Epoch 003: Follow-up of infants starting 43 days post-delivery/birth and ending at Visit 4-NB (1 year post-birth). *Any safety and disease surveillance data collected after Visit 2-NB will be collected in Epoch 003.

Synopsis Table 2 Study groups and epochs foreseen in the study

Study Groups	**Number of subjects** enrolled	**Age (Min/Max)**	**Epochs**		
			Epoch 001	**Epoch 002**	**Epoch 003**
Maternal subjects	Up to ~ 2300	18 years - 45 years	x	x	
Infants	Up to ~ 2300	NA		x	x

Approximately 200 to 300 subjects per country. To achieve the enrollment targets noted above, the number of pregnant women SCREENED in each country may exceed the country-specific enrolment target.

- Surveillance for pregnancy outcomes and pregnancy-related events of interest that occur from Visit 1 up to 42 days after delivery (Visit 6).
- Surveillance for neonatal events of interest that occur from birth up to 28 days of age
- Surveillance for RSV LRTI and RSV hospitalization in infants: from birth up to 1 year of age

Number of subjects

- Approximately 2300 pregnant women. Neonates of enrolled pregnant women who consent to the infant's continued study participation will also be enrolled.

Endpoints (Amended 29-MAY-2020)

Primary

- Pregnancy outcomes. Of note, fetal death/stillbirth has multiple subcategories. For example, fetal death/stillbirth with no congenital anomalies is an outcome with two subcategories that include: 1) antepartum stillbirth; 2) intrapartum stillbirth. For each outcome, the investigator should select the applicable sub-category.
  - Live birth with no congenital anomalies,
  - Live birth with congenital anomalies,
  - Fetal death/stillbirth (loss at or after 22 weeks of gestation) with no congenital anomalies:
    - Antepartum stillbirth
    - Intrapartum stillbirth
  - Fetal death/still birth (loss at or after 22 weeks of gestation) with congenital anomalies:
    - Antepartum stillbirth
    - Intrapartum stillbirth
  - Elective/therapeutic termination with no congenital anomalies,
  - Elective/therapeutic termination with congenital anomalies.
- Pregnancy related events of interest from Visit 1 through Visit 6. Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study. They are listed below. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and

3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.

- Maternal death
- Hypertensive disorders of pregnancy:
  - Gestational hypertension,
  - Pre-eclampsia,
  - Pre-eclampsia with severe features (including eclampsia)
- Antenatal bleeding:
  - Morbidly adherent placenta
  - Placental abruption
  - Cesarean Scar Pregnancy
  - Uterine rupture
- Postpartum hemorrhage
- Fetal growth restriction
- Dysfunctional labor
  - first stage of labor
  - second stage of labor
- Gestational diabetes mellitus,
- Non reassuring fetal status
- Pathways to preterm birth:
  - Premature preterm rupture of membranes,
  - Preterm labor,
  - Provider-initiated preterm birth.
- Chorioamnionitis
- Oligohydramnios
- Polyhydramnios
- Gestational Liver Disease:
  - Intrahepatic Cholestasis of Pregnancy (ICP)
  - Acute Fatty Liver of Pregnancy
- Maternal Sepsis
- Any other pregnancy related event considered by the investigator to be of concern (specify)

- Neonatal events of interest from birth through 28 days of age. Neonatal events of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study. They include:
  - Small for gestational age,
  - Low birth weight including very low birth weight,
  - Neonatal encephalopathy,
  - Congenital microcephaly,
    - Postnatally diagnosed
    - Prenatally diagnosed
  - Congenital anomalies,
    - Major external structural defects
    - Internal structural defects
    - Functional defects
  - Neonatal death,
    - Neonatal death in a preterm live birth (gestational age>=28 to < 37 weeks)
    - Neonatal death in a term live birth
  - Neonatal infections,
    - Blood stream infections
    - Meningitis
    - Respiratory infection
  - Respiratory distress in the neonate,
  - Preterm birth,
  - Failure to thrive,
  - Large for gestational age,
  - Macrosomia,
  - Any other neonatal event considered by the investigator to be of concern (specify, e.g. neurodevelopment delay)

Secondary

- Pregnancy related events of interest from Visit 1 through Visit 6 (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible)

- Neonatal events of interest from birth through 28 days of age (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible)

Of note, some events of interest fall under a single category but have multiple subcategories. For each event, the investigator should identify the event and select the applicable sub-category and the GAIA level of diagnostic certainty.

- RSV-A neutralizing antibody titers in maternal blood at delivery.
- RSV-A neutralizing antibody titers in cord blood at delivery.
- Episode(s) of RSV-LRTI from birth up to 1 year of age.
- Episode(s) of RSV hospitalization from birth up to 1 year of age.

Tertiary

- Co-infections of RSV-LRTI with other respiratory viruses in infants, confirmed by PCR of nasal swabs in infants from birth up to 1 year of age:
  - Influenza A virus (Flu A)
  - Influenza B virus (Flu B)
  - Human Influenza A virus subtype H1 (Flu A-H1)
  - Human Influenza A virus subtype H3 (Flu A-H3)
  - Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)
  - Human adenovirus (AdV)
  - Human metapneumovirus (MPV)
  - Human enterovirus (HEV)
  - Human parainfluenza virus 1 (PIV1)
  - Human parainfluenza virus 2 (PIV2)
  - Human parainfluenza virus 3 (PIV3)
  - Human parainfluenza virus 4 (PIV4)
  - Human bocavirus 1/2/3/4 (HBoV)
  - Human rhinovirus A/B/C (HRV)
  - Human coronavirus 229E (229E)
  - Human coronavirus NL63 (NL63)
  - Human coronavirus OC43 (OC43)
- ***Episodes of LRTIs/Severe LRTIs up to one year of age - using alternative case definitions***

- Potential risk factors for pregnancy related and neonatal events of interest.
- Any further exploratory characterization of immune responses to RSV and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood). (***For example, levels of RSV-B neutralizing antibodies).***

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TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF APPENDICES

PAGE

LIST OF ABBREVIATIONS (Amended 29-MAY-2020)

AE	Adverse Event
BMI	Body mass index
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
COVID-19	***Corona Virus Disease 2019***
eCRF	electronic Case Report Form
EoS	End of Study
FU	Follow-Up
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LLOQ	Lower Limit of Quantification
LMP	Last Menstrual Period
LRTI	Lower Respiratory Tract Illness
LSLV	Last Subject Last Visit
NB	Newborn

PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
RBC	Red Blood Cell
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SPM	Study Procedures Manual
SpO2	Blood oxygen saturation as measured by pulse oximetry
WBC	White Blood Cell
WHO	World Health Organization

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Body Mass Index	A key index for relating weight to height. Calculated as follows: Weight (kg) / (Height (m))^2
Child	A young human being below the legal age of majority (generally < 18 years of age).
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 study:	A form of epidemiological 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).
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment	Pregnant woman who meet all eligibility criteria at the Screening visit and return to the study site for Visit 1 are considered enrolled. Live born neonates who meet all eligibility criteria and complete Visit 1-NB are considered enrolled.

Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
End of Study (Synonym of End of Trial)	For studies with collection of Human Biological Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV
Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfill the purpose of the epoch. Typical examples of epochs are screening, immunogenicity follow-up, safety follow-up, ESFU, follow-up.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 11.3 for details on criteria for evaluability).
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy. A project that aims to improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in low to middle income countries.
Gestational age:	A measure of the age of a pregnancy where the origin is the first day of the woman's last normal menstrual period, or the corresponding age as estimated by other methods. Gestational age will be described in weeks of pregnancy completed + number of days completed of the following week. For example: 28 0/7 means completed 28 weeks of pregnancy + 0 days of the 29th week and 28 6/7 means completed 28 weeks of pregnancy + 6 days of the 29th week.

Infant	A child younger than 1 year of age
Interventional Human Subject Research:	Studies in which participants are administered medical care, medicinal products and/or medical/scientific procedures as described in a research protocol.
Legally acceptable representative (LAR)	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the trial. (The terms legal representative or legally authorized representative are used in some settings.)
Level 2 ultrasound (or fetal morphology ultrasound)	Comprehensive, detailed evaluation of fetal anatomy and development that is usually performed at approximately 20 weeks of gestational age. In addition to standard ultrasound parameters such as fetal heart activity and gestational age estimation, a Level 2 ultrasound usually includes assessment of amniotic fluid levels; assessment of the condition of the placenta, cervix, and uterus; and detection of fetal anomalies. May also be referred to as a fetal anomaly scan or fetal morphology assessment.
Local healthcare provider	A healthcare provider who provides subjects with medical care per local standards. This individual may or may not be a member of the study staff.
Neonate (or Newborn)	An infant ≤ 28 days old.
Neonatal events of interest	Clinically significant events that occur from birth through 28 days of age and may be considered adverse events if they occur after vaccination. They are listed in Section 11.1 and described in detail in APPENDIX D
Parental concern	The parent(s) / Legally Acceptable Representative(s) or their designates are concerned about the infant's respiratory tract illness, or general health in the context of the respiratory tract illness, and intend to seek medical care
Pregnancy related events of interest	Clinically significant events that occur up to 42 days after delivery and may be considered adverse events if they occur after vaccination. They are listed in Section 11.1 and described in detail in APPENDIX D

Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial/ pharmaco-epidemiological study was concluded according to the pre-specified protocol or was terminated.
Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives.
Protocol amendment:	The International Council for 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 study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Self-contained study:	Study with objectives not linked to the data of another study.
Serious Adverse Event (SAE) related to study participation	Any untoward medical occurrence related to study participation (e.g., protocol mandated procedures, invasive tests) that: • Results in death, • Is life-threatening, • Requires hospitalization or prolongation of an existing hospitalization, • Results in disability /incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.
Study population:	Sample of population of interest.

1. INTRODUCTION

1.1. Background and rationale for the study

Maternal immunization aims to prevent diseases in neonates and infants via transplacental antibody transfer from the mother to the fetus following vaccination of the pregnant woman. Several marketed vaccines are already recommended for and routinely administered to pregnant women, including influenza, tetanus and Tdap vaccines [CDC, 2013a, CDC, 2013b]. There are also a number of maternal vaccines in development that aim to protect neonates and infants from pathogens in addition to, respiratory syncytial virus (RSV). GlaxoSmithKline (GSK) is developing an investigational vaccine for use in pregnant women, against RSV disease. Of note this vaccine is developed solely for immunization in pregnancy.

Maternal immunization is implemented worldwide and has the potential to make a major contribution to reducing RSV lower respiratory tract illnesses (LRTI) and the burden of other diseases in infants globally. Therefore, it is imperative that clinical trials are conducted across different countries in different settings. GSK is proactively addressing potential challenges of conducting clinical trials in pregnant women in low- and middle income countries (LMIC).

Before conducting clinical trials it is important to understand the frequency of pregnancy outcomes and the maternal and neonatal events of interest (i.e. clinically significant events that may be considered adverse events if they occur after vaccination) in each setting where clinical trials may be conducted for better interpretation of safety data. Also, to ensure safety of the participating women, and to characterize the safety profile of the product, adverse events (AEs) in pregnancy should be appropriately detected and managed. This study addresses gaps in understanding of anticipated rates of pregnancy outcomes as well as events of interest in pregnant women and neonates. Furthermore, this study will be conducted at potential sites for future maternal immunization trials and will help assure the capacity of sites to detect and manage clinically significant events of interest in pregnant women and their neonates.

Secondarily, the study will establish surveillance mechanisms for RSV associated illnesses in the neonate/infant (through the first 12 months of life. Whilst there is good documentation of the global burden of RSV disease, incidence of RSV-LRTI according to the World Health Organization (WHO) 2015 case definitions [Modjarrad, 2016] is limited in the literature, particularly in many LMIC settings. Hence, this study will also estimate the incidence of infant RSV-LRTI using WHO case definitions across geographically distinct locations to support incidence rate assumptions for planning of future efficacy trials.

To achieve these goals, GSK will be guided by the WHO recommendations on antenatal care for a positive pregnancy experience [WHO, 2016] and the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) case definitions [Bonhoeffer, 2016; Bauwens, 2016; Kochhar, 2017]. Standardization of surveillance methodology and case definitions (applicable to maternal immunization AEs) may support comparison of data across different countries [Jones, 2016].

1.2. Rationale for the study population

The intention of this epidemiological study is to obtain an estimate of the background rate of adverse pregnancy outcomes and events that may be seen in future vaccine trial populations and, separately, to assess whether sites are suitable for Phase II/III vaccine trials. The study aims to enroll healthy women with normal uncomplicated pregnancies so that event rates for pregnancy and neonatal events of interest are applicable to the intended population for future vaccine trials. Regardless of enrollment location, healthy pregnant women aged 18 to 45 years with normal, uncomplicated, singleton pregnancies, who have had a level 2 (fetal morphology) ultrasound without any significant findings will be eligible for possible study participation. Inclusion / exclusion criteria have been structured in a way that resembles those of Phase II/III criteria to ensure good comparability between the current study population and that of anticipated future vaccine trials.

Pregnant women $24^{0/7}$ up to and including $27^{6/7}$ weeks of gestation will be enrolled, to ensure that they are followed as of the time of potential vaccination in a clinical trial.

Women who do not meet the enrollment criteria will be referred for appropriate local standard of care.

1.3. Rationale for the surveillance of pregnancy related events of interest

There are particular challenges in conducting clinical trials in pregnant women, among them limited data on background rates of pregnancy outcomes as well as what may be observed in clinical trials as maternal and neonatal adverse events. A large number of countries aim to strengthen their ability to provide comprehensive antenatal care for all and to enable a positive pregnancy experience. The WHO 2016 recommendations on antenatal care for a positive pregnancy experience [WHO, 2016] give guidance on the frequency of clinic visits, examination procedures and screening tests.

To achieve these goals, GSK will be guided by the WHO recommendations on antenatal care for a positive pregnancy experience [WHO, 2016] and the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) case definitions [Bonhoeffer, 2016; Bauwens, 2016; Kochhar, 2017]. Standardization of surveillance methodology and case definitions (applicable to maternal immunization AEs) may support comparison of data across different countries [Jones, 2016].

The number and timing of study visits was informed by WHO recommendations on antenatal care [WHO, 2016]. However, local standards of care differ from country-to country. Women should follow the local standard of care. Study data will be collected, in part, from records of the data obtained during the locally recommended antenatal care visits.

In this study, best efforts will be made to work with local healthcare providers to collect the key data on maternal, fetal, neonatal and infant health from routine health records to avoid duplication and an undue burden on the trial subjects.

1.4. Rationale for the use of Global Alignment of Immunization safety Assessment in pregnancy (GAIA) case definitions

GAIA, a Brighton collaboration project, aims to develop standardized case definitions and criteria for diagnostic certainty of maternal outcomes and events of interest and neonatal events of interest in the context of immunization trials [Bauwens, 2016; Bonhoeffer, 2016; Kochhar, 2017].

GAIA was established in response to a WHO request to work on a globally aligned approach to monitor safety of maternal immunization clinical trials. The application of these case definitions (APPENDIX D) aims to improve the quality of data generated and to support safety assessment. The goal is to pilot these case definitions prior to the initiation of large maternal immunization trials. To achieve this, the level of diagnostic certainty (APPENDIX D) will be collected for all of the events of interest for which GAIA criteria have been developed.

1.5. Rationale for the active and passive surveillance for RSV associated respiratory tract illnesses (RTI) with suspicion of difficulty in breathing/wheezing or with parental concern in neonates/ infants

RSV infects 50-70% of infants in their first year of life, and practically all children have experienced RSV infection and / or illness by their third birthday [Hall, 2009]. In industrialized countries, approximately 2% of infants under one year of age are hospitalized as a consequence of RSV-induced lower respiratory tract illnesses (LRTI) each year. Infants younger than six months have the highest risk of developing severe RSV-induced LRTI. Approximately half of all pediatric LRTI occur in the first six months of life, and LRTI is the leading cause of hospitalization in this age group [Boyce, 2000; Deshpande, 2003; Hall, 2009; Holman, 2004; Iwane, 2004; Nair, 2010; Vicente, 2003].

The implementation of surveillance will also assist in establishing robust infrastructure and processes for RSV-LRTI and RSV hospitalization detection in future vaccine trials.

2. BENEFIT: RISK ASSESSMENT

The following section outlines the risk assessment and mitigation strategy for this study protocol:

2.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood sample collection- While giving blood the subject may feel faint, or locally experience mild pain, bruising, irritation or redness.	Spontaneous data	Sample collection will only be performed by appropriately trained study personnel. All subjects will remain under observation, post venipuncture, through completion of the applicable study visit. Subjects will be notified of this risk in the informed consent form.
Nasal swab collection from infant subjects may cause discomfort	Spontaneous data	Sample collection will only be performed by appropriately trained personnel. Subjects' parent(s)/LAR(s) will be notified of this risk in the informed consent form.

2.2. Benefit Assessment

Study participation may have limited or no benefit for the study subjects themselves.

Study procedures aim to ensure surveillance for maternal outcomes and events of interest and neonatal events of interest. The attention to surveillance may enhance the ability to detect these safety events and to refer subjects for management according to local standard of care. The protocol also includes procedures that may enhance surveillance for RSV, and possibly other lower respiratory tract illnesses, in neonates and infants. Thus, the procedures described in this protocol may enhance the ability to detect these events or illnesses and to refer subjects for management according to local standard of care.

Data collected during the study may enhance understanding of the frequency of maternal events of interest in women with low risk pregnancies, neonatal events of interest, and RSV-associated lower respiratory tract illnesses in neonates and infants.

Surveillance methods explored and data collected during this study may inform future care and prevention efforts and will be used to design robust monitoring systems for future clinical trials of maternal immunization.

2.3. Overall Benefit:Risk Conclusion (Amended 29-MAY-2020)

This is an epidemiologic study that describes the prevalence of pregnancy outcomes and maternal/neonatal events of interest. The study does not include the administration of any investigational vaccine. It is not expected that the participation of pregnant women and their babies in the study would create any further risk to study participants. The study includes the establishment of a surveillance system for lower respiratory tract infections (LRTI) which may facilitate detection of respiratory tract infections, including COVID-19 cases, that might be diagnosed in children enrolled in the study.

Potential risks to subjects participating in this study are limited to those associated with the collection of biological specimens. Taking into account the measures to minimize these potential risks for subjects participating in this study, the potential or identified risks are justified by the potential benefits of enhanced surveillance for the subjects, and by the knowledge gained about the frequency of events of interest.

3. OBJECTIVES

3.1. Primary objectives

In healthy pregnant women with uncomplicated pregnancies:

- To determine the frequencies of pregnancy outcomes.
- To determine the frequencies of pregnancy related events of interest from enrollment (Visit 1) through 42 days after delivery (Visit 6). (Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.)

In all neonates live-born to women enrolled in the study:

- To determine the frequencies of neonatal events of interest.

Neonatal events of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study.

Refer to Section 11.1.1 for the definition of the primary endpoints.

3.2. Secondary objectives

In healthy pregnant women with uncomplicated pregnancies at enrollment:

- To determine frequencies of pregnancy related events of interest according to GAIA levels of diagnostic certainty (where these are specified) (APPENDIX D) from enrollment (Visit 1) through 42 days after delivery (Visit 6). (Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.)
- To describe the distribution of RSV-A antibody titers in maternal blood at delivery.

In all neonates live-born to women enrolled in the study:

- To determine frequencies of neonatal events of interest according to GAIA levels of diagnostic certainty (where these are specified). (APPENDIX D). Neonatal events of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study.
- To describe the distribution of RSV-A antibody titers in cord blood at delivery.

In all neonates/infants live-born to women enrolled in the study, from birth through 1 year of age:

- To determine the incidence of all, of severe, and of very severe RSV-lower respiratory tract illnesses (LRTIs).
- To determine the incidence of RSV hospitalization.
- **Refer to Section 11.1.2 for the definition of the secondary endpoints.**

Refer to the GLOSSARY OF TERMS for the definition of enrollment.

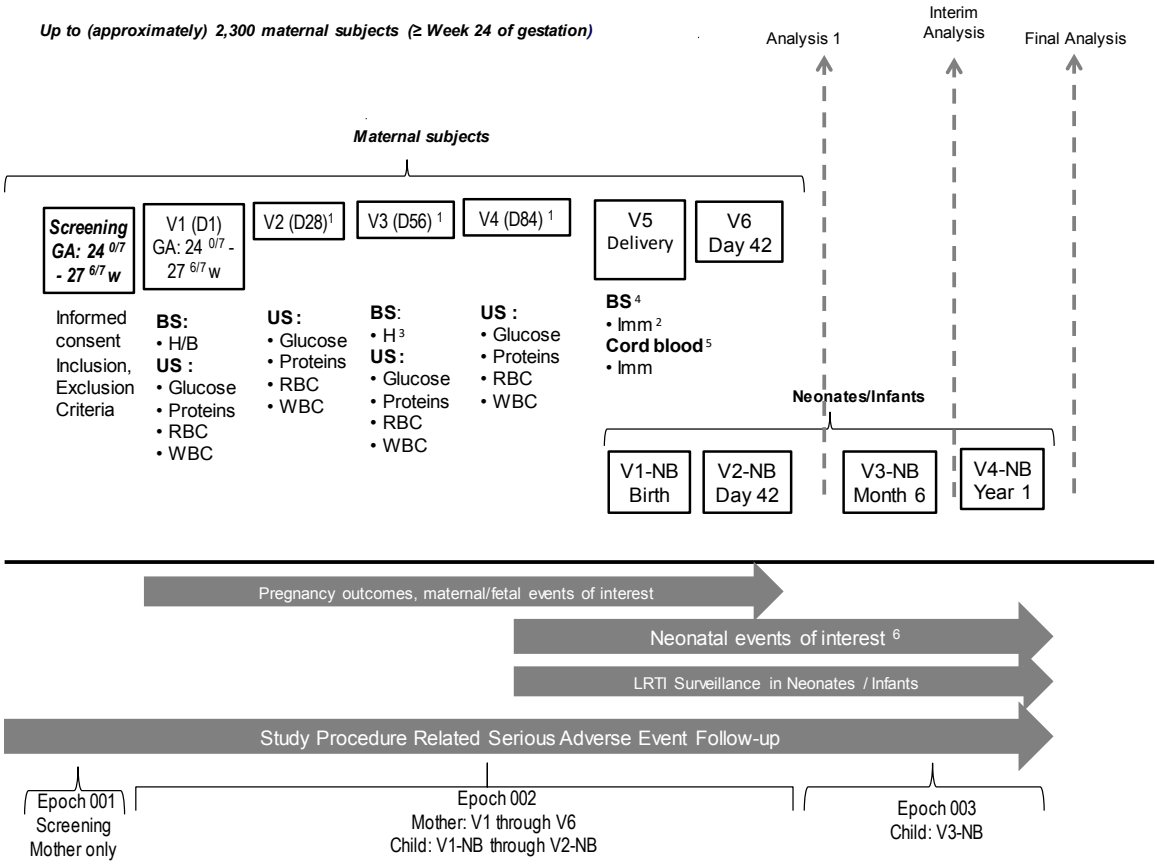
3.3. Tertiary objectives (Amended 29-MAY--2020)

- To describe co-infections of RSV-LRTI with other respiratory viruses in infants.
- To estimate the association of RSV-LRTI in neonates/infants and the level of RSV neutralizing antibodies in cord blood.
- ***To determine the incidence of LRTIs/Severe LRTIs (using alternative case definitions)***
- To determine risk factors for pregnancy-related and neonatal events of interest.
- If deemed necessary, to further characterize the immune responses to RSV and other infections in maternal subjects and infants (based on maternal serum and cord blood).

Refer to Section 11.1.3 for the definition of the tertiary endpoints.

4. STUDY DESIGN OVERVIEW (AMENDED 29-MAY-2020)

Figure 1 Study design (Amended 29-MAY-2020)



D = day; M = month; V = visit; W = week; Y = year. NB = newborn; GA = Gestational age; BS = blood sample; US = urine sample for dipstick testing; IMM = immune response; HB = hematology/biochemistry; RBC = red blood cell(s); WBC = white blood cell(s); RSV = respiratory syncytial virus; RTI = respiratory tract illness; LRTI = lower respiratory tract illness;

Refer to Section 11.11 for additional information about the analyses indicated above.

[1] If delivery occurs prematurely, skip to Visit 5 ("at delivery").

[2] At Delivery, RSV-A antibody titers for all women

[3] At V3, only hemoglobin testing.

[4] Allowed interval for blood sample collection begins with start of labor (e.g. when the mother arrives at the hospital to deliver and an intravenous line is inserted) and ends 72 hours after delivery.

[5] RSV-A antibodies in cord blood

[6] Neonatal events of interest occur (by definition) between 0 and 28 days after birth. They will be reported once site staff become aware of them (whether this occurs during the first 28 days after birth, or at a later time).

NOTE: Covid-19 cases identified within the surveillance framework of the study in maternal and infant subjects will also be recorded.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 8.3), are essential and required for study conduct.

- Type of design: Prospective, epidemiological, interventional (without administration of medicinal products as described in a research protocol), multi-country, cohort study.
- Study population: The study will be conducted in multiple countries, in pregnant women and their infants.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

Table 1 Sampling schedule for maternal subjects

		Visit				
Sample	**Parameter(s) evaluated**	**1**	**2**	**3**	**4**	**Delivery**
Maternal **Blood**	Hematology/ biochemistry[1, 4]	x		x[3]		
	Antibody titer (RSV-A)					≤ 72 hours after delivery[5]
Cord Blood	Antibody titer (RSV-A)					x
Urine	Protein, glucose, RBC, WBC [2, 4]	x	x	x	x	

[1] To be performed preferentially by local healthcare providers, as per local practice. To be performed by the investigator/study staff ONLY if not done by the local healthcare provider within 2 weeks before the study visit.
[2] The investigator/site staff will perform a urine dipstick test using supplies provided by GSK.
[3] Hemoglobin only
[4] If results are abnormal, subjects will be referred per local standard of care.
[5] This sample may be collected from start of labor (e.g. when the mother arrives at the hospital to deliver and an intravenous line is inserted) through 72 hours after delivery.

- Sampling schedule for **neonates/infants**: Surveillance for RSV LRTI will be conducted in infants through the 12 month study period. During this 1-year post-birth surveillance period, for each RTI with suspicion of difficulty in breathing, or wheezing, or with parental concern, a nasal swab will be collected at a visit to assess potential RSV associated RTIs/LRTIs.
- Primary Completion Date (PCD): 42 days post-delivery/birth (i.e. Visit 6 for maternal subjects and Visit 2-NB for infant subjects) or last visit of Epoch 002.
- End of Study (EoS): Last testing results released of samples collected up to Visit 4-NB (assays related to primary and secondary endpoints).
- Duration of the study: Approximately 4.5 to 6 months for maternal subjects; approximately 1 year for infant subjects.
  - Epoch 001: Screening
  - Epoch 002: Primary starting at Visit 1 and ending 42 days post-delivery/birth (Visit 6 for maternal subjects and Visit 2-NB for infant subjects).*
  - Epoch 003: Follow-up of infants starting 43 days post-delivery/birth and ending at Visit 4-NB (1 year post-birth).

*Any safety and disease surveillance data collected after Visit 2-NB will be collected in Epoch 003.

Table 2 Study groups and epochs foreseen in the study

Study Groups	Number of subjects enrolled	Age (Min/Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
Maternal subjects	Up to ~ 2300	18 years - 45 years	x	x	
Infants	Up to ~ 2300	NA		x	x

Approximately 200 to 300 per country. To achieve the enrollment targets noted above, the number of pregnant women SCREENED in each country may exceed the country-specific enrolment goal.

- Surveillance for pregnancy outcomes and pregnancy-related events of interest(Section 8.5.8) that occur from Visit 1 up to 42 days after delivery (Visit 6).
- Surveillance for neonatal events of interest(Section 8.6.3) that occur from birth up to 28 days of age.
- Surveillance for RSV LRTI and RSV hospitalization (refer to Section 8.6.8) in infants, from birth up to 1 year of age.

5. CASE DEFINITIONS

5.1. Pregnancy related events of interest

Pregnancy related events of interest are briefly defined in the GLOSSARY OF TERMS, listed in Section 11.1 and described in detail in APPENDIX D.

5.2. Neonatal events of interest

Neonatal events of interest are briefly defined in the GLOSSARY OF TERMS, listed in Section 11.1 and described in detail in APPENDIX D.

5.3. Respiratory tract illness (RTI) / Lower respiratory tract illness (LRTI)

During data analysis, cases of respiratory tract illness (RTI) identified from birth up to 1 year of age will be classified according to the case definitions in Table 3.

5.4. RSV infection (Amended 29-MAY-2020)

Nasal swabs will be analyzed by the sponsor for the presence of RSV A/B. A positive test result constitutes a case of RSV infection. Refer to Section 8.6.7.3.

Table 3 RTI/LRTI case definitions for data analysis

RSV-RTI	Runny nose, OR Blocked nose, OR Cough AND Confirmed RSV infection [4]
RSV-LRTI	History of cough OR difficulty in breathing [1] AND SpO_2 < 95% [2], OR RR increase [3] AND Confirmed RSV infection [4]
RSV-severe LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93%, OR lower chest wall in-drawing
RSV-very severe LRTI	Meeting the case definition of RSV-LRTI AND SpO2 < 90%, OR inability to feed OR failure to respond / unconscious
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]
All-cause RTI	Runny nose, OR Blocked nose, OR Cough
All-cause LRTI	History of cough OR difficulty in breathing [1] AND SpO2 < 95% 2, OR RR increase [3]

Definitions based on [Modjarrad, 2016]

RTI = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.

[1] Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnoea).

[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.

[3] RR increase defined as:

> 60/minute (< 2 months of age)
> 50/minute (2 to < 12 months of age)
> 40/minute (12 to 24 months of age)

[4] RSV infection confirmed on nasal swab positive for RSV A or B by quantitative reverse transcription polymerase chain reaction (qRT-PCR).

[5] RSV sampling and testing is described in Sections 8.6.7, 8.6.8 and 8.6.9.

[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider

Table 4 Alternative LRTI / Severe LRTI Case Definitions (Amended 29-MAY-2020)

	RSV confirmed	*Documented physical examination (PE) findings indicating lower respiratory tract involvement (at least one symptom)*	*Objective measures of clinical severity (at least one symptom)*
LRTI	*Confirmed RSV infection*	*Rhonchi*[1] *Rales*[1] *Crackles* *Wheeze*	*Increased respiratory rate (bpm)* *≥ 60 for < 2 mo* *≥ 50 for 2-6 mo*
			Hypoxemia: *SpO2 <95% at ≤1800 meters* *SpO2 <92% at > 1800 meters*
			New onset apnea
			Nasal flaring
			Retractions[2]
			Grunting
Severe LRTI	*Confirmed RSV infection*	*Rhonchi*[1] *Rales*[1] *Crackles* *Wheeze*	*Hypoxemia* *SpO2 <93% at ≤1800 meters* *SpO2 <90% at > 1800 meters*
			Acute hypoxic or ventilatory failure[3]
			Dehydration due to respiratory distress requiring IV hydration[4]
			Failure to respond or unconscious

[1]Term not listed in the eCRF page in this study.

[2] Intercostal recession or chest wall indrawing are considered synonymous with and will be used as alternatives to the term "retractions," which is not listed in the eCRF page for this study.

[3] Acute hypoxic or ventilatory failure is not listed in the eCRF page for this study. Instead, the presence of either respiratory support excluding mechanical ventilation OR requirement for mechanical ventilation or both will be used.

[4] Dehydration due to respiratory distress requiring IV hydration is not listed in the eCRF page for this study. Skin turgor > 2 seconds or administration of IV fluid therapy will be used instead.

6. STUDY POPULATION

6.1. Number of subjects/ centers (Amended 29-MAY-2020)

The study will be conducted at multiple centers in multiple countries. The total enrolled study population will consist of up to (approximately) 2,300 pregnant women and their neonates.

In each participating country, approximately 200 to 300 pregnant women $\geq 24^{0/7}$ and $\leq 27^{6/7}$ weeks of gestation will be enrolled. Neonates of enrolled pregnant women who consent to their child's study participation will also be enrolled.

6.2. Inclusion criteria for enrollment

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

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

6.2.1. Maternal subjects:

- Healthy pregnant women 18-45 years of age who are ≥ 24 0/7 weeks GA at screening and ≤ 27 6/7 weeks GA at Visit 1, as established by ultrasound examination and/or last menstrual period (LMP) date*

* The level of diagnostic certainty of the gestational age should be established by using the GAIA gestational age assessment form (provided in APPENDIX C).

- Women with pre-pregnancy body mass index (BMI) ≥18.5 and ≤ 39.9 kg/m^2.
- Women whose pregnancy is considered low risk, based on medical history, obstetric history, and clinical findings during the current pregnancy.
- Women who had no significant findings (such as abnormal fetal morphology, amniotic fluid levels, placenta, or umbilical cord) observed during a Level 2 ultrasound (fetal morphology assessment).
- HIV uninfected women who have been tested within the past year and have documented HIV negative test results.
- Individuals who give written or witnessed/thumb printed informed consent after the study has been explained according to local regulatory requirements.
  - The informed consent given at screening should either include consent for both the mother's participation and participation of the infant after the infant's birth (if consistent with local regulations/guidelines), or consent for the mother's participation and expressed willingness to consider permitting the infant to take part after the infant has been born (if local regulations/guidelines require parent(s) to provide an additional informed consent after the infant's birth).
  - Both mother and father should consent if local regulations/guidelines require it.
- Individuals who consent to have cord blood collected at delivery for the purpose of the study;
- Individuals who plan to reside in the study area for at least one year after delivery.
- Individuals who are in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator;
- Individuals who, in the opinion of the investigator can and will comprehend and comply with all study procedures (e.g., return for study follow-up visits, be contactable and available on a regular basis for surveillance).

6.2.2. Infants (Amended 29-MAY-2020):

- Infants who were in utero at the time maternal (and paternal, if required) informed consent was given, and who are live-born.
- If local law requires it: Written or witnessed/thumb printed informed consent for study participation of the infant obtained from parent(s)/LAR(s) within ***21*** days of birth.

6.3. Exclusion criteria for enrollment

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

The following criteria should be checked at the screening visit and at Visit 1. If ANY exclusion criterion applies, the subject must not be included in the study:

6.3.1. Maternal subjects:

- Individuals determined to have one of the following conditions associated with increased risk for a serious obstetrical complication (specify any/all that apply in the eCRF)
  - Gestational hypertension;
  - Gestational diabetes uncontrolled by diet and exercise;
  - Pre-eclampsia or eclampsia;
  - Multiple pregnancy;
  - Intrauterine growth restriction;
  - Placenta previa;
  - Polyhydramnios;
  - Oligohydramnios.
- Individuals determined to have (during the current pregnancy) one of the following infections or conditions associated with risk of adverse outcome (specify any/all that apply in the eCRF):
  - Known or suspected:
    - Syphilis infection,
    - Parvovirus B19,
    - Rubella infection,
    - primary genital herpes simplex infection,
    - primary cytomegalovirus infection,
    - varicella infection,

  - Zika infection,
  - Active tuberculosis infection,
- Incompetent cervix or cerclage

- Individuals who have any underlying condition or infection that would predispose them to increased risk for a serious obstetrical complication that is not mentioned above.
- Individuals who have behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, could interfere with the subject's ability to participate in the study.
- Individuals who have known or suspected impairment of the immune system, an active autoimmune disorder that is not well-controlled, or who are receiving systemic immunosuppressive therapy.
- Individuals participating in any concurrent clinical trial during the current pregnancy.
- Individuals pregnant with a fetus with a confirmed or suspected major congenital anomaly at the time of enrollment.

6.3.2. Infants:

- Child in care

Please refer to the GLOSSARY OF TERMS for the definition of child in care.

7. CONDUCT OF THE STUDY

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

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), 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 pediatric population (ICH E11) and all other applicable ethical guidelines.

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

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

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

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

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

GSK Biologicals will prepare a model Informed Consent Form (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.

8. DETAILED STUDY PROCEDURES

8.1. Subject identification

Subject numbers for pregnant women (mothers) who consent to participate in the study will be assigned at screening. Subject numbers for their (yet to be born) neonates will be assigned at Visit 1. Subject numbers will be assigned sequentially according to the range of numbers allocated to each study centre. Subject numbers of mother –infant pairs will be clearly linked.

8.2. General study aspects

Critical study conduct information not mandated to be present in this protocol is provided in the Study Procedures Manual (SPM). As such, the SPM should be viewed as a companion document that should be read carefully to fully understand the study protocol. The SPM provides the investigator and the site personnel with detailed operational information that is essential for correct study execution and does not impact the safety of the subjects.

Study visits and procedures in this protocol are defined to ensure that maternal and neonatal events of interest, as well as RSV-associated LRTIs and RSV hospitalization in infants, are captured. Prenatal screening and care will be provided by local healthcare providers (in accordance with local standards).

Study visits are not intended to replace local standard of care antenatal visits. If local standard of care recommends additional visits/medical evaluations during pregnancy, women participating in this study should comply with their regular antenatal care visit schedules, per local recommendations.

Study procedures are not intended to replace procedures performed by local healthcare providers as part of standard care.

8.2.1. Study procedures during special circumstances (Amended 29-MAY-2020)

During special circumstances (e.g., the 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 subjects if deemed feasible by the investigator.

- ***If it is not possible to conduct a protocol-specified, scheduled or event-driven (e.g., LRTI assessment) visit as described in Section 8.3, the visit may be replaced with a contact conducted by telephone, videotelephony or telemedicine. SMS and email are not allowed.***
- ***Biological samples may be collected at a different location* other than the study site, or at the subject's home. Biological samples should not be collected if they cannot be obtained within the visit interval (Section 8.4), processed in a timely manner or appropriately stored until the intended use.***
  - ***Nasal swabs should only be collected using centrally provided supplies.***
  - ***Cord Blood for assessment of immune response may be collected locally but must be retrieved, processed and stored in accordance with the Investigator Laboratory Manual.***
  - ***Additional blood samples for assessment of immune response should only be collected using centrally provided supplies.***
- ***Diary cards may be transmitted from and to the site by electronic mail, and / or conventional mail.***

Impact on the per protocol sets for analysis will be determined on a case by case basis.

Any impact of the above mentioned measures on the study results will be described in the clinical study report.

**** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.***

8.3. Outline of study procedures (Amended 29-MAY-2020)

Potential study participants (pregnant women) are to be screened at ≥ 24 $^{0/7}$ weeks gestational age. Pregnant women for whom eligibility has been confirmed are to complete Visit 1 not later than at 27 $^{6/7}$ weeks gestational age.

Table 5 List of study procedures for maternal subjects (Amended 29-MAY-2020)

Gestational age	24 $^{0/7}$ – 27 $^{6/7}$	24 $^{0/7}$ – 27 $^{6/7}$						
Epoch	Epoch 001	Epoch 002						
Type of contact	Screening	Visit 1	Visit 2 [2]	Visit 3 [2]	Visit 4 [2]	Visit 5	Visit 6 [3,4]	Additional antenatal/medical evaluations [5]
Timepoints		Day 1	Day 28	Day 56	Day 84	At Delivery	Post-Delivery Day 42	
Eligibility Review and Confirmation								
Informed consent [1]	●							
Check inclusion/exclusion criteria	●	O						
Assign subject study number (mother)	●							
Assign subject study number (child)		O						
Ensure that site study physicians (both obstetrician(s) and pediatrician(s)) are informed		O				O		
Medical History / Examinations								
Distribute Maternal Subject Card		O						
Distribute maternal diary card		O	O	O	O	O		
Review and collect maternal diary card			O	O	O	O	O	
Transcribe applicable diary card data to the eCRF			●	●	●	●	●	
Record demographic data	●							
Record lifestyle characteristics		●						
Record outcome of Level 2 ultrasound (fetal morphology scan) [9]	●							
Record outcome(s) of subsequent ultrasounds if clinically significant [5]		O [5]	O [5]	O [5]	O [5]	O [5]		● [5]
Review and collect medical history	O	●						
Review and collect obstetric history from past pregnancies	●							

Gestational age	24 0/7 – 27 6/7	24 0/7 – 27 6/7						
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	**Screening**	**Visit 1**	**Visit 2** [2]	**Visit 3** [2]	**Visit 4** [2]	**Visit 5**	**Visit 6** [3,4]	**Additional antenatal/medical evaluations** [5]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Review and collect obstetric history from current pregnancy, including: gestational age, expected date of delivery and method of EDD estimation including pre-pregnancy weight	●							
Travel history to, or living in, countries/regions with Zika virus transmission (during the current pregnancy)	O	●	O	O	O	O		●
Where authorized by the local Ethics Committee, inquire whether mother would have agreed to take part in the study if an investigational vaccine were given		●						
Record outcome of HIV test [10]	●							
Record results of General and Obstetric examination [11]	●	●	●	●	●		●	● [14]
Check and record prescription medications, vaccinations, folate and/or iron (independently or included in a multivitamin) [13]	●	●	●	●	●	●	●	●
Biological Specimens / Laboratory Test Results								
Collect blood sample for antibody assessment by sponsor (~5 ml)						●		
Collect cord blood for antibody assessment by sponsor (~5 to 10 ml)						●		
Record results of local hematology/ biochemical analysis (Visit 1~5.5 ml; Visit 3~2 ml – hemoglobin only) [6]		●		●				● [14]
Record results of urine dipstick to check for presence of proteins, glucose, RBC, WBC [8]		●	●	●	●			● [14]
Record results of oral glucose challenge / tolerance test(s) if performed by local healthcare provider and available [7]	●	O [5]	O [5]	O [5]	O [5]			● [5]
Record results of any clinically significant abnormal laboratory tests (including positive urine culture) if performed by local healthcare provider and available [5]		O [5]	O [5]	O [5]	O [5]	O [5]	O [5]	● [5]

Gestational age	24 0/7 – 27 6/7	24 0/7 – 27 6/7						
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	**Screening**	**Visit 1**	**Visit 2** [2]	**Visit 3** [2]	**Visit 4** [2]	**Visit 5**	**Visit 6** [3,4]	**Additional antenatal/medical evaluations** [5]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Labor / Delivery								
Collect and record labor and delivery information [12]						●		
Outcomes and Events of Interest								
Record Pregnancy/Delivery outcome(s)						●		
Record pregnancy-related events of interest. Record other clinically significant events or diagnoses [15]		●	●	●	●	●	●	●
Record all hospitalizations (except hospitalization for delivery), and all extensions of hospitalizations (including extension of hospitalization for delivery) [5]		●	●	●	●	●	●	●
Serious Adverse Events								
Record SAEs related to study participation	●	●	●	●	●	●	●	
Screening/Study Conclusion								
Screening conclusion	●							
Study conclusion							●	
Investigator sign-off on eCRF before analysis	●						●	

SAE = serious adverse event; ● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF)
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

[1] Refer to Section 6.2.1, ***sixth*** bullet.

[2] If delivery occurs prematurely, skip to Visit 5 ("at delivery").

[3] Visit 6 (Day 42) may take place in the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator

[4] To coincide with Visit 2-NB (Day 42) for infants.

[5] Information from additional antenatal / medical evaluations (external to study visits/procedures) may be collected during, before or after a scheduled study visit but should only be recorded in the additional antenatal/medical evaluations eCRF

[6] To be performed preferentially by local healthcare providers as per local practice. To be performed by the investigator/site staff ONLY if not done by the local healthcare provider within 2 weeks before the study visit. If results are abnormal, subjects will be referred per local standard of care.

[7] If results of an oral glucose challenge / tolerance test are not available to confirm that the subject does not have Gestational Diabetes at screening, then fasting blood glucose or hemoglobin A1C test results (if performed by local healthcare provider and available) may be used as described in Table 27.

[8] The Investigator/ site staff will perform a urine dipstick test to detect the presence of proteins, glucose, RBC and WBC.

[9] If ultrasound results are not available at time of screening, the ultrasound can be performed as a study procedure under certain conditions. Refer to SPM for further details. If abnormal, subjects will be referred per local standard of care.

[10] ***Where*** HIV testing is not part of the standard of care for pregnant women, the screening HIV test can be performed locally as a study procedure. Refer to SPM for further details. If results are positive, subject will be referred per local standard of care.

[11] Height at screening. Weight, temperature, systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest, blood oxygen saturation by pulse oximetry, fetal heart tones, fetal movement, and fundal height at Screening and Visits 1 – 4. Temperature, systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest, and blood oxygen saturation by pulse oximetry at Visit 6.

[12] Includes date and time of rupture of membranes, date and time of delivery, type of delivery, and other delivery information related to the health and safety of the mother and fetus.

[13] Beginning the month before the estimated date of conception and while on study. (Routine medications administered during labor and delivery need not be collected.)

[14] Record clinically significant abnormal results

[15]Includes events or diagnoses that could impact the pregnancy including COVID-19 cases

Table 6 List of study procedures for neonates/ infants (Amended 29-MAY-2020)

Epoch	Epoch 002		Epoch 003		Epoch 002 and Epoch 003	
Age	**0-*21* days**	**42 Days**	**6 Months**	**12 months**	**0-12 months**	
Type of contact	**Visit 1-NB**	**Visit 2-NB** [b]	**Visit 3-NB** [b]	**Visit 4-NB** [b]	**Contact for active/ passive surveillance**	**Visit to assess potential LRTI** [b]
Timepoints	**Birth**	**Day 42**	***M6***	**Y1**		
Check inclusion/exclusion criteria	●					
Obtain post-delivery informed consent from parent(s)/LAR(s) if required per local regulations	● [a]					
Record infant's subject number	●					
Record Apgar assessment	●					
Record demographic data	●					
Record lifestyle characteristics		●				
Distribute Infant's Subject Card	O					
Distribute infant diary card [d]	O	O	O			O
Review infant diary card		O	O	O		O
Collect infant diary card [e] [f]		O	O	O		O
Transcribe applicable infant diary card data to eCRF		●	●	●		●
Weight, length, head circumference, results of targeted medical history, and results of physical examination	●	●	●	●		
Record prescription medications / vaccinations	●	●	●	●	●	●
Record neonatal events of interest	●	●	●	●		
Clinical evaluation of potential LRTI						●
Nasal swab [b]						● [c]
Record all hospitalizations and clinically significant events [h]	●	●	●	●	●	●
Record SAEs related to study participation	●	●	●	●	●	●
Study conclusion				●		
Investigator sign-off on eCRF before analysis		●	● [g]	●		

LAR = legally acceptable representative; **LRTI** = lower respiratory tract illness; **NB** = newborn; **RTI** = respiratory tract illness; **SAE** = serious adverse event; ***M=month***; **Y** = year. Grey shaded columns represent study procedures to be performed for active/passive surveillance of RTIs/LRTIs which are applicable throughout the entire study period (from birth up to study end). **Note:** The double-line borders indicate primary analyses.

● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF).

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

[a] If local regulations require that written consent / confirmation of consent for the infant's participation be obtained at birth.
[b] Visits 2-, 3-, and 4-NB and LRTI assessment visits may take place in the subject's home (if the standard of care allows for home visits), at the investigator's clinical facility or at another facility per the investigator's judgment.
[c] If more than one assessment visit is conducted to evaluate a potential LRTI, additional nasal swabs may be collected at the discretion of the Investigator.
[d] Distribute at V1-NB: Distribute additional diary cards at subsequent visits as needed.
[e] Collect diary cards that are fully filled out and / or document (L)RTI symptoms that have ended. Provide new diary cards as needed.
[f] Collect all diary cards for potential RTIs that are considered resolved. Collect the diary card for the current potential LRTI once the LRTI symptoms have ended.
[g] When approximately 50% of infants have completed up to Visit 3-NB, an interim analysis ***may*** be conducted to assess the accumulated RSV LRTI cases and the distribution of maternal and cord blood serum RSV Ab. .
[h] ***Includes COVID-19 cases***

8.4. Intervals between study visits (Amended 29-MAY-2020)

Whenever possible, the investigator should arrange study visits within the interval described in Table 7.

Table 7 Intervals between study visits/contacts/observations* (Amended 29-MAY-2020)

Interval	Optimal interval	Allowed interval**
Screening → Visit 1	1 days	0 - 28 days
Visit 1 → Visit 2**	28 days	21 –35 days
Visit 1 → Visit 3**	56 days	49 – 63 days
Visit 1 → Visit 4**	84 days	77 – 91 days
Maternal blood sample collection "at" Visit 5 (delivery)	0 days	0 (Start of labor) - 3 days (i.e., 72 hours post-delivery)
Visit 5 → Visit 6	42 days	35 – 49 days
Birth → Visit 1-NB	0 days	0 - ***21*** days
Birth → Visit 2-NB	42 days	35 - 49 days
Birth → Visit 3-NB	180 days	166 -194 days
Birth → Visit 4-NB	365 days	351 - 379 days

*If other visits and medical evaluations are performed (outside of study visits/procedures), data should be collected in the electronic case report forms (eCRFs) (see Section 8.5.7).
**If a subject returns for the visit outside the allowed time interval, he/she may still be considered for analysis.

Investigators should make at least 3 documented attempts (through telephone call(s) or any other convenient procedure) to contact (as relevant) the pregnant woman/mother or the child's parents/ LAR(s) (or their designates) if they do not return for scheduled visits or follow-up. Additional details can be found in the SPM.

8.5. Description of study procedures for maternal subjects

This section lists procedures to be performed / data to be recorded during the study and presents additional details where relevant. For the study procedures schedule, refer to Table 5.

8.5.1. Eligibility Review and Confirmation

- Obtain Informed consent as described in Sections 6.2.1 and 7.1.
- Check all applicable inclusion and exclusion criteria as described in Sections 6.2 and 6.3 before enrollment and record results.
- Assign / record subject study number (pregnant woman)
- Assign subject study number (infant) for eligible pregnant women who complete Visit 1.
- For eligible pregnant women who complete visit 1 (are enrolled): ensure that site study physicians (both obstetrician(s) and pediatrician(s)) are informed. In particular, the study pediatrician and/or staff should be notified as soon as possible after a pregnant woman's enrolment to ensure the study pediatrician is informed of the approximate date of delivery and potential enrolment of the neonate.

8.5.2. History for maternal subjects

- Distribute the Maternal Subject Card (Section 9.3).
- Distribute the Maternal Diary Card to the subject (Section 8.5.4).
- Record demographic data, which may include (but are not limited to) information such as geographic ancestry (race), month and year of birth, and ethnicity.
- Record information about lifestyle characteristics (exposures), which may include (but are not limited to) data on highest level of education, factors such as smoking status/exposures, household environment, and other factors that could place subjects at risk of study outcomes.
- Record information about whether (during the current pregnancy) the subject has travelled to / is living in countries / regions with Zika virus transmission.
- Where authorized by the local Ethics Committee, inquire whether mother would have agreed to take part in the study if an investigational vaccine were given and record the answer.
- Record outcome of Level 2 ultrasound (fetal morphology assessment). Please see GLOSSARY OF TERMS for description. If Level 2 ultrasound results are not available at screening, then the ultrasound can be performed as a study procedure under certain conditions. Refer to the SPM for further details.
- ONLY record outcome(s) of any subsequent ultrasound(s) if clinically significant.
- Record the subject's pre-pregnancy weight (i.e., weight during the months before the subject became pregnant) in the subject's eCRF. This information can be obtained either via medical record review or subject interview.
- Confirm that the subject's pre-pregnancy BMI is within the range specified in Section 6.2.1. This information can be obtained from the medical record, or, if unavailable, may be calculated based on the subject's height and reported pre-pregnancy weight.
- Obtain the subject's medical and obstetric history by interview and/or review of her medical records. Record any pre-existing conditions or signs and/or symptoms present before participation in the study
  - For past pregnancies, record:
    - Number of past pregnancies and their outcome(s),
    - Presence of caesarian section scars (if any).
  - For the current pregnancy, record:
    - Gestational age, along with GAIA level of certainty, using priorities defined in APPENDIX C.
    - Expected date of delivery (EDD) and method of estimation
    - Number of prenatal visits attended up to the date of the study Screening visit,

- Approximate date of first prenatal visit,
- Results of any clinically significant, abnormal pregnancy screening laboratory tests,
- Results of any procedures intended to screen for congenital anomalies.

8.5.3. Examinations of maternal subjects

Record results of General and Obstetric examinations.

- Record height at screening. Height measurements should be performed preferentially by local healthcare providers, in which case the information will be collected and recorded in the mother's eCRF. If not done by the local healthcare provider as per local practice, the investigator/study staff should perform the measurement.
- Unless the study visit is performed concurrently with a routine care visit at which the below data are collected, the investigator/study staff should perform General and Obstetric examinations as follows:
  - Screening and Visits 1 - 4 should include assessment of weight, fetal heart tones, fetal movement, and fundal height;
  - Screening, Visits 1 to 4, and Visit 6 should include assessment of temperature, systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest) and blood oxygen saturation by pulse oximetry.
  - If the Screening Visit and Visit 1 occur on the same day, only one General and Obstetric examination will be performed.

8.5.4. Maternal Diary Card

A maternal diary card will be provided to each subject at visit 1, then collected and replenished throughout the study as needed. It will document any prescription medications, folate and/or iron (independently or included in a multivitamin) taken, any vaccinations received during pregnancy and after delivery, and any additional visits the subject may make to a healthcare provider not affiliated with the study.

The diary card will be reviewed with the subject during study visits. If review indicates that the subject visited a healthcare provider not affiliated with the study, study staff should (if permitted by local regulation) contact that healthcare provider to obtain the medical record(s) for the visit.

Refer to the SPM for additional details.

8.5.5. Biological Specimens / Laboratory Data for maternal subjects

- The Investigator/site staff will arrange for collection of maternal blood and cord blood samples at delivery.
- The Investigator/site staff will perform urine dipstick tests using supplies provided by GSK.

- If HIV test results are not available at time of screening, the HIV test can be performed as a study procedure under certain conditions. Refer to the SPM for further details. If results are positive, the subject will be referred per local standard of care.
- It is preferred that local healthcare providers perform hematology and biochemistry tests per local practice; the investigator/site staff will then collect and record the results. The investigator/site staff will only perform hematology/biochemistry tests if not done by the local healthcare provider within 2 weeks before a study visit.
- If performed by local healthcare provider and results are available, the investigator/site staff will also:
  - Record oral glucose challenge / oral glucose tolerance test results
  - Record any positive urine bacterial culture results
  - Record abnormal and clinically significant laboratory test results
  - Record results of Group B Streptococcus screening test(s).

8.5.6. Labor / Delivery

Record information related to labor and delivery, including:

- Any medications administered during labor and delivery as per standard of care if not considered routine
- Date and time of rupture of membranes
- Date and time of delivery
- Type of delivery
- Other delivery related information relevant to the health and safety of the mother and fetus

8.5.7. Medications, vaccinations, and supplements administered to maternal subjects as per standard of care

Record medications / vaccinations / folate and iron supplements beginning the month before the estimated date of conception and while on study. Folic acid and/or iron supplements should be reported when taken independently and/or when included in a multivitamin mineral supplement.

8.5.8. Outcomes and Events of Interest in maternal subjects (Amended 29-MAY-2020)

- Record delivery and pregnancy outcomes. Of note, fetal death/stillbirth has multiple subcategories. For example, fetal death/stillbirth with no congenital anomalies is an outcome with two subcategories that include: 1) antepartum stillbirth; 2) intrapartum stillbirth. For each outcome, the investigator should select the applicable sub-category.

- If there is no live birth, all study visits and procedures related to the maternal subject should still be followed up to study end.
- Record pregnancy related events of interest.
  - The investigator will review all medical records pertaining to prenatal care based on GAIA definitions (APPENDIX D) when applicable.
  - Maternal events of interest (including, but not limited to, those described in Section 11.1.1) occurring up to Visit 6 (Post-delivery Day 42) should be recorded in the eCRF along with additional details pertinent to the diagnosis, GAIA assessment and level of diagnostic certainty (APPENDIX D), when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.
  - Information about maternal hospitalizations, clinically significant events, and diagnoses that could impact the pregnancy will be recorded.
  - Any events of interest in mother or fetus will be referred to and managed by the routine health services as locally appropriate.
- Record all hospitalizations and/or clinically significant events, ***including COVID-19 cases.***
- Record all study participation related SAEs as specified in Section 9.

8.5.9. Additional Antenatal / medical evaluations external to study visits / procedures

For any additional antenatal / medical evaluations at which a pregnancy related event of interest is identified, record information that supports the diagnosis of the event, if available.

8.6. Description of study procedures for Neonates / Infants (Amended 29-MAY-2020)

This section lists procedures to be performed / data to be recorded during the study and presents additional details where relevant. For the study procedures *schedule*, refer to Table 6. Note that the investigator or study staff will perform (if not performed by local healthcare provider) a minimum of 2 clinical examinations: one at birth (or up to ***21*** days after birth), and another at approximately 42 days of age.

8.6.1. Eligibility Review and Confirmation for Neonates

- Check all applicable inclusion and exclusion criteria as described in Sections 6.2.2 and 6.3.2.
- Record subject study number.

8.6.2. History and Examinations for Neonates / Infants (Amended 29-MAY-2020)

- Record demographic data including month and year of birth, gender, geographic ancestry (race) and ethnicity.
- Record Apgar scores at 1, 5, 10 min after birth (when available).
- Record lifestyle characteristics. Data may include (but are not limited to) passive smoking and contact with young children under 6 years of age.
- Record weight, length, head circumference, results of targeted medical history, and results of physical examinations.
- Record prescription medications/ vaccinations.
- Distribute the Infant Subject Card to the parent(s)/LAR(s)/designate(s). (Section 9.3).
- Distribute the Infant Diary Card to the parent(s)/LAR(s)/designate(s) (Section 8.6.3).
- Record all hospitalizations and/or clinically significant events, ***including COVID-19 cases.*** For hospitalizations where an RSV infection is suspected, refer to Section 8.6.8.
- Record all study participation related SAEs (Section 9).

8.6.3. Infant Diary Cards

Infant diary cards will be provided at the infant Visit 1 NB. They should be completed by the Parent(s)/LAR(s)/designate(s) of the infant subject.

The infant diary cards will be used to document:

- RTI symptoms experienced by the infant, including start and end dates for those symptoms, and
- Additional visits to a pediatric healthcare provider not affiliated with the study, as well as prescription medications (including those taken to treat an RTI) and vaccinations administered to the infant. (If the infant subject was taken to a healthcare provider not affiliated with the study, the study staff should (if permitted by local regulation) contact that healthcare provider to obtain the medical record(s) for the visit.)

At each study visit (including any assessment visits), RTI symptoms may have ended or may be ongoing.

If blocked nose, cough and symptoms of difficulty in breathing (including wheezing) have ended by the time of a study visit:

- Study staff should collect the Diary card(s), and replenish the parent(s)/LAR(s)/designate(s) supply of blank cards as needed.

If blocked nose, cough or symptoms of difficulty in breathing (including wheezing) are ongoing at the time of a study visit (including any assessment visit):

- Study staff should review the diary card, make a photocopy of it, and return it to the parent(s)/LAR(s)/designate(s) so information can continue to be collected until the symptoms have ended.
- As soon as possible after these symptoms have ended, study staff must collect the completed diary card by a site visit, home visit, or postal mail, whichever is most effective based on local practice. The site should make every effort to collect completed diary cards as soon after the symptoms have ended as possible. If diary card collection occurs during a visit to the study site or to the subject's home, a brief clinical evaluation may be performed to confirm that the symptoms have ended.

Refer to the SPM for additional details.

8.6.4. Surveillance for Neonatal events of interest

To detect events of interest in neonates, the investigator will collect a medical history and review all medical records pertaining to medical events in the neonatal period (birth – 28 days), including assessment of congenital anomalies.

8.6.5. Surveillance for potential Lower Respiratory Tract Illness (LRTI)

8.6.5.1. Definitions

Symptoms of Respiratory Tract Illness (RTI) include:

- Regular bursts of cough,
- Nasal discharge running freely out of the infant's nose (runny nose), or
- Breathing through the mouth because the infant's nose is blocked (blocked nose).

A potential lower respiratory tract illness (LRTI) is one in which the infant has one or more of the RTI symptoms listed above AND at least one of the following:

- Difficulty in breathing (fast breathing, poor feeding, working hard to breathe, or making unusual sounds when breathing);
- Wheezing (a whistling sound when the infant breathes out) (another sign of difficulty in breathing**)**;
- Parental concern (the parent(s)/LAR(s) or their designate(s) are concerned about the infant's respiratory tract illness, or general health in the context of the respiratory tract illness, and intend to seek medical care).

Worsening means any clinically observed/diagnosed symptoms and signs that are reported during the same respiratory tract illness and reflect a deterioration in the child's respiratory tract functions.

Start and stop dates will be collected in the diary card for cough, runny nose, blocked nose, wheezing and difficulty in breathing.

Start dates for all symptoms will also be recorded in the eCRF.

Only stop dates for cough and difficulty in breathing will be recorded in the eCRF so that GSK may later define the end of each LRTI episode (Section 5.4)

8.6.5.2. Overview (Amended 29-MAY-2020)

Surveillance for potential LRTIs begins at birth ***(or after additional consent, has been provided for the infant's participation in the study, if required,)*** and ends with the Year 1 study visit.

It will be accomplished via two types of contact. Both may be made with/ by either the Parent(s)/ LAR(s), or a person designated by the parent(s)/LAR(s), such as grandparents or a nanny (as long as the parent(s)/LAR(s) have given approval).

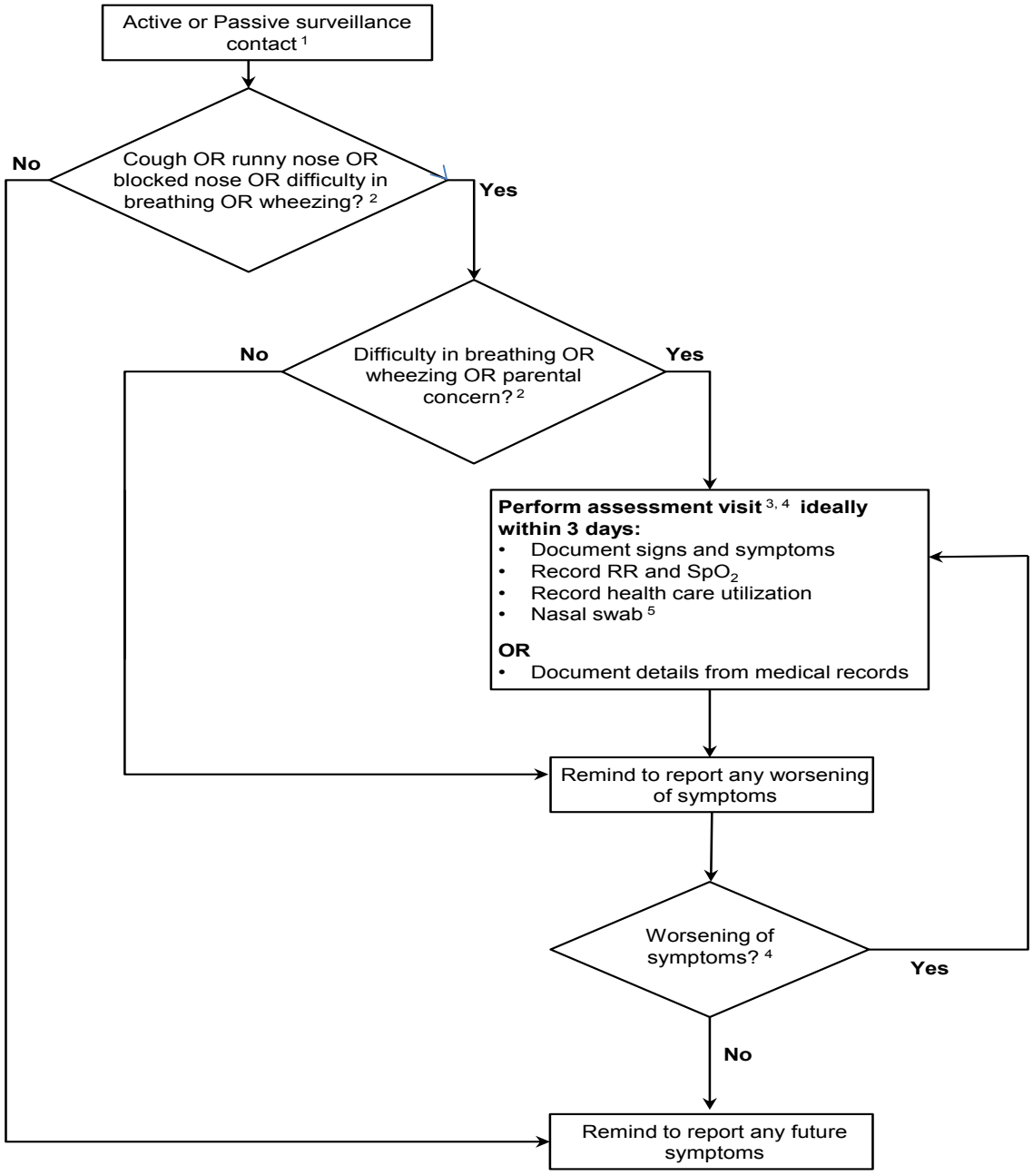
- In an Active contact, site personnel contact the subject's parent(s) / LAR(s) or their designate(s). Active contacts will occur at regular intervals and will be scripted.
- In a Passive contact, the subject's parent(s) / LAR(s) or their designate(s) contact site personnel. Site personnel will use a script to guide data collection once a passive contact has been made.

Site staff will use information gathered during each active or passive surveillance contact to determine whether a visit to assess a potential LRTI (Sections 8.6.6 and 8.6.7) should be scheduled.

For all interactions between parent(s)/LAR(s)/designates and study staff, the safety of the infant is paramount. For any reported illness, the investigator/study staff should assess the need for any intervention and advise the parent(s) / LAR(s) to seek care as necessary. This study is not intended to replace local standards of care.

A decision tree for active and passive surveillance is provided in Figure 2, which is presented on the next page.

Figure 2 Active and Passive Surveillance Decision Tree



RR: Respiratory rate: **SpO_2**: Blood oxygen saturation by pulse oximetry.

[1]Details regarding Active and Passive Surveillance are provided in Sections 8.6.5.3, 8.6.5.4, and the SPM.

[2]Cough, runny nose, blocked nose, difficulty in breathing, wheezing and parental concern are defined in Section 8.6.5.1.

[3]Details regarding the assessment visit to evaluate a potential LRTI are provided in Sections 8.6.6 and 8.6.7 and the SPM.

[4] Post-visit follow up is described in Section 8.6.8 and in the SPM. Worsening is defined in Section 8.6.5.1

[5]If a follow-up assessment visit is conducted, collection of additional nasal swabs are at the Investigator's discretion.

8.6.5.3. Active surveillance

In countries where RSV transmission is seasonal: The study staff will contact the infant's parents/ LAR(s) (or their designates) (phone call, SMS or by other means, depending on local best practice) approximately every week during the RSV season and approximately every month outside the RSV season, up to study end.

In countries with year-round RSV transmission: The study staff will contact the infant's parents/ LAR(s) (or their designates) (phone call, SMS or by other means, depending on local best practice) approximately every 2 weeks, up to study end.

Three attempts should be made to contact the infant's parents/ LAR(s) (or their designates) within the week of a scheduled contact. If these attempts are unsuccessful, that active contact is considered a missed contact. The next active contact will be made according to schedule.

The purpose of the contact is to check with the infant's parent(s)/LAR(s) or their designate(s) if, as defined in Section 8.6.5.1:

- the infant has developed (new) symptoms of RTI, difficulty in breathing, or wheezing;
- there is parental concern as defined in Section 8.6.5.1.

8.6.5.4. Passive surveillance

Infants' parents/LAR(s) or their designate(s) will be instructed to contact the site whenever:

- the infant has developed (new) symptoms of RTI, difficulty in breathing, or wheezing as defined in Section 8.6.5.1,
- the infant's symptoms worsen as defined in Section 8.6.5.1,
- there is parental concern as defined in Section 8.6.5.1.

Contact may be via phone call, SMS or other means, depending on local best practice. If the study site is the primary treating facility for the child, Parent(s)/LAR(s) or their designate(s) may also make "contact" by taking the child directly to the study site.

8.6.6. Decision to conduct a Visit to assess a potential LRTI

If there is NO suspicion of difficulty in breathing, nor wheezing, nor parental concern in the context of the RTI:

- No assessment visit will be conducted.
- The study staff will remind the infant's parent(s)/LAR(s) to report any worsening of symptoms.

If there IS difficulty in breathing, or wheezing (both based on parental assessment), or there is parental concern in the context of the RTI:

An assessment visit will be conducted as soon as possible, ideally within 3 calendar days after learning of the potential LRTI case. Note that the visit may be conducted, and a nasal swab collected, even if beyond the ideal 3-day window as long as symptoms are ongoing.

8.6.7. Visit to assess a potential LRTI

8.6.7.1. Overview (Amended 29-MAY-2020)

The purpose of the visit is to objectively document signs and symptoms by an appropriately qualified person (i.e. medical or nursing), provide medical advice, and take a nasal swab for detection of RSV infection.

The appropriately qualified person will also evaluate whether the LRTI might be related to COVID19. The appropriately qualified person must follow the local standard of care regarding the reporting, and management of COVID-19 cases (suspected, probable or confirmed COVID-10 case), and complete both the COVID-19 form and LRTI form in the CRF. Refer to Section 8.7.

The visit may take place in the subject's home (if allowed per standard of care), the investigator's clinical facility or another medical facility, as appropriate per the judgment of the investigator.

Note that if the reported symptoms are severe enough to warrant urgent care, the parent(s)/LAR(s)/designates should be advised to seek such care (e.g. Emergency Room).

8.6.7.2. Clinical evaluation *(Amended 29-MAY-2020)*

The investigator/study staff will evaluate the clinical signs and symptoms of the RTI. Data to be collected and recorded include (but are not limited to):

- Temperature
- Respiratory rate
- Blood oxygen saturation (measured by pulse oximetry in room air, if feasible)
- Signs of difficulty in breathing (including wheezing, tachypnoea, nasal flaring, chest in-drawing and apnoea)
- ***Possible presence of COVID-19 infection (Section 8.7). As noted above, both the LRTI and COVID-19 eCRFs are to be completed (whether or not the investigator/study staff consider the LRTI to be due to COVID-19.***

Refer to the Study Procedures Manual (SPM) for additional details.

8.6.7.3. Nasal swab

A nasal swab will be collected using sponsor-provided supplies and sent to the sponsor (or sponsor-designated) laboratory for detection of RSV-A/B using quantitative RT-qPCR.

Each nasal swab positive for RSV by quantitative RT-qPCR will also be assessed using a multiplex PCR for detection of a panel of respiratory viruses (Allplex™ Respiratory Panel or similar). Further assessment of RSV-A/B negative samples with multiplex PCR may be performed if deemed necessary.

If more than one assessment visit is conducted to evaluate a potential LRTI, additional nasal swabs may be collected (using sponsor-provided supplies and sent to the sponsor laboratory) at the discretion of the Investigator.

Note: Only the results generated by the sponsor (or sponsor-designated) laboratory (analyzing nasal swabs collected using sponsor-provided supplies) will be used when applying the case definitions for data analysis in Table 3. If other nasal swabs are collected and tested locally as per routine standard of care, results will be required to be entered into the eCRF however this will not form part of the sponsor's application of case definitions for data analysis.

Therefore where mandated by the protocol every effort should please be made to obtain samples for analysis by the sponsor (or sponsor-designated) laboratory.

8.6.7.4. Missed assessment visit

If the criteria for an assessment visit have been met, but the visit cannot take place while symptoms are ongoing, it is a missed assessment visit.

If it is truly not possible to perform an assessment visit (for example, if the child develops a potential LRTI while the family is travelling, and all symptoms have resolved by the time the family returns), then the LRTI assessment visit page of the eCRF should be filled in as completely as possible using available medical history and medical records.

8.6.8. Follow-up after an assessment visit to evaluate a potential LRTI

After an assessment visit (Section 8.6.7) the child will be followed with at least weekly active surveillance contacts, until the RTI/LRTI has resolved. During these active contacts, worsening of symptoms (clinically observed/diagnosed symptoms and signs that are reported during the same respiratory tract illness and reflect a deterioration in the child's respiratory tract functions; for example, onset of additional symptoms or an increase in the intensity of a previously reported symptom) will be assessed. Parent(s) / LAR(s) / designate(s) will be reminded to call/contact/visit the site if symptoms worsen.

If parent(s)/LAR(s)/designates report during an active or passive contact that symptoms have worsened, the site should perform a follow-up visit.

During the follow-up visit, collection of a nasal swab is at the Investigator's discretion.

After symptoms that resulted in one or more assessment visits have ended (Section 8.6.5.1), site staff will ensure that the diary card for those symptoms is returned to the site via site visit, home visit, or postal mail (depending on the most effective local best practice for prompt retrieval of the completed infant diary card following the end of the symptoms).

Important details are provided in the SPM.

8.6.9. RSV Hospitalization

If the child is admitted to hospital for an acute medical event and RSV infection is suspected, during the surveillance period:

- The event will be documented in the eCRF.
- If possible, a nasal swab will be collected from any subject who is hospitalized with a RTI (or soon after release, as long as symptoms are ongoing, per SPM specifications). The nasal swab should be collected using sponsor-provided supplies, for transmission to and testing by the sponsor laboratory.
- If other specimens are collected and tested locally as per routine standard of care, results will be entered into the eCRF. However, only the sponsor laboratory results will be used when applying the case definitions for data analysis in Table 3.

8.7. Reporting Covid-19 Cases – Maternal and Infant subjects (Amended 29-MAY-2020)

In addition to satisfying local reporting requirements for COVID-19 cases, maternal and infant COVID-19 cases identified within the existing framework of the study will be captured and reported on the COVID-19 eCRF for the study.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition [WHO, 2020] using one of the following terms:

- ***Suspected COVID-19 infection***
- ***Probable COVID-19 infection***
- ***Confirmed COVID-19 infection***

8.8. SAEs related to study participation

The subjects will be instructed to contact the investigator immediately should they (or their neonates/infants) manifest any signs or symptoms they perceive as serious.

Refer to Section 9 for procedures for the investigator to record SAEs, and for guidelines on how to submit SAE reports to GSK Biologicals.

8.9. Study Conclusion

The investigator will review data collected to ensure accuracy and completeness and complete the Study Conclusion screen in the pregnant woman's (mother's) and infant's eCRFs.

8.10. Screening failures

Screening failures are defined as subjects who withdraw or are withdrawn from the study after giving informed consent, but before study eligibility (presence of all inclusion and absence of all exclusion criteria) is confirmed.

Discovery during screening of any pregnancy related-event of interest or other condition that violates the requirements for study eligibility should be considered a screening failure.

Discovery during Visit 1 of any condition that violates the requirements for study eligibility should also be considered a screening failure.

The development of such conditions (after Visit 1) does not constitute screening failure and should be captured on the eCRF, as applicable.

Limited data for screening failures will be reported to the eCRF. This limited data set is specified in the eCRF.

8.11. Biological sample handling and analysis

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

Samples will not be labeled 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 use of 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.

If additional testing is performed, the priority ranking given in Section 8.11.4.1 may be changed.

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

Refer also to the Investigator Agreement, where it is noted 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, 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.

8.11.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 11.3 for the definition of study cohorts/data sets to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

8.11.2. Biological samples

Table 8 Biological samples

Sample Type†	Quantity	Unit	Timepoint	Group
Samples collected by Investigator / site staff				
Maternal Blood for antibody titers	~ 5	ml	Visit 5 (Delivery)	All Maternal subjects
Cord blood	~ 5 up to 10	ml	Visit 5 (Delivery)	All Maternal subjects
Urine (dipstick)	-	-	Visit 1 (Day 1) Visit 2 (Day 28) Visit 3 (Day 56) Visit 4 (Day 84)	All Maternal subjects
Nasal swab	-	-	Visit to assess potential LRTI	All Infants event-driven
Samples preferentially collected by local health care provider per local practice[1]				
Maternal Blood for hematology/ biochemistry [1]	Up to 5.5	ml	Visit 1 (Day 1)	All Maternal subjects
Maternal Blood for Hemoglobin	Up to 2	ml	Visit 3 (Day 56)	

[1]To be performed preferentially by local healthcare providers, as per local practice. To be performed by the investigator/study staff ONLY if not done by the local healthcare provider within 2 weeks before the study visit.

8.11.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the addresses of the clinical laboratories used for sample analysis.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.11.3.1. Antibody determination (Amended 29-MAY-2020)

- Functional (neutralizing) antibody titers against RSV-A will be measured by neutralization assay on serum samples (Table 9).

Table 9 Humoral immunity (Antibody determination) (Amended 29-MAY-2020)

System	Component	Method	Kit / Manu-facturer	Unit	Cut-off	Laboratory*
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALISATION	In house	ED60 ***and/or IU/ML***	***ED60: 18; IU/ml: 56***	GSK Biologicals** or GSK designated lab***

Ab = antibody; **ED60** = serum dilution inducing 60% inhibition in plaque forming units; ***IU/mL: International Unit/milliliter***

* Refer to APPENDIX B for the laboratory addresses.

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. Marburg, Germany

*** Testing may possibly be outsourced to a laboratory designated by GSK. In this case, the method and unit may be different than the one indicated in this table.

8.11.3.2. Molecular biology

Table 10 Molecular biology

System	Component****	Kit / Manufacturer	Method	Unit	Laboratory
Nasal swab	RSV A RNA RSV B RNA	In-house	QRTPCR*	Copies/ml	GSK Biologicals or GSK designated lab**
Nasal swab	Influenza A virus (Flu A) Human Influenza A virus subtype H1 (FLU A-H1) Human Influenza A virus subtype H3 (FLU A-H3) Human Influenza A virus subtype H1pdm09 (FLU A-H1pdm09) Influenza B virus (Flu B) Human respiratory syncytial virus A (RSV A) Human respiratory syncytial virus B (RSV B) Human adenovirus (AdV) Human metapneumovirus (MPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus 1/2/3/4 (HBoV) Human rhinovirus A/B/C (HRV) Human coronavirus 229E (229E) Human coronavirus NL63 (NL63) Human coronavirus OC43 (OC43)	Allplex™ Respiratory Panel (Seegene) or equivalent***	Multiplex real-time PCR	Qualitative assay (positive /negative)	GSK Biologicals or GSK designated lab**

* RSV-A/B quantitative reverse transcription PCR will be performed on all specimens of infants with RTI with suspicion of difficulty in breathing/wheezing or parental concern, reported during active or passive surveillance.

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. Marburg Germany

*** Respiratory Viruses Panel (Allplex PCR) will be performed for all specimens RSV A/B-positive and if deemed necessary for RSV A/B-negative samples.

****The list of components might be subject to change in case equivalent kit is used for multiplex RVP testing.

8.11.3.3. Hematology, biochemistry and urinalysis

Hematology and biochemistry tests are to be performed preferentially by local healthcare providers, as per local practice. They are to be performed by the investigator/study staff ONLY if not done by the local healthcare provider within 2 weeks before the study visit.

The investigator will perform urine dipstick tests to detect the presence of proteins, glucose, RBCs and/or WBCs. These tests do not replace those performed by local healthcare practitioners, per local practice, for clinical management of study subjects.

Table 11 Hematology, biochemistry, urine tests

System	Discipline	Component	Time Point	Method	Scale	Laboratory
Whole blood	Hematology	Hemoglobin	Visit 1 Visit 3	As per local practice	Quantitative	Local laboratory
		Leukocytes (White Blood Cells)	Visit 1			
		Neutrophils	Visit 1			
		Lymphocytes	Visit 1			
		Monocytes	Visit 1			
		Basophils	Visit 1			
		Eosinophils	Visit 1			
		Platelets	Visit 1			
Serum	Biochemistry	Alanine Aminotransferase (ALT)	Visit 1	As per local practice	Quantitative	Local laboratory
		Aspartate Aminotransferase (AST)	Visit 1			
		Creatinine	Visit 1			
		Urea Nitrogen	Visit 1			
Urine	-	Protein	Visit 1 Visit 2 Visit 3 Visit 4	As per local practice, dipsticks provided by GSK Biologicals	Ordinal	Local laboratory
		Glucose	Visit 1 Visit 2 Visit 3 Visit 4			
		Hemoglobin (RBC)	Visit 1 Visit 2 Visit 3 Visit 4			
		Leukocyte esterase (WBC)	Visit 1 Visit 2 Visit 3 Visit 4			

8.11.3.4. Additional tests

Additional exploratory testing on the disease under study and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns may be performed within the framework of the study if deemed necessary for accurate interpretation of the data/ should such assay(s) become available at GSK. These assays may not be represented in the objectives/ endpoints of the study protocol.

8.11.4. Biological samples evaluation

8.11.4.1. Immunological read-outs

Table 12 Immunological read-outs

Blood sampling timepoint Type of contact and time point	Group	No. subjects	Component	Component priority rank
Maternal Blood				
Visit 5 (Delivery)	All Maternal subjects	~2300	Respiratory Syncytial Virus A Ab (RSV-A neutralising antibody)	1
Cord Blood				
Visit 5 (Delivery)	All Maternal subjects (provides infant antibody levels)	~2300	Respiratory Syncytial Virus A Ab (RSV-A neutralising antibody)	1

8.11.4.2. Molecular biology

Table 13 Molecular biology for nasal swab specimen analysis

Nasal swab sampling timepoint		Group	No. subjects	Component
Type of contact (timepoint)	Sampling timepoint			
Visit to assess potential LRTI	Unscheduled	All Infants *	Event-driven**	QRTPCR (quantitative reverse transcription PCR): RSV A RNA and RSV B RNA
Visit to assess potential LRTI	Unscheduled	All infants*	Event-driven***	Multiplex PCR including: Influenza A virus (Flu A) Influenza B virus (Flu B) Human respiratory syncytial virus A (RSV A) Human respiratory syncytial virus B (RSV B) Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3) Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09) Human adenovirus (AdV) Human metapneumovirus (MPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus 1/2/3/4 (HBoV) Human rhinovirus A/B/C (HRV) Human coronavirus 229E (229E) Human coronavirus NL63 (NL63) Human coronavirus OC43 (OC43)

* Refer to Section 8.6.7.

** RSV-A/B quantitative PCR (RSV-A/B RNA) will be performed on all specimens.

*** Respiratory Viruses Panel (Multiplex PCR) will be performed for all specimens RSV-A/B positive and if deemed necessary for RSV-A/B-negative sample.

8.11.4.3. Hematology/blood chemistry

Table 14 Hematology/blood chemistry tests

Blood sampling timepoint Type of contact (timepoint)	Group	No. subjects	Component
Visit 1 (Day 1)	All maternal subjects	~2300*	Hematology (Leukocytes, Hemoglobin, Platelets) Biochemistry (ALT, AST, Creatinine, blood urea nitrogen)
Visit 3 (Day 56)	All maternal subjects	~2300	Hematology (Hemoglobin)

* 200 to 300 subjects per country. Tests to be performed preferentially by local healthcare providers and information will be collected and recorded in the eCRF. The investigator/study staff will collect biological samples for the specified testing if not done by the local healthcare provider as per local practice.

9. SERIOUS ADVERSE EVENTS RELATED TO STUDY PARTICIPATION

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the SAE definition.

Treatment of any SAE **related to study participation** (e.g., protocol-mandated procedures, invasive tests) is at the sole discretion of the investigator and according to current good medical practice.

9.1. Definition

An SAE **related to study participation** (e.g., protocol-mandated procedures, invasive tests) is any untoward medical occurrence related to study participation that:

- Results in death,
- Is life-threatening,

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

- Requires hospitalization or prolongation of an existing hospitalization,

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

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

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

- Results in disability/incapacity,

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

  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 hospitalization 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 hospitalization.

9.2. Event Identification

Blood and urine samples will be collected from pregnant women enrolled in the study. Nasal swabs will be collected from neonates/ infants enrolled in the study. Serious adverse events (SAEs) associated with collection of these biological specimens or any other study procedures will be documented and reported from the time the pregnant woman (mother) consents to participate / consents to her infant's participation until the pregnant woman (mother) / her infant is discharged from the study.

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

9.3. Subject cards

Study subjects/parents/LARs must be provided with the address and telephone number of the main contact for information about the clinical study. The investigator (or designate) must therefore provide subjects/parents/LARs with a "subject card."

For this study, a subject card will be provided to each pregnant woman who enrolls. A second subject card will be provided for each infant who is enrolled.

In an emergency situation these cards serve to inform the responsible attending physician(s) that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

In a non-emergency situation, if subjects visit a local healthcare provider not affiliated with the study, these cards serve to inform the responsible local healthcare provider that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator. Further, subject will have information on the card to contact the study site at any time.

Subjects/parents/LARs must be instructed to keep the subject cards in their possession at all times during the study.

9.4. GSK Contact information, GSK Reporting Timeframes, and Regulatory reporting requirements

Procedure related SAEs that occur during the study will be reported to the GSK representatives specified in Table 15, within the timeframes described in Table 16 once the investigator determines that the event meets the protocol definition provided in the Glossary of Terms.

The investigator will promptly report all SAEs related to study participation to GSK Biologicals as detailed in Table 15 and Table 16. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies (as applicable, per country) about the event. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Table 15 Contact information for reporting SAEs related to study participation to GSK

Study Contact for Reporting SAEs: Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs: 24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Outside US & Canada sites: Fax: PPD or PPD Email address: PPD

Table 16 Timeframes for submitting SAEs related to study participation to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs related to study participation	24 hours**‡	electronic Expedited Adverse Event Report	24 hours*	electronic Expedited Adverse Event Report

* Timeframe allowed after receipt or awareness of the information.
** Timeframe allowed after the diagnosis is established and known to the investigator.
‡The investigator will be required to confirm review of the procedure related SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Event Report within 72 hours of submission of the procedure related SAE

9.5. Information to be reported

The nature of the SAE, date and time of onset, outcome, intensity and possible relationship to the study procedure(s) should be established and recorded in the eCRF.

Any medication administered for the treatment of the SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF.

The outcome of the SAE related to study participation should be assessed, as follows:

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

9.6. SAE Report Completion and transmission to GSK

Once an investigator becomes aware that a study-related SAE has occurred in a study subject, the investigator (or designee) must complete the information in the electronic Expedited Adverse Event Report WITHIN 24 HOURS. The report 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 an SAE, the report should still be completed within 24 hours. Once additional information is received, the report should be updated WITHIN 24 HOURS.

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

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

If the electronic reporting system does not work, the investigator (or designee) must complete, then date and sign a paper Expedited Adverse Event Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

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

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

When additional SAE information is received after removal of write access to the subject's eCRF, new or updated information should be recorded on a paper Expedited Adverse Event Report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (see the Sponsor Information) within the designated reporting time frames specified in Table 16.

9.7. Follow-up of SAEs related to study participation (Amended 29-MAY-2020)

The investigator will follow-up subjects with SAEs related to study participation until the event has resolved, subsided, ***stabilized***, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

9.7.1. Follow-up during the study

After the initial SAE report, the investigator is required to proactively follow each subject and provide further relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs, refer to Table 16).

All SAEs documented at a previous visit/ contact and recorded as not recovered/ not resolved or recovering/ resolving will be reviewed at subsequent visits/ contacts until the last visit of the subject.

9.7.2. Follow-up after the subject is discharged from the study (Amended 29-MAY-2020)

If the investigator receives additional relevant information on a previously reported SAE, he/ she will provide this information to GSK Biologicals using a paper Expedited Adverse Event Report.

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 SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a ***recognized*** follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

10.2. Subject withdrawal

Subjects who are withdrawn because of an event of interest or SAEs related to study participation must be clearly distinguished from subjects who are withdrawn for other reasons. The investigator will follow subjects who are withdrawn as the result of an SAE related to study participation until resolution of the event (see Section 9.7.2).

Withdrawals will not be replaced.

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit in the protocol.

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

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

Investigators will make at least 3 attempts to contact a subject who does not return for a scheduled visit as described in Section 8.4 and in the SPM.

A subject will be defined as lost to follow-up if there is no contact with the subject /subject's parent(s) / LAR(s) over a period of at least 3 months after a planned visit (see SPM for details). Efforts to contact the subject/subject's parents should be recorded in the source documents. The subject's data will be censored at the time of last contact once this definition is met.

Information relevant to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject herself, by the subject's parent(s) or LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Study participation related SAE.
- Pregnancy related event of interest(specify). Note: includes maternal deaths.
- Maternal deaths not related to pregnancy/delivery (specify cause).
- Neonatal event of interest(specify). Note: includes death in infants from birth – 28 days old
- Death in infants > 28 days old (specify cause). Note that death in neonates from birth – 28 days old is captured as a neonatal event of interest).
- Protocol violation (specify).
- Consent withdrawal*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because she/the subject's parent(s)/ LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/ the subject's parent(s)/LAR(s), in the CRF.

Subjects who are withdrawn from the study because of study participation related SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a study participation related SAE until resolution of the event (see Section 9.7.2).

11. STATISTICAL METHODS

The primary analysis will be performed by country and possibly by region or other relevant grouping if standard of antenatal care is similar in the different sites. This will be determined during site selection when more information is available.

11.1. Endpoints

11.1.1. Primary endpoints

11.1.1.1. Pregnancy outcomes.

These include:

- Live birth with no congenital anomalies,
- Live birth with congenital anomalies,
- Fetal death/stillbirth (loss at or after 22 weeks of gestation) with no congenital anomalies,
  - Antepartum stillbirth
  - Intrapartum stillbirth
- Fetal death/still birth (loss at or after 22 weeks of gestation) with congenital anomalies,
  - Antepartum stillbirth
  - Intrapartum stillbirth
- Elective/therapeutic termination with no congenital anomalies,
- Elective/therapeutic termination with congenital anomalies.
- Of note, fetal death/stillbirth has multiple subcategories. For example, fetal death/stillbirth with no congenital anomalies is an outcome with two subcategories that include: 1) antepartum stillbirth; 2) intrapartum stillbirth. For each outcome, the investigator should select the applicable sub-category.

11.1.1.2. Pregnancy related events of interest from Visit 1 through Visit 6.

Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study. They are listed below. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should select the event and the applicable sub-category.

- Maternal death
- Hypertensive disorders of pregnancy:
  - Gestational hypertension,
  - Pre-eclampsia,
  - Pre-eclampsia with severe features (including eclampsia)
- Antenatal bleeding:
  - Morbidly adherent placenta
  - Placental abruption
  - Cesarean Scar Pregnancy
  - Uterine rupture
- Postpartum hemorrhage
- Fetal growth restriction
- Dysfunctional labor
  - first stage of labor
  - second stage of labor
- Gestational diabetes mellitus,
- Non reassuring fetal status
- Pathways to preterm birth:
  - Premature preterm rupture of membranes,
  - Preterm labor,
  - Provider-initiated preterm birth.
- Chorioamnionitis
- Oligohydramnios
- Polyhydramnios
- Gestational Liver Disease:
  - Intrahepatic Cholestasis of Pregnancy (ICP)
  - Acute Fatty Liver of Pregnancy
- Maternal Sepsis
- Any other pregnancy related event considered by the investigator to be of concern (specify)

For events of interest that include subcategories, the frequency of the main event of interest and of each event subcategory will be included in the analysis. The overall frequency will include mothers who present with at least one of the subcategory events.

11.1.1.3. Neonatal events of interest from birth through 28 days of age

Neonatal events of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study. They include:

- Small for gestational age,
- Low birth weight including very low birth weight,
- Neonatal encephalopathy,
- Congenital microcephaly,
  - Postnatally diagnosed
  - Prenatally diagnosed
- Congenital anomalies,
  - Major external structural defects
  - Internal structural defects
  - Functional defects
- Neonatal death,
  - Neonatal death in a preterm live birth (gestational age>=28 to < 37 weeks)
  - Neonatal death in a term live birth
- Neonatal infections,
  - Blood stream infections
  - Meningitis
  - Respiratory infection
- Respiratory distress in the neonate,
- Preterm birth,
- Failure to thrive,
- Large for gestational age,
- Macrosomia,
- Any other neonatal event considered by the investigator to be of concern (specify, e.g. neurodevelopment delay)

For events of interest that include subcategories, the frequency of the main event of interest and of each event subcategory will be included in the analysis. The overall frequency will include infants who present at least one of the subcategory events.

11.1.2. Secondary endpoints

- Pregnancy related events of interest from Visit 1 through Visit 6 (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible).
- Neonatal events of interest from birth through 28 days of age (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible).

Of note, some events of interest fall under a single category but have multiple subcategories. For each event, the investigator should identify the event and select the applicable sub-category and the GAIA level of diagnostic certainty.

- RSV-A neutralizing antibody titers in maternal blood at delivery
- RSV-A neutralizing antibody titers in cord blood at delivery.
- Episode(s) of RSV-LRTI from birth up to 1 year of age.
- Episode(s) of RSV hospitalization from birth up to 1 year of age.

11.1.3. Tertiary endpoints (Amended 29-MAY-2020)

- Co-infections of RSV-LRTI with other respiratory viruses in infants, confirmed by PCR of nasal swabs in infants from birth up to 1 year of age:
  - Influenza A virus (Flu A)
  - Influenza B virus (Flu B)
  - Human Influenza A virus subtype H1 (Flu A-H1)
  - Human Influenza A virus subtype H3 (Flu A-H3)
  - Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)
  - Human adenovirus (AdV)
  - Human metapneumovirus (MPV)
  - Human enterovirus (HEV)
  - Human parainfluenza virus 1 (PIV1)
  - Human parainfluenza virus 2 (PIV2)
  - Human parainfluenza virus 3 (PIV3)
  - Human parainfluenza virus 4 (PIV4)
  - Human bocavirus 1/2/3/4 (HBoV)
  - Human rhinovirus A/B/C (HRV)
  - Human coronavirus 229E (229E)
  - Human coronavirus NL63 (NL63)
  - Human coronavirus OC43 (OC43)

- Potential risk factors for pregnancy related and neonatal events of interest.
- Any further exploratory characterization of immune responses to RSV and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood) (***For example, levels of RSV-B neutralizing antibodies.)***
- ***Episode(s) of RSV-LRTI/severe LRTI based on alternative case definitions, from birth up to 1 year of age.***

11.2. Determination of sample size

The target will be to enroll up to approximately 200 to 300 eligible subjects (pregnant women) by country. Subjects may drop-out from the study due to a variety of reasons, e.g. migration from the study area. Assuming a drop-out rate of about 10% during the course of follow-up, there will be up to approximately 180 to 270 evaluable subjects by country.

Considering a sample size of up to approximately 180 to 270 evaluable subjects by country, Table 17 illustrates the precision (exact 95% confidence interval [CI]) one can get on the percentage of subjects with maternal, fetal and neonatal events of interest. Precision (exact 95% CI) has also been computed for a sample size of 270, 180 and 100 evaluable subjects for estimate by study site.

The percentages of subjects with maternal, fetal and neonatal events of interest for the primary objectives are expected to range from 0 to 35%.

Table 17 Precision (exact 95% confidence interval) on the percentage of subjects with maternal, fetal and neonatal events of interest for sample size of 270, 180 and 100 subjects

	270 subjects			180 subjects			100 subjects		
%	N	Lower limit	Upper limit	N	Lower limit	Upper limit	N	Lower limit	Upper limit
35	94.5	29.3	41	63	28.1	42.4	35	25.7	45.2
30	81	24.6	35.8	54	23.4	37.3	30	21.2	40
25	67.5	19.9	30.6	45	18.9	32	25	16.9	34.7
20	54	15.4	25.3	36	14.4	26.6	20	12.7	29.2
15	40.5	11	19.8	27	10.1	21.1	15	8.6	23.5
10	27	6.7	14.2	18	6	15.3	10	4.9	17.6
5	13.5	2.7	8.3	9	2.3	9.3	5	1.6	11.3
3	8.1	1.3	5.8	5.4	1	6.8	3	0.6	8.5
1	2.7	0.2	3.1	1.8	0.1	3.9	1	0	5.4
0	0	0	1.4	0	0	2	0	0	3.6

%= Percentage of subjects with maternal, fetal and neonatal events of interest
N= Number of subjects with maternal, fetal and neonatal events of interest
Lower and upper limits are exact 95% confidence intervals

11.3. Cohorts for Analyses (Amended 29-MAY-2020)

11.3.1. Exposed Sets (ES)

11.3.1.1. Pregnant women (mothers)

The ES will include all pregnant women (mothers) ***who signed a valid*** informed consent ***form*.**

11.3.1.2. Neonates/Infants

Not applicable.

11.3.2. Enrolled sets

11.3.2.1. Pregnant women (mothers)

The enrolled set will include all pregnant women (mothers) with a valid informed consent who completed Visit 1.

11.3.2.2. Neonates/Infants

The Enrolled Set will include all neonates/infants

- born to pregnant women in the enrolled set, and
- Who have a valid ICF signed by the mother/ parent(s) /LAR(s) (as appropriate per local regulations).

11.3.3. Per Protocol Sets (PPS) (Amended 29-MAY-2020)

11.3.3.1. Pregnant women (mothers)

The maternal PPS will include all pregnant women (mothers) ***in the enrolled set who*** meet all eligibility criteria up to the time of their censoring, either at study completion or prematurely as drop-out (e.g. withdrawn consent, lost-to-follow-up).

11.3.3.2. Neonates/Infants

The infant PPS will include all neonates / infants

- ***born to pregnant women in the PPS and***
- ***who*** meet all eligibility criteria up to the time of their censoring, either at study completion or prematurely as drop-out (e.g. withdrawn consent, lost-to-follow-up) who have at least one time point evaluation (see Table 5).

11.4. Derived and transformed data

Age of the infant subject at time of the LRTI case will be expressed in months and will be computed as the difference between the start date of the LRTI case and the date of birth.

Age of the mother at the time of childbirth will be expressed in years and will be computed as the difference between the birth date of the subject and the birth date of the mother.

Duration of the study for each subject will be computed as the difference between the date of last contact (i.e., active or passive surveillance contact or the date of the censoring) and the date when ICF was first signed by the subject / subject's parent[s]/LAR[s]).

All potential LRTI cases identified during the surveillance period will be classified as RTI, LRTI or severe LRTI according to the LRTI case definition and severity scale (refer to Table 3). The cases will also be classified according to the classification of WHO [Modjarrad, 2016].

11.4.1. Handling of missing values/censoring/discontinuations

For a given subject and a given demographic variable, missing measurements will not be replaced.

The number of missing values per variable may be provided for selected variables of interest as a separate category. Missing values will be examined to help determine if it is necessary to use multiple imputation or other techniques to deal with missing data.

11.5. Analysis of demographic and baseline characteristics

For the maternal PPS cohort, analyses of demographic and baseline characteristics at Visit 1 will be described.

For the infant PPS cohort, analyses of demographic characteristics at Visit 1-NB will be described. Analyses of lifestyle characteristics will be described at Visit 2 NB.

For Screening Failures, reasons for non-eligibility will be described.

Continuous variables will be summarized by providing the number of observations, mean, 95% confidence interval (CI), standard deviation (SD), median, and range. Categorical variables will be summarized by tabulating counts (N) and the percentage (%) of total subjects having the given characteristics, with missing data considered a separate category.

11.6. Analysis of primary objectives (Amended 29 May 2020)

The primary objectives analyses will be performed on the PPS cohorts overall and possibly by region or other relevant grouping. ***If there is a difference of 5% or more between the number of participants in the enrolled set and the PPS, primary objectives analyses on the enrolled set will also be performed.***

In healthy pregnant women with uncomplicated pregnancies at time of enrollment:

- To determine the frequencies of pregnancy outcomes.

  The number and percentage (with exact 95% CI) of women presenting the following outcomes: live birth, fetal death/stillbirth (antepartum or intrapartum), and elective/therapeutic termination will be reported for each event by presence or absence of congenital anomalies.

- To determine the frequencies of pregnancy related events of interest as specified in Section 11.1.1.2.

  The number and percentage (with exact 95% CI) of pregnant women presenting with the events of interest specified in Section 11.1.1.2 will be tabulated for each event within appropriate time windows to be specified in the statistical analysis plan (SAP). Missing data may be considered a separate category.

In all neonates live-born to women enrolled in the study:

- To determine the frequencies of neonatal events of interest. as specified in Section 11.1.1.3.

  The number and percentage (with exact 95% CI) of neonates presenting the events of interest specified in Section 11.1.1.3 will be tabulated for each event. Missing data may be considered a separate category.

11.7. Analysis of secondary objectives (Amended 29-MAY-2020)

The secondary objectives analyses will be performed on the PPS cohorts (maternal or infant as applicable) overall and possibly by region or other relevant grouping. ***If there is a difference of 5% or more between the number of participants in the enrolled set and the PPS, secondary objectives analyses on the enrolled set will also be performed.***

In healthy pregnant women with uncomplicated pregnancies at time of enrollment:

- To determine frequencies of pregnancy related events of interest according to GAIA levels of diagnostic certainty (where these are specified) (APPENDIX D)
  - Considering all pregnant women followed from enrollment through Visit 6, the number and percentage of subjects with at least one maternal event of interest will be computed by GAIA levels of diagnostic certainty, with exact 95% CI.
- To describe the distribution of RSV-A antibody titers in maternal blood at delivery.
  - Geometric mean titers (GMTs) will be tabulated with 95% CI.
  - Percentage of subjects above thresholds will be tabulated.

In all neonates live-born to women enrolled in the study:

- To determine frequencies of neonatal events of interest according to GAIA levels of diagnostic certainty (where these are specified). (APPENDIX D)
  - Considering all neonates the number and percentage of subjects with at least one neonatal event of interest will be computed by GAIA levels of diagnostic certainty, with exact 95% CI.

- To describe the distribution of RSV-A antibody titers in cord blood at delivery.
  - Geometric mean titers (GMTs) will be tabulated with 95% CI.
  - Percentage of subjects above thresholds will be tabulated.

In all neonates/infants live-born to women enrolled in the study:

- To determine the incidence of all, of severe, and of very severe RSV-lower respiratory tract illnesses (LRTIs).
  - Considering all infants followed from visit 1-NB to visit 4-NB, the percentage of subjects with at least one LRTI illness, exact 95% CI will be presented.
  - Incidence rates of LRTI illnesses will be calculated, with exact 95% CI.
  - Frequencies of repeat occurrences of LRTI will be tabulated.
- To determine the incidence of RSV hospitalization.
  - Considering all infants followed from visit 1-NB to visit 4-NB, the percentage of subjects with at least one RSV hospitalization, with exact 95% CI.
  - Incidence rates of RSV hospitalizations will be calculated, with exact 95% CI.
  - Frequencies of repeat occurrences of RSV hospitalization will be tabulated.

Continuous variables will be summarized by providing the number of observations, mean, 95% CI, SD, median, and range. Categorical variables will be summarized by tabulating N and % of total subjects having the given characteristics, with missing data considered a separate category.

11.8. Analysis of tertiary objectives (Amended 29-MAY-2020)

The following tertiary objectives analyses will be performed on infants within the PPS cohort,overall and possibly by region or other relevant grouping. ***If there is difference of 5% or more between the number of participants in the enrolled set and the PPS, tertiary objectives analyses on the enrolled set will also be performed.***

- To describe co-infections of RSV-LRTI with other respiratory viruses in infants.
  - Considering all infants followed from visit 1-NB to visit 4-NB, the percentage of subjects with the occurrence of RSV-LRTI and having other respiratory viral co- infection identified by multiplex PCR, with exact 95% CI; classified by respiratory viruses.
- To estimate the association of RSV-LRTI in neonates/infants and the level of RSV neutralizing antibodies in cord blood.
  - Correlation analysis will be done comparing the levels of RSV antibodies present in cord blood and the presence or absence of RSV-associated LRTI, RSV-associated severe LRTI, and RSV-associated very severe LRTI in infants. Details will be described in the SAP.

The following tertiary objectives analyses will be performed on the PPS cohorts (maternal or infant as applicable) by country, region, or other relevant grouping:

- To determine risk factors for pregnancy-related and neonatal events of interest.
  - Risk factors will be described in the SAP.
  - The maternal events of interest will be described according to variables collected in the mother's clinical examination and obstetric risk factors. Frequency tables will be generated for categorical variables.
  - The neonatal events of interest will be described according to variables collected in the mother's clinical examination and obstetric risk factors. Frequency tables will be generated for categorical variables.
  - Furthermore, multiple variable analyses (such as multiple logistic regression for binary outcomes and multiple Poisson/negative binomial and/or other appropriate models for count outcomes) will be conducted to adjust for covariates of interest, provided there are sufficient numbers of events of interest.
- ***To determine the incidence of LRTIs/Severe LRTIs (using alternative case definitions)***
- If deemed necessary, to further characterize the immune responses to RSV and other infections in maternal subjects and infants (based on maternal serum and cord blood).
  - ***For example, for levels of neutralizing antibodies to RSV-B:***
    - GMTs/ GMCs may be tabulated with 95% CI.
    - Percentage of subjects above various thresholds, depending on the antibody tested, may be tabulated with exact 95% CI.
    - Other relevant exploratory analyses may be defined in the SAP.

11.9. Interpretation of analyses

Analyses will be descriptive with the aim to characterize different sub-groups of women. These sub-groups will be defined prior to analyses and will be related to e.g. risk factors for maternal and neonatal events of interest and endemic disease. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

Further details will be provided in the SAP.

11.10. Analysis of safety

Serious adverse events (SAEs) related to study participation will be recorded throughout the study period. In case of occurrence of SAE(s) related to study participation, a listing of SAEs will be provided.

11.11. Conduct of analyses

All analyses will be done on cleaned data.

Analyses will be performed in a stepwise manner after all subjects in all countries have completed all study visits in Epoch 002 and again after completion of all study visits in Epoch 003.

Analyses of pregnancy outcomes, pregnancy related events of interest, and neonatal events of interest will be performed when all data up to 42 days post-delivery are available (Epoch 002). For these analyses a statistical report but no CSR will be prepared.

Final analyses will be performed when all data up to study end are available (Epoch 002 and Epoch 003). An integrated *CSR* including all available data will be written and made available to the investigator(s).

If the data for tertiary endpoints become available at a later stage, additional analysis/analyses will be performed. These data will be documented in annex(es) to the study report and made available to the investigators.

Additional analyses may be performed if deemed necessary to inform the design or implementation of future clinical trials.

Analyses, and the sequence in which they will occur, will be described in detail in the SAP.

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.

11.11.1. Statistical considerations for interim analyses *(Amended 29-MAY-2020)*

Interim analysis for RSV LRTIs

If deemed necessary, an interim analysis ***may*** be performed on RSV surveillance data as part of the secondary objective of determining incidence of RSV LRTI. This interim analysis ***may*** be performed to obtain preliminary information on the performance of the case definitions used for RSV LRTI, severe LRTI, and very severe LRTI (Table 3) and to assess levels of RSV neutralising antibody in maternal and cord blood at delivery. The interim analysis ***may*** occur after the database freeze at the time point when approximately 50% of infants will have completed up to 6 months of follow up during the surveillance period following birth (up to Visit 3-NB). ***If an interim analysis is performed,*** data cleaning plans will be scheduled as needed to supply data for interim analyses in a timely manner. This interim analysis ***may*** be performed on data that is as clean as possible. Preliminary results will be made available in a timely manner for use in the potential adjustment of the RSV LRTI case definitions to be used in pivotal clinical trials scheduled to begin shortly thereafter. The results pertaining to this analysis ***(if performed)*** will be purely descriptive, with no adjustment of type I error, and will be reported in an interim statistical report. No CSR will be prepared.

12. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, ownership, public disclosure requirements and publications must be met.

12.1. Electronic Case Report Form instructions

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

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

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

12.2. Study monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

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

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

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

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

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the 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.

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

12.3. Study and site closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

12.4. Record retention

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

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP any institutional requirements or applicable laws or regulations, or GSK standards/procedures otherwise, the minimum retention period will default to 25 years after completion of the study report.

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

12.5. Quality assurance

To ensure compliance with GCP 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.

12.6. Posting of information on publicly available registers and publication policy

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

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

Studies that do not evaluate vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge or are relevant for patient care, and will be considered for disclosure on the GSK website and in publicly accessible regulatory registry(ies).

12.7. Provision of study results to investigators

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

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

12.8. Data Sharing

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

13. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

14. REFERENCES (AMENDED 29-MAY-2020)

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World Health Organization [WHO]. Global Surveillance for COVID-19 caused by human infection with COVID-19 virus: Interim Guidance. March 2020. Available at: https://apps.who.int/iris/rest/bitstreams/1272502/retrieve. Accessed 8 May 2020.

APPENDIX A LABORATORY ASSAYS

Assay descriptions could be subjects to change, due to assay re-development and/or qualification.

Neutralization assay

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize RSV entry and replication in a host cell line.

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a monolayer of Vero cells (African Green Monkey, kidney, Cercopitheus aethiops, ATCC CCL-81) and incubated for three days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell monolayer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (anti-RSV IgG) and a secondary antibody conjugated to horse-radish peroxidase (HRP), allowing the visualization of plaques by immunofluorescence after coloration with TrueBlueTM peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with Axiovision software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at that dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody titer is expressed in ED60 (Estimated Dilution 60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others [Barbas, 1992; Bates, 2014].

PCR

- Quantitative RT-PCR able to discriminate RSV-A and RSV-B subtypes:

Briefly, RSV A and RSV B RNAs extracted from the nasal swabs are detected in a duplex PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involves nucleic acids extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real- time PCR reaction using a calibration curve (absolute quantitation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

- Qualitative multiplex RT-PCR for detection of a panel of viruses.

A qualitative RT-PCR multiplex assay is used for the detection and identification of multiple respiratory virus nucleic acids in nasal swabs from individuals suspected of respiratory tract infections. The following virus types and subtypes can be identified in the assay:

- Influenza A virus (Flu A)
- Influenza B virus (Flu B)

- Human Influenza A virus subtype H1 (Flu A-H1)
- Human Influenza A virus subtype H3 (Flu A-H3)
- Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)
- Human respiratory syncytial virus A (RSV A)
- Human respiratory syncytial virus B (RSV B)
- Human adenovirus (AdV)
- Human metapneumovirus (MPV)
- Human enterovirus (HEV)
- Human parainfluenza virus 1 (PIV1)
- Human parainfluenza virus 2 (PIV2)
- Human parainfluenza virus 3 (PIV3)
- Human parainfluenza virus 4 (PIV4)
- Human bocavirus 1/2/3/4 (HBoV)
- Human rhinovirus A/B/C (HRV)
- Human coronavirus 229E (229E)
- Human coronavirus NL63 (NL63)
- Human coronavirus OC43 (OC43)

Following total nucleic acids extraction, viruses are detected by multiplex real-time RT-PCR assays targeting the above mentioned viruses. A comparative analysis of the fluorescence intensities of each target is performed to detect the viruses present in the sample.

APPENDIX B CLINICAL LABORATORIES

Table 18 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Clinical Laboratory Sciences, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
GSK Biologicals Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre – Belgium
GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany	Emil-von-Behring-Str. 76 35041 Marburg Germany

Table 19 Outsourced laboratories

Laboratory	Address
DDL Diagnostic Laboratory B.V.	Headquarters Visseringlaan, 25 2288 ER Rijswijk - NL

APPENDIX C GAIA GESTATIONAL AGE ASSESSMENT FORM

This gestational age (GA) assessment tool is based on the maternal immunization guideline matrix prepared by Jones, 2016 (March GAIA Meeting Washington, DC, 29 March 2016).

LEVELS OF CERTAINTY OF GESTATIONAL AGE ASSESSMENT

Level	Description
Level 1 Highest level of certainty	• Certain LMP or IUI date or ET WITH confirmatory 1st trimester U/S, or • 1st trimester U/S
Level 2A	• Certain LMP WITH 2nd trimester U/S*, or • Certain LMP WITH 1st trimester physical examination**
Level 2B	• Uncertain LMP WITH 2nd trimester U/S
Level 3A	• Certain LMP WITH 3rd trimester U/S***, or • Certain LMP WITH confirmatory 2nd trimester FH, or • Certain LMP WITH birth weight, or • Uncertain LMP WITH 1st trimester physical examination
Level 3B Lowest level of certainty	• Uncertain LMP WITH FH, or • Uncertain LMP WITH neonatal physical assessment (New Ballard score), or • Uncertain LMP WITH birth weight

grey highlights: applicable for enrollment in this study.

1st trimester U/S: ≤$13^{6/7}$ weeks, 2nd trimester U/S: $14^{0/7}$ to $27^{6/7}$ weeks, 3rd trimester U/S: ≥$28^{0/7}$ weeks.

GA: gestational age; U/S: ultrasound examination; LMP: last menstrual period; IUI: intrauterine insemination; ET: embryo transfer, FH: fundal height;

* If LMP and U/S do not correlate, default to U/S GA assessment

** For singleton pregnancies only. Unreliable if obesity, or uterine anomalies.

*** Depending on gestational age at Screening Visit/ Visit 1 and depending on the local standard of care, this will be applicable for inclusion in the study.

METHODS OF GESTATIONAL AGE ASSESSMENT

Adapted from [ACOG, 2014]: The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice, American Institute of Ultrasound in Medicine and Society for Maternal-Fetal. Committee Opinions: Method for estimating Due Date. Number 611, October 2014 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Method-for-Estimating-Due-Date).

Gestational age range	Method of measurement	Discrepancy between U/S dating and LMP dating
1st trimester ≤13$^{6/7}$ weeks		
≤8$^{6/7}$ weeks	CRL	> 5 days
9$^{0/7}$ to 13$^{6/7}$ weeks		> 7 days
2nd trimester 14$^{0/7}$ to 27$^{6/7}$ weeks		
14$^{0/7}$ to 15$^{6/7}$ weeks	BPD, HC, AC, FL	> 7 days
16$^{0/7}$ to 21$^{6/7}$ weeks		> 10 days
22$^{0/7}$ to 27$^{6/7}$ weeks		> 14 days

U/S: ultrasound examination; LMP: last menstrual period; CRL: crown-rump length; BPD: biparietal diameter; HC: head circumference; AC: abdominal circumference; FL: femur length

APPENDIX D DEFINITIONS OF MATERNAL, FETAL AND NEONATAL EVENTS OF INTEREST AS PER GAIA

The articles explaining the events of interest in detail and all corresponding information can be found in the following issues of Vaccine:

Bauwens J, Bonhoeffer J, Chen RT, editors. Harmonising Immunisation Safety Assessment in Pregnancy. Vaccine. 2016. 34 (49): 5991 – 6110.

Kochhar S, Bauwens J, Bonhoeffer J, editors. Harmonising Immunization Safety Assessment in Pregnancy – Part II. Vaccine. 2017. 35 (48): 6469-6582.

References specific to each event of interest are given at the end of the relevant Table.

Definitions and Levels of Diagnostic Certainty are presented in the following Tables.

Pregnancy Outcomes	
Stillbirth	Table 20
Maternal Events of Interest	
Maternal Death	Table 21
Hypertensive Disorders of Pregnancy	Table 22
Antenatal bleeding	Table 23
Postpartum hemorrhage	Table 24
Fetal Growth restriction	Table 25
Dysfunctional Labor	Table 26
Gestational Diabetes Mellitus	Table 27
Non-reassuring fetal status	Table 28
Pathways to Preterm Birth	Table 29
Standard definitions for events of interest not defined as such in GAIA (Chorioamnionitis, Oligohydramnios, Polyhydramnios, Intrahepatic Cholestasis of Pregnancy (ICP), Acute Fatty Liver of Pregnancy, Maternal Sepsis)	Table 30
Neonatal Events of Interest	
Small for Gestational Age	Table 31
Low Birth Weight	Table 32
Neonatal encephalopathy	Table 33
Congenital Microcephaly	Table 34
Congenital Anomalies	Table 35
Neonatal Death	Table 36
Neonatal Infections	Table 37
Respiratory Distress in the Neonate	Table 38
Preterm Birth	Table 39
Failure to thrive	Table 40
Standard definitions for events of interest not defined as such in GAIA (large for gestational age, macrosomia)	Table 41

Table 20 Fetal death / Stillbirth

Fetal death occurring before birth after 20 to 28 weeks of gestation (variation due to country definitions). Descriptions are provided for reference in selecting the appropriate subcategory (antepartum or intrapartum). GAIA levels of diagnostic certainty will not be assessed in this protocol.

Antepartum Stillbirth (Fetal death occurs prior to the evidence of labor.)	
Level	Description
1	Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined by physical examination after delivery (with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry). AND Prenatal ultrasound examination documenting lack of fetal cardiac activity or movement before the onset of labor. OR Auscultation for fetal heart tones (using electronic devices or non-electronic devices) documenting lack of fetal heartbeat. AND Maternal report of lack of fetal movement for 24 h or more. OR Maternal physical examination confirming lack of fetal movement. OR Radiology findings consistent with intrauterine fetal death. AND Attended delivery followed by fetal physical examination afterbirth consistent with antepartum death, by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, or pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, mid-wife, nurse practitioner, a physician's assistant or other qualified trained practitioner). OR Fetal/placental pathology report consistent with antepartum death. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1 or 2 in GA assessment algorithm).
2	Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined physical examination after delivery. AND Maternal report of lack of fetal movement for 24 h or more. OR Maternal physical examination confirming lack of fetal movement. OR Auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND Attended delivery followed by physical examination after birth consistent with antepartum death, by specialist or qualified trained practitioner appropriate to the health care setting. OR Fetal/placental pathology report consistent with antepartum death. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm).

Antepartum Stillbirth (Fetal death occurs prior to the evidence of labor.) (continued)	
Level	Description
3	Delivery of an infant reported to have no of signs of life at birth(No spontaneous movements, no umbilical cord pulse, no heart-beat, no cry or spontaneous respirations, no chest movement, and whole body cyanosis). AND Maternal report of lack of fetal movement for 24 h or more prior to delivery. OR Report of auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND Non-attended delivery followed by physical examination of the fetus after birth consistent with antepartum death by a healthcare professional appropriate to the level of standard of care in the health care setting. OR Verbal history by a trained health care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth and with physical features consistent with antepartum death. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level2–3 in GA assessment algorithm).
4	Report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made) •Maternal information insufficient to assess gestational age
Intrapartum stillbirth (Fetal death occurs during labor and before delivery)	
Level	Description
1	Delivery of an infant with no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and Apgar score of 0 at 1 and 5 min Determination of the absence of signs of life is made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry. AND Evidence of live fetus prior to onset of labor (documentation of fetal movement and of fetal heart tones by ultrasound prior to onset of labor) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND Attended delivery followed by physical examination afterbirth consistent with intrapartum death by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, midwife, or other qualified trained practitioner). AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal-neonatal parameters (Level 1 in GA assessment algorithm)

Intrapartum stillbirth (Fetal death occurs during labor and before delivery) (continued)	
Level	**Description**
2	Delivery of an infant with no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and Apgar score of 0 at 1 and 5 min. Determination of the absence of signs of life is made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry OR documentation of lack of response to resuscitation efforts. AND Evidence of live fetus prior to onset of labor (maternal report of fetal movement prior to onset of labor and documentation of fetal heart tones by auscultation or hand held Doppler) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND Attended delivery followed by physical examination after birth consistent with intrapartum death by a health care professional appropriate to the level of standard of care in the health care setting. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm).
3	Delivery of an infant reported to have no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no cry, no spontaneous respirations or chest movement, and whole body cyanosis. AND Evidence of live fetus prior to onset of labor (maternal report of fetal movement prior to onset of labor OR auscultation of fetal heart tones) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND (Non-attended delivery followed by physical examination of the fetus after birth consistent with intrapartum death by a healthcare professional appropriate to the level of standard of care in the health care setting OR Verbal history by a trained health care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth.) AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level2–3 in GA assessment algorithm).
4	Report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made). Maternal information insufficient to assess gestational age.

Reference: DaSilva FT, Gonik B, McMillan M, et al. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2016; 34(49):6057-6068.

Table 21 Maternal Death

The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. (As ICD-10 terminology).

In the context of immunization: "Death of a woman during pregnancy, childbirth and the puerperium that is closely related temporally to an immunization event of the mother which is likely the single or contributory cause

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Diagnosis of pregnancy established by any of the following documented criteria: a. Ultrasound examination b. Fetal heart tones c. Positive serum or urine human chorionic gonadotropin pregnancy test d. Delivery of a neonate or other products of conception (abortus, stillborn) AND Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy AND Documentation of Cause of death as: a. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications b. Indirect: non obstetric complications c. Death during pregnancy, childbirth and the puerperium: other or coincidental
2	Diagnosis of pregnancy established by any of the following criteria in the absence of Level 1 criteria: a. LMP date b. Serial Symphysio Fundal Height examinations AND Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy And Documentation of Cause of death as: a. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications b. Indirect: non-obstetric complications c. Death during pregnancy, childbirth and the puerperium: other or coincidental d. Unspecified: unknown or undetermined
3	Absence of Level 1 or 2 criteria for establishing diagnosis of pregnancy and: a. Unsure LMP b. No clinical examination **documented** AND Death of the mother temporal to pregnancy, childbirth or the postpartum period when exact timing of death is unknown AND Documentation of cause of death as: a. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric com-plications, unanticipated complications b. Indirect: non-obstetric complications c. Death during pregnancy, childbirth and the puerperium: other or coincidental d. Unspecified: unknown or undetermined.

Reference: Patwardhan M, Eckert LO, Spiegel H, et al. Maternal death: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6077-6083.

Table 22 Hypertensive disorders of pregnancy (Gestational hypertension, Pre-eclampsia, Pre-eclampsia with severe features including eclampsia)

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Gestational Hypertension	
Level	**Description**
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h WITHOUT severe features (see preeclampsia with severe features category) and WITHOUT proteinuria
1	No proteinuria (as defined by 24 h urine collection < 300 mg, spot protein:creatinine ratio <0.3)
2	No proteinuria (as defined by urine dipstick negative or trace)
In Ev	Blood pressure cannot be measured OR No proteinuria evaluation is available
Preeclampsia has conventionally been defined as the development of gestational hypertension and proteinuria after 20 weeks gestation. Proteinuria can be quantified by: - 24 h urine collection, - a spot protein:creatinine ratio, or - with urinary dipstick. Proteinuria of ≥300 mg in a 24 h urine specimen (the gold standard for measurement of proteinuria), or ≥0.30 on a spot protein:creatinine ratio, or ≥1+ on a dipstick meets the criteria for preeclampsia.	
Level	**Description**
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND New onset proteinuria
1	Proteinuria diagnosed with ≥300 mg of protein on 24 h urine collection OR ≥0.3 on spot protein:creatinine ratio
2	Proteinuria diagnosed with ≥1+ protein on urine dipstick
In Ev.	Blood pressure cannot be measured OR no proteinuria evaluation is available (note diagnosis of preeclampsia with severe features does not require proteinuria, see definition below)

In Ev = Insufficient Evidence

Hypertensive Disorders of Pregnancy Continued

Preeclampsia with severe features *NOTE :can be diagnosed in the presence or absence of proteinuria***.**

•Vascular:
◦ Severely elevated blood pressures, with systolic blood pressure≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only minutes (to facilitate timely anti-hypertensive treatment)
•Neurologic:
◦ Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen/paracetamol)
◦ Eclampsia
◦ Development of visual changes (including photopsia, scotomata,cortical blindness)
•Hematologic:
◦ New onset thrombocytopenia, with platelet count <100,000/L
•Gastrointestinal:
◦ New onset of nausea, vomiting, epigastric pain
◦ Transaminitis (AST and ALT elevated to twice the upper limit of normal)
◦ Liver capsular hemorrhage or liver rupture
•Renal:
◦ Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine(absent other renal disease)
◦ Oliguria (urine output <500 mL/24 h)
•Respiratory:
◦ Pulmonary edema (confirmed on clinical exam or imaging)

Level	Description
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND At least one of the criteria for severe disease:
1	At least one of the following: • Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110mmHg, which is confirmed after only minutes OR • Development of severe, persistent headache OR • Development of visual changes OR • Eclampsia* OR • New onset thrombocytopenia (platelets <100,000/L) OR • New onset unremitting epigastric pain OR • AST and ALT elevated to twice upper limit of normal OR • Evidence of liver capsular hematoma or liver rupture (diagnosed on clinical exam or with imaging) OR • Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease) or oliguria (<500 cc/24 h) OR • Pulmonary edema (confirmed on imaging with chest X-ray, or on clinical exam)
2	New onset nausea and vomiting
In Ev	Blood pressure cannot be measured

◦* ECLAMPSIA, or new-onset grand mal seizures in a patient with pre-eclampsia, without other provoking factors (such as evidence of cerebral malaria or preexisting seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status:

In Ev = Insufficient Evidence

Reference: Rouse CE, Eckert LO, Wylie BJ, et al. Hypertensive disorders of pregnancy: Case definitions & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6069-6076

Table 23 Antenatal Bleeding

Antenatal bleeding is a clinical syndrome characterized by bleeding in the second or third trimester of pregnancy. Pathologic etiologies attributable to the pregnant state include placenta previa, vasa previa and intra-abdominal pregnancy (categories that are not applicable in this study, as women with these conditions are ineligible), and morbidly adherent placentation, placental abruption, cesarean scar pregnancy and uterine rupture.

For both levels of diagnostic certainty for each etiology of antenatal bleeding:

Bleeding is either documented vaginally or suspected to be occurring intrauterine, intraperitoneally, or (rarely) retroperitoneally, based on clinical signs and symptoms.

In the case of ultrasound-based diagnosis, transvaginal ultrasound is more specific than transabdominal ultrasound, and transvaginal ultrasound is recommended where available.

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Morbidly adherent placenta	
Level	**Description**
1	**There are two definitions of equal specificity.** 1. Second- or third-trimester ultrasound or MRI evidence of placenta previa, AND One of the following ultrasound features: • Greyscale: loss of the retroplacental sonolucent zone, irregular retroplacental sonolucent zone, thinning or disruption of the hyperechoic serosa–bladder interface, presence of focal exophytic masses invading the urinary bladder, abnormal placental lacunae • Color Doppler: diffuse or focal lacunar flow, vascular lakes with turbulent flow (peak systolic velocity over 15 cm/s), hypervascularity of serosa–bladder interface, markedly dilated vessels over peripheral subplacental zone • 3D Power Doppler: numerous coherent vessels involving the whole uterine serosa–bladder junction (basal view), hypervascularity (lateral view), inseparable cotyledonal and intervillous circulations, chaotic branching, detour vessels (lateral view) AND One of the risk factors: prior cesarean delivery, prior uterine surgery (including endometrial ablation or dilation and curettage) or cesarean scar pregnancy OR 2. Morbidly adherent placentation found on histology in a hysterectomy or partial wedge resection specimen.
2	**There are two definitions of equal specificity.** 1. Ultrasound evidence of placenta previa, AND hypervascularity at the site of the uteroplacental interface,, diagnosed at laparotomy. OR 2. Difficulty with placental separation after delivery of the infant, at either a vaginal or cesarean delivery with resultant hemorrhage due to partial separation.

Antenatal Bleeding continued	
Placental abruption	
Level	**Description**
1	**There are two definitions of equal specificity.** 1. In the absence of placenta previa on ultrasound, vaginal bleeding in the second or third trimester, AND one of the following: Either uterine irritability or labor, Or clinical signs of hypovolemic shock or coagulopathy. OR 2. Placental pathology with histologic findings of a chronic abruption.
2	**There are two definitions of equal specificity.** 1. Vaginal bleeding in the second or third trimester, AND uterine irritability or labor, without clinical signs of hypovolemic shock or coagulopathy OR 2. Vaginal bleeding in the second or third trimester, AND Clinical evidence of retroplacental clot or visually evident placental infarcts at the time of delivery.
Cesarean Scar Pregnancy	
Level	**Description**
1	**There are two definitions of equal specificity.** 1. Transvaginal ultrasound with the following characteristics: empty uterine cavity, AND Empty cervical canal, without contact with the gestational sac, AND Presence of gestational sac, +/- fetal pole, +/- cardiac activity, in the anterior uterine segment adjacent to the cesarean scar, AND Absence or defect in myometrium between bladder and gestational sac, AND Gestational sac well perfused on Doppler ultrasound (to differentiate from an expulsing, avascular gestational sac). OR 2. Hysterectomy specimen with evidence of pregnancy implanted into the cesarean scar.
2	**There is no Level 2 definition for this event.**
Uterine Rupture	
Level	**Description**
1	Complete uterine disruption at the time of laparotomy in the context of vaginal or intra-abdominal bleeding.
2	**There is no Level 2 definition for this event.**

Reference: Prabhu M, Eckert LO, Belfort M et al. Antenatal bleeding: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35: 6529-6537.

Table 24 Postpartum hemorrhage

Genital tract bleeding after delivery (up to 42 days) of a foetus or infant that leads to an adverse clinical outcome, such as hypovolemia or anaemia e.g. exertional dyspnoea, postural presyncope, tiredness or reduced consciousness. At the furthest extreme uncorrected hypovolaemic shock can lead to organ-dysfunction and maternal death.

ICD-10 definition: "heamorrhage after delivery of a foetus or infant"

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Genital bleeding after delivery leading to severe maternal out-come (maternal death or maternal near miss) as defined by WHO[1].
2	Genital bleeding after delivery with at least one of the following: measured abnormal bleeding (1000 ml or more), or any bleeding leading to hypotension or blood transfusion.
3	Genital bleeding after delivery estimated at 1000 ml or more

Reference: Kerr R, Eckert LO, Winikoff B, et al. Postpartum haemorrhage: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6102-6109.

[1] Can be found in Kerr (*op cit*), Table 1.

Table 25 Fetal growth restriction

A fetus with a sonographic estimation of fetal weight below the tenth percentile for a given gestational age with increasing specificity for adverse perinatal outcomes below the third percentile.

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
	Fetal growth restriction is a sonographic finding characterized by:
1a	Level 1* evidence of pregnancy dating AND Estimated fetal weight below 3% using locally-accepted growth curve OR • Estimated fetal weight below 10% using locally-accepted growth curve AND • Absent or reversed end-diastolic flow of the umbilical artery Doppler OR • Oligohydramnios as defined as amniotic fluid index (AFI) < 8 cm or deepest vertical pocket (DVP) < 2 cm in the presence of intact membranes without concern for fetal anomalies contributing to its etiology
1b	Level 1* evidence of pregnancy dating AND Estimated fetal weight below 10%ile using locally-accepted growth curve AND Lack of absent or reversed end-diastolic flow of the umbilical artery or oligohydramnios (as defined above, cfr. Level 1a)
2a	Level 2 evidence of pregnancy dating AND • Estimated fetal weight below 3% using locally-accepted growth curve OR • Estimated fetal below 10% using locally-accepted growth curve AND • Absent or reversed end-diastolic flow of the umbilical artery Doppler. OR • Oligohydramnios (as defined above, cfr. Level 1a).

Fetal Growth Restriction continued	
Level	**Description**
2b	• Level 2 evidence of pregnancy dating AND Estimated fetal weight below 10%ile using locally-accepted growth curve AND No findings of absent or reversed end-diastolic flow of the umbilical artery or oligohydramnios (as defined above, cfr Level 1a). OR • Level 1* evidence of pregnancy dating AND Estimated fetal weight below 10% using locally-accepted growth curve with no findings of oligohydramnios (as defined abopve, cfr. Level 1a) with inability to assess umbilical artery Doppler.
In Ev	Absence of ultrasound for use in assessment of estimated fetal weight.

*Level 1 evidence of pregnancy dating as defined by the Preterm Birth Working Group of the Brighton Collaboration. Level 1 pregnancy dating depends on a confirmatory ultrasound performed ≤13 $^{6/7}$ weeks gestation

In Ev = Insufficient Evidence

Reference: Easter SR, Eckert LO, Boghossian N, et al. Fetal growth restriction: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35: 6546-6554.

Table 26 Dysfunctional labor

This is defined as prolonged labor at or after 37 weeks and before 42 weeks of gestational age in singleton pregnancies.

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
First stage of labor For both levels of diagnostic certainty the woman is in established labor defined by regular contractions and cervical dilation of at least 4cm.	
Level	**Description**
1	Progress of less than 0.5 cm cervical dilation per hour, for at least 4 hours, in women in established labor (i.e. have regular contractions and cervical dilation of at least 4cm) and with confirmed ruptured membranes.
2	Progress of less than 0.5cm cervical dilation per hour in women, for at least 4 hours, with established labor, (i.e. that is, regular contractions and cervical dilation of at least 4cm) without certainty of ruptured membranes.
Second stage of labor The definitions below are applicable in cases with or without regional analgesia.	
Level	Description
1	Full dilation of the cervix AND onset of the active stage (active maternal effort (i.e. pushing) or visible baby) AND In nulliparous women:> 2h of pushing In multiparous women: > 1h of pushing OR Use of instrument delivery (forceps vacuum/ventouse) for the indication of dystocia OR Caesarean delivery for the indication of dystocia.
2	Full dilation of the cervix in any phase of the second stage AND no delivery within 3 hours of full dilation OR use of instrument for the indication of dystocia OR caesarean delivery for the indication of dystocia.

Reference: Boatin AA, Eckert LO, Boulvain M, et al. Dysfunctional labor: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35:6538-6545.

Table 27 Gestational diabetes mellitus (pregnancy induced hyperglycemia)

Gestational diabetes mellitus (GDM) is a clinical syndrome characterized by the absence of pre-gestational diabetes diagnosis, defined by

- Previous diagnosis of diabetes while not pregnant
  OR
- First trimester hemoglobin A1c level of ≥ 6.5% (47.5 mmol/mol)
  OR
- First trimester fasting blood glucose 126 mg/dL / ≥ 7mmol/L
  AND

Identification of sustained hyperglycemia during pregnancy not due to other known causes (i.e. corticosteroids, beta-mimetics, etc.)

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Absence of pre-gestational diabetes mellitus diagnosis in the first trimester as defined above with level 1-2 certainty for gestational age using GAIA definition for gestational age (APPENDIX C) AND Diagnosis of gestational diabetes based on a positive internationally recognized oral glucose tolerance test ("major criteria" [1,2]) using venous blood sample/samples
2	Absence of pre-gestational diabetes mellitus diagnosis in the first trimester as defined above with at least level 1-2 certainty for gestational age using GAIA definition for gestational age (APPENDIX C) AND Diagnosis of gestational diabetes based on positive internationally recognized oral glucose tolerance test ("major criteria" [1,2]) using capillary blood sample/samples

Gestational Diabetes Mellitus continued	
Level	**Description**
3	Absence of pre-gestational diabetes mellitus diagnosis in the first trimester as defined above with at least level 3 certainty for gestational age using GAIA definition for gestational age AND Diagnosis of gestational diabetes based on positive internationallyrecognized oral glucose tolerance test (see below "major criteria"[1,2])using venous blood or capillary blood sample/samples OR Diagnosis of gestational diabetes based on fasting plasma glucose of 5.1-6.9 mmol/l (92-125 mg/dL) using venous or capillary blood samples.
In Ev	Blood glucose cannot be measured OR Elevated postprandial blood glucose level without confirmatory fasting venous blood or capillary glucose level OR Use of Hemoglobin A1c alone for the diagnosis of GDM without a diagnostic oral glucose tolerance test (OGTT) or elevated fasting plasma glucose level. OR Clinical and laboratory findings such as glucosuria, fundal height greater than dates, obesity, prior history of GDM or family history for the diagnosis of gestational diabetes mellitus without a diagnostic test.

In Ev = Insufficient Evidence

Reference(s): Kachikis A, Eckert LO, Walker C, et al. Gestational diabetes mellitus: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35:6555-6562.

[1] Major criteria (presented in Kachikis op cit)

Major criteria	
Endocrine	
Oral glucose Tolerance tests	75 g OGTT IADPSG WHO NICE 100 g OGTT Carpenter-coustan NDDG
Fasting plasma glucose level	Based on WHO criteria (1)
[Absence of] pregestational diabetes mellitus criteria	See above

[2] Further details regarding oral glucose tolerance tests presented in footnote 1 (Major Criteria); also presented in Kachikis (op cit)

Table 1
Diagnostic oral glucose tolerance tests based on organization or country guidelines.

Test	Guidelines	Number of abnormal values necessary for diagnosis	Fasting plasma glucose mmol/l (mg/dl)	1-h plasma glucose mmol/l (mg/dl)	2-h plasma glucose mmol/l (mg/dl)	3-h plasma glucose mmol/l (mg/dl)	Timing
75 g OGTT							
	WHO 2013 [1]	1	⩾5.1–6.9 (92–125)	⩾10.0 (180)	⩾8.5–11.0 (153–199)	N/A	24–28 wks
	IADPSG [25]	1	⩾5.1 (92)	⩾10.0 (180)	⩾8.5 (153)	N/A	
	NICE (UK) [26]	1	⩾5.6 (101)	Not required	⩾7.8 (140)	N/A	24–28 wks
100 g OGTT							
	Carpenter Coustan [27]	2	⩾5.3 (95)	⩾10.0 (180)	⩾8.6 (155)	⩾7.8 (140)	24–28 wks
	NDDG [27]	2	⩾5.8 (105)	⩾10.6 (190)	⩾9.2 (165)	⩾ 8.0 (145)	

OGTT (Oral glucose tolerance test); IADPSG (International Association of Diabetes and Pregnancy Study Groups); WHO (World Health Organization); NICE (The National Institute for Health and Care Excellence, UK); NDDG (National Diabetes Data Group).

Table 28 Non-reassuring fetal status

Indicator of underlying event resulting in temporary or permanent oxygen deprivation to the fetus which may lead to fetal hypoxia and metabolic acidosis

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Category III fetal heart rate tracings detected via continuous cardiotocography as defined by NICHD Absent baseline fetal heart rate variability AND any of the following: - recurrent late decelerations - recurrent variable deceleration - bradycardia (<110 bpm) OR Sinusoidal pattern AND Umbilical cord blood analysis consistent with metabolic acidosis (pH < 7.0 and Base deficit >12 mmol/L)
2	Category III fetal heart rate tracings detected via continuous cardiotocography as defined by NICHD Absent baseline fetal heart rate variability AND any of the following: - recurrent late decelerations - recurrent variable deceleration - bradycardia (<110 bpm) OR Sinusoidal pattern
3	Fetal heart pattern detected via intermittent auscultation suggestive of fetal hypoxia Baseline Fetal Heart rate (FHR) <110 bpm or >160 bpm Presence of repetitive or prolonged (>3 min) decelerations More than 5 contractions in a 10 min period

Reference: Gravett C, Eckert LO, Gravett MG, et al. Non-reassuring fetal status: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6084-6092.

Table 29 Pathways to preterm birth

Premature preterm rupture of membranes; Preterm labor; Insufficient cervix (not applicable to this study, as women with insufficient cervix are ineligible); Provider-initiated preterm birth

Preterm = Birth at less than 37 gestation-completed weeks (less than 259 days).

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Premature Preterm rupture of membranes	
Level	**Description**
All	Patient is determined to be preterm as defined above. On presentation, patient is determined to not be in preterm labor, having ≤4 contractions per hour documented clinically or on tocodynometer, with <2 cm cervical dilation (greater than 4 contractions per hour would qualify the patient as having preterm labor) Fluid can be noted to be clear, blood-tinged, meconium-tinged (fetal stool), purulent-tinged (yellowish, suggesting infection)
1	Clinical history of rupture of membranes AND Visible leakage of fluid on vaginal speculum exam AND Visible arborization (ferning) on microscopy of amniotic fluid OR Ultrasound with oligohydramnios (AFI <5 or MVP <2) AND Documented membrane rupture by a diagnostic test (one of the below options): Positive intra-amniotic dye-injection method Positive result on amniotic fluid alpha-fetoprotein test kit Amniotic fluid pH measurement (nitrazine paper test) Amniotic fluid placental alpha macroglobulin-1 protein assay (PAMG-1) test (AmniSure test) Amniotic fluid insulin-like growth factor binding protein(IGFBP-1) test (Actim PROM test)
2	Clinical history of rupture of membranes AND Visible leakage of fluid on vaginal speculum examination AND Visible arborization (ferning) on microscopy of amniotic fluid OR Documented membrane rupture by a diagnostic test (one of those listed above) OR Ultrasound with oligohydramnios (AFI <5 or MVP <2)
3	Clinical history of rupture of membranes AND Visible leakage of presumed amniotic fluid; this may be on vaginal speculum examination (pooling in vagina), on inspection of the perineum (wet perineum due to leakage of fluid from the vagina), or fluid soaked cloth/clothes/sanitary pad.

Preterm labor	
Level	**Description**
All	Patient is determined to be have delivered preterm (at less than 37 gestation-completed weeks (less than 259 days)).
1	On presentation, >4 documented uterine contractions per hour as determined by a tocodynometer AND Documented change in length or dilation of cervix by physical examination or transvaginal ultrasound over a two hour period, with clinical criteria for documenting cervical change by exam including: a. Cervical dilation 2 cm or greater at the internal os by digital examination b. Cervical length of 1 cm or less by digital examination c. 50% or greater effacement by digital examination
2	Greater than 4 uterine contractions per hour as determined by a tocodynometer or clinical assessment AND Documented change in length or dilation of cervix by physical examination, with clinical criteria including: a. Cervical dilation 2 cm or greater at the internal os by digital examination b. Cervical length of 1 cm or less by digital examination c. 50% or greater effacement by digital examination
3	Greater than 4 documented uterine contractions per hour determined by clinical assessment AND Documented change in cervical examination (change in dilation or effacement) over a two hour period
Provider-initiated preterm birth	
Level	**Description**
All	Patient is determined to be preterm (birth at less than 37 gestation-completed weeks (less than 259 days).
1	Documentation in the healthcare record by a patient's delivering provider that there were no signs or symptoms of the spontaneous onset of preterm labor AND Documentation in the healthcare record by a patient's delivering provider that the patient needed to undergo induction of labor or cesarean delivery which led to the preterm delivery
2	From recall, delivering provider confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND Delivering provider reports from recall that he or she decided that the patient needed to undergo induction of labor or cesarean delivery
3	From recall, patient confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND Patient reports from recall that the healthcare provider indicated that she needed to undergo induction of labor or cesarean delivery

Reference: Harrison MS, Eckert LO, Cutland C, et al. Pathways to preterm birth: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6093-6101.

Table 30 Standard Definitions for Maternal Events of interest not defined as events in GAIA

Event of Interest	Definition
Chorioamnionitis	Chorioamnionitis also known as intra-amniotic infection is an inflammation of the fetal membranes due to a bacterial infection. Clinical signs and symptoms of chorioamnionitis include the following: • Fever (an intrapartum temperature >100.4ºF or >37.8ºC) • Significant maternal tachycardia (>120 beats per minute [bpm]) • Fetal tachycardia (>160-180 bpm) • Purulent or foul-smelling amniotic fluid or vaginal discharge • Uterine tenderness • Maternal leukocytosis (total blood leukocyte count >15,000-18,000 cells/µL) Of these criteria, intrapartum maternal fever appears to be the most frequent. When at least 2 of the aforementioned criteria are present, the risk of neonatal sepsis is increased. Each clinical sign and symptom of chorioamnionitis, however, is by itself of low predictive value
Oligohydramnios	Amniotic fluid index (AFI) < 8 cm or deepest vertical pocket (DVP) < 2 cm in the presence of intact membranes without concern for fetal anomalies contributing to its etiology
Polyhydramnios	Polyhydramnios is the presence of excess amniotic fluid in the uterus. By definition, polyhydramnios is diagnosed if the deepest vertical pool is more than 8 cm or amniotic fluid index (AFI) is more than 95th percentile for the corresponding gestational age
Gestational liver disease (Intrahepatic Cholestasis of Pregnancy or ICP)[1]	Intrahepatic cholestasis also called obstetric cholestasis should be suspected when pruritis develops during pregnancy in the absence of a rash. Lab evidence of cholestasis includes elevated bile acids (Glyco and Taurochenodeoxycholic Acid)(> 10 umol/L). Up to 60% of patients will have elevated transaminases and 20% of patients will have increased direct bilirubin levels. Jaundice may or may not be present. ICP typically is transient and resolves after delivery. Women that had ICP in previous pregnancy have higher risk to developing ICP in the following pregnancies or other hepatobiliary disorders in later life. ICP is associated with adverse fetal outcome like meconium-stained liquor, fetal asphyxia, spontaneous preterm delivery and intrauterine death.
Gestational liver disease (Acute Fatty Liver of Pregnancy)[2]	Acute fatty liver of pregnancy (AFLP) is a rare, potentially fatal complication that occurs in the third trimester or early postpartum period. AFLP is characterized by microvesicular fatty infiltration of hepatocytes without any inflammation or necrosis. Most frequent signs and symptoms are the following: • Jaundice • Abdominal Pain (usually right upper quadrat, midepigastric or radiating to back) • Central nervous system (altered sensorium, confusion, disorientation, psychosis, restlessness, seizures or even coma) • Disseminated intravascular coagulation • Nausea and vomiting • Gastrointestinal bleeding • Acute renal failure • Oliguria • Tachycardia • Late onset pyrexia • Hypoglycemia • ALT<500 U/L • Hyperbilirubinemia, elevated ammonia, leukocytosis, hypofibrinogenemia Ultrasound examination and computed tomography may demonstrate fatty infiltration of the liver but are not sufficient for diagnosis

<table>
<tr><th>Event of Interest</th><th>Definition</th></tr>
<tr><td>Maternal Sepsis[3]</td><td>Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, child-birth, post-abortion, or post-partum period.
Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.</td></tr>
<tr><td></td><td>Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]
<table><tr><th></th><th colspan="5">Score</th></tr><tr><th>System</th><th>0</th><th>1</th><th>2</th><th>3</th><th>4</th></tr><tr><td>Respiration</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Pao_2/Fio_2, mm Hg (kPa)</td><td>≥400 (53.3)</td><td><400 (53.3)</td><td><300 (40)</td><td><200 (26.7) with respiratory support</td><td><100 (13.3) with respiratory support</td></tr><tr><td>Coagulation</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Platelets, $\times 10^3/\mu L$</td><td>≥150</td><td><150</td><td><100</td><td><50</td><td><20</td></tr><tr><td>Liver</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Bilirubin, mg/dL (μmol/L)</td><td><1.2 (20)</td><td>1.2-1.9 (20-32)</td><td>2.0-5.9 (33-101)</td><td>6.0-11.9 (102-204)</td><td>>12.0 (204)</td></tr><tr><td>Cardiovascular</td><td>MAP ≥70 mm Hg</td><td>MAP <70 mm Hg</td><td>Dopamine <5 or dobutamine (any dose)[b]</td><td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]</td><td>Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]</td></tr><tr><td>Central nervous system</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Glasgow Coma Scale score[c]</td><td>15</td><td>13-14</td><td>10-12</td><td>6-9</td><td><6</td></tr><tr><td>Renal</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Creatinine, mg/dL (μmol/L)</td><td><1.2 (110)</td><td>1.2-1.9 (110-170)</td><td>2.0-3.4 (171-299)</td><td>3.5-4.9 (300-440)</td><td>>5.0 (440)</td></tr><tr><td>Urine output, mL/d</td><td></td><td></td><td></td><td><500</td><td><200</td></tr></table>Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.
[a] Adapted from Vincent et al.[27]
[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.
[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.</td></tr>
<tr><td></td><td>MAP = mean arterial pressure; qSOFA = quick SOFA; SOFA = Sequential [Sepsis-related] Organ Failure Assessment</td></tr>
</table>

References: 1 Geenes V et al . Intrahepatic cholestasis of pregnancy
2 Can J Gastroenterol Vol 20 26 No 1 January 2006
3 Bonet et al. Reproductive Health (2017) 14:67

Table 31 Small for Gestational Age

Weight below 10th percentile for gestational age as assessed against a validated global, regional or local standard.

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
1	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: o Newborn weighed within 24 hours of birth o Weight assessed using a calibrated electronic scale with 10 g resolution AND • The following for assessment of gestational age: o Certain LMP or IUI or embryo transfer date AND confirmatory ultrasound in first trimester OR o First trimester ultrasound
2a	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: o Newborn weighed within 24 hours of birth on any scale with a < 50 g resolution, tared to zero and calibrated AND • The following for assessment of gestational age: o Certain LMP with first or second trimester ultrasound OR o Certain LMP with first trimester physical exam
2b	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: o Newborn weighed within 24 hours of birth on any scale with a < 50 g resolution, tared to zero and calibrated AND • The following assessment of gestational age: o Uncertain LMP with second trimester ultrasound
3a	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: o Infant weighed within the first 48 hours of life o Newborn weighed on any scale with a < 50 g resolution, tared to zero and calibrated AND • The following assessment of gestational age: o Certain LMP with third trimester ultrasound OR o Certain LMP with confirmatory 2nd trimester fundal height OR o Certain LMP with birthweight OR o UncCertain LMP with first trimester physical exam

Small for Gestational Age (continued)	
Level	**Description**
3b	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: – Infant weighed within the first 48 hours of life – Newborn weight assessed by measuring the difference between an adult holding the infant and the adult being weighed alone on any scale AND • The following assessment of gestational age: – Uncertain LMP with fundal height OR – Uncertain LMP with newborn physical assessment OR Uncertain LMP with birthweight
4	• Baby noted to be small, but no actual weight • Baby with GA assessed only by infant examination • Diagnosis extracted from billing codes or chart, with no documentation of actual birth weight or GA

Reference: Schlaudecker EP, Munoz FM, Bardají A, et al. Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017; 35:6518-6528.

Table 32 Low Birth Weight (LBW)

Regardless of gestational age:

- Low birth weight (LBW): <2500 grams.
- Very low birth weight (VLBW): <1500 grams
- Extremely low birth weight (ELBW): <1000grams

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
1	1.Newborn infant weighed within 24 hours of birth AND 2. Use electronic scale which is graduated to 10 grams AND 3. Scale is calibrated at least once a year AND 4. Scale placed on level, hard surface AND 5. Scale tared to zero grams AND 6. Weight recorded as <2500 grams OR 1.Birth weight recorded as <2500 grams AND 2. Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 5 above.

Low Birth Weight (continued)	
Level	**Description**
2	1. Newborn infant weighed within 24 hours of birth AND 2. Scale (electronic/spring) is graduated to at least 50 grams AND 3. Scale is calibrated at least once a year, or more often if moved AND 4. Scale tared to zero grams or 0.00kg AND 5. Weight recorded as <2500 grams OR 1. Birth weight recorded as <2500 grams AND 2. Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 4 above. (Scale used could be electronic or spring scale, including colour-coded scale)
3	1. Newborn infant weighed on day 1 or 2 of life (first 48 hours of life) AND 2. Weight measured using dial/spring/colour-coded scale AND 3. Weight assessed as <2500 grams
4	1. Newborn weight assessed between day 1 and 2 of life (first 48 hours) AND 2.. Proxy measure (newborn foot length, chest circumference, mid upper arm circumference) of birth weight used AND 3. Weight CATEGORY assessed as <2500 grams

Reference: Cutland CL, Lackritz EM, Mallett-Moore T, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35:6492-6500.

Table 33 Neonatal encephalopathy

Disease, malfunction of damage of the brain in a newborn (1–28 days) born at or beyond 35 weeks of gestation, that may be due to a variety of etiologies including but not limited to hypoxia/ischemia, metabolic disturbance, infection and traumatic processes

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
1	(Definite) Abnormal level of alertness or seizures AND Difficulty with initiating and maintaining respiration AND Depression of tone
2	(Probable) Abnormal level of alertness or seizures AND Difficulty with initiating and maintaining respiration OR Depression of tone
3	(Possible) Abnormal level of alertness or seizures without difficulty with initiating and maintaining respiration nor depression of tone

Reference: Sell E, Munoz FM, Soe A, et al. Neonatal encephalopathy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017; 35: 6501-6505.

Table 34 Congenital Microcephaly

Congenital microcephaly, also referred to as primary microcephaly due to its presence in utero or at birth, is a descriptive term for a structural defect in which a fetus or infant's head (cranium) circumference is smaller than expected when compared to other fetuses or infants of the same gestational age, sex and ethnic background

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Postnatally Diagnosed Microcephaly	
Level	**Description**
1	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of Gestational Age (GA)~ AND Head Circumference (HC) 2 Standard Deviations (SD) below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured between 24–36 hours after birth or end of pregnancy. *~GA assessed based on certain Last Menstrual Period (LMP) with confirmatory 1st trimesteror 2nd trimester ultrasound (US) scan, intrauterine insemination (IUI), or embryo transfer date*
2a	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA~ AND HC 2 SD below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured within the first 24 hours§ OR >36 hours and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly *~GA assessed based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, IUI, or embryo transfer date* *§Take into account the variability in this period based on molding of the head*
2b	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA~ AND HC 2 SD below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND – within the first 24 hours§ OR >36 hours and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly *~GA assessed based on uncertain LMP with 2nd trimester US scan* *§Take into account the variability in this period based on molding of the head*

Postnatally Diagnosed Microcephaly (continued)	
Level	**Description**
3a	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA~_ AND HC 2 SD below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA P37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly *~GA based on LMP without confirmatory 1st or 2nd trimester Ultrasound*
3b	Live birth, stillbirth, or spontaneous or therapeutic abortion AND Case meets criteria for microcephaly using a validated algorithm: 1 inpatient diagnosis OR 2 outpatient diagnoses OR 1 outpatient diagnosis AND death in first year using the following diagnostic codes ICD-9-CM code 742.1 or ICD-10-CM code Q02
4	Live birth, stillbirth, or spontaneous or therapeutic abortion AND Diagnosis of congenital microcephaly based on: – physical inspection without HC measurement OR – ICD-9-CM or ICD-10-CM code that does not meet validated algorithm criteria above.
Prenatally Diagnosed Microcephaly	
Level	**Description**
1a	Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester (<14 weeks) or 2nd trimester US scan IUI, or embryo transfer date AND HC 2 SD below mean or <3rd percentile according to fetal ultrasound (US) examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3rd percentile) by: – at least one additional US after 24 weeks and at least one week after first US OR – HC measurement with standard tape measure at birth or autopsy
1b	Fetus of at least 24 weeks GA based on uncertain LMP with 2nd trimester US AND HC 2 SD below mean or <3rd percentile according to fetal ultrasound (US) examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) by: – at least one additional US after 24 weeks and at least one week after first US OR – HC measurement with standard tape measure at birth or autopsy

Prenatally Diagnosed Microcephaly (continued)	
Level	**Description**
2	Fetus of at least 24 weeks GA based on certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US scan AND HC 2 SD below mean or <3rd percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) with femur length and abdominal circumference concordant with GA assessment AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) by: – at least one additional US scan after 24 weeks and at least one week after first US OR – HC measurement with standard tape measure at birth or autopsy
3a	Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, uncertain LMP with 2nd trimester US, IUI, or embryo transfer date AND HC 2 SD below mean or <3rd percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) with femur length and abdominal circumference concordant with GA assessment AND No additional data to confirm microcephaly (i.e., No additional prenatal US scan or confirmation of microcephaly with any additional US or by HC measurement at birth or autopsy at birth or autopsy)
3b	Fetus of at least 24 weeks GA based on certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US AND HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population (e.g., WHO growth reference charts if GA P37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) with femur length and abdominal circumference concordant with GA assessment AND No additional data to confirm microcephaly (i.e., No additional prenatal US scan or confirmation of microcephaly by HC measurementat birth or autopsy)
4	Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, uncertain LMP with 2nd trimester US, IUI, embryo transfer date, or certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US scan AND HC 2 SD below mean or <3% according to fetal US examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND HC at birth or autopsy is in the normal range using appropriate standardized reference charts according to GA and gender for the population, which means that this is NOT a case of prenatally diagnosed congenital microcephaly

Reference: DeSilva M, Munoz FM, Sell E, et al. Congenital microcephaly: Case definition & guidelines for data collection, analysis, and presentation of safety data after maternal immunisation. Vaccine. 35; 6472 – 6482.

Table 35 Major Congenital anomalies

Congenital anomalies, also commonly referred to as birth defects, congenital disorders, congenital malformations, or con-genital abnormalities. Major congenital anomalies are events of prenatal origin that a represent at birth, potentially impacting an infant's health, development and/or survival.

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Major External Structural Defects	
Level	**Description**
1	Alterations in external anatomy visible: – at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR – in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of morphology training for the specific setting
2	Alterations in external anatomy visible: – at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR – in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed by documentation of a diagnosis made by a clinician with some experience diagnosing congenital anomalies
3	Alterations in external anatomy visible: – at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR – in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed: by documentation of a diagnosis made by a trained maternal or child health care provider with at least minimal experience diagnosing congenital anomalies OR – For live births, by using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated
4	(Insufficient evidence to confirm) Alterations in external anatomy visible: – at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR – in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed: – by medical record review OR in claims data (ICD-9/ICD-10 diagnoses)

Internal Structural Defects	
Level	**Description**
1	Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND •Confirmed by definitive imaging study or intraoperative diagnosis OR •Alterations in internal anatomy detected during autopsy for a stillbirth, spontaneous or therapeutic abortion confirmed by documentation by a pathologist or other relevant subspecialist
2	Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND •Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of morphology training for the specific setting without definitive imaging or intraoperative evaluation OR •For stillbirth, spontaneous or therapeutic abortion, internal structural defect is visible by ultrasound or other imaging modality prenatally
3	•Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND •Confirmed: by documentation of a diagnosis made by a clinician with some experience diagnosing congenital anomalies OR using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated
4	(Insufficient evidence to confirm) Alterations in internal anatomy present: at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR at time of stillbirth, spontaneous abortion, or induced abortion AND •Confirmed: through medical record review, with the medical record demonstrating that the anomaly was present at the time of live birth or time of fetal demise, and that the anomaly was diagnosed by a trained maternal or child health care provider with minimal experience diagnosing congenital anomalies OR by claims data (ICD-9/ICD-10 diagnoses)

Functional Defects	
Level	**Description**
1	For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at the time of birth (or propensity to develop alteration present at live birth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed by definitive diagnostic study
2	For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at livebirth (or propensity to develop alteration present at live birth),and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of training in the diagnosis of functional defects for the specific setting
3	For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at livebirth (or propensity to develop alteration present at live birth),and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed: – by documentation of a diagnosis made by a clinician with some experience diagnosing functional defects OR – using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome(individual code or algorithm) has been validated
4	(Insufficient evidence to confirm) For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at the time of live birth (or propensity to develop alteration present at livebirth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed: – through medical record review, with the medical record demonstrating that the anomaly was present at the time of live birth or time of fetal demise, and that the anomaly was diagnosed by a trained maternal or child healthcare provider who is not a qualified geneticist, neonatologist, pathologist, subspecialist, pediatrician, obstetrician, or family medicine practitioner OR – by claims data (ICD-9/ICD-10 diagnoses)

Reference: DeSilva M, Munoz FM, Mcmillan M, et al. Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6015-6026.

Table 36 Neonatal Death

Death of a live born infant regardless of gestational age at birth, within the first 28 completed days of life

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Neonatal death in a non-viable live birth	
Level	**Description**
1	1. Live born infant AND 2. Gestational age <22 weeks (GA level of certainty = 1) OR 3. Birth weight <500 g AND 4. Death of infant in first 28 days of life AND 5. Medically-confirmed death
2	1. Live born infant AND 2. Gestational age/size of newborn assessed as at least one of: a. Gestational age <22 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight <500 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death
3	1. Live born infant AND 2. Gestational age <5 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death
Neonatal death in an extremely preterm live birth	
Level	**Description**
1	1. Live born infant AND 2. Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1) OR 3. Birth weight ≥500 g but <1000 g AND 4. Death of infant in first 28 days of life AND 5. Medically-confirmed death
2	1. Live born infant AND 2. Gestational age/size of newborn assesses as one or more of: a. Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight ≥500 g but <1000 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death

Neonatal death in an extremely preterm live birth (continued)	
Level	**Description**
3	1. Live born infant AND 2. Gestational age ≥5 months but <7 months according to neonate's parent (mother/father)/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death
Neonatal death in a preterm live birth (gestational age ≥28to <37 weeks)	
Level	**Description**
1	1. Live born infant AND 2. Gestational age ≥28 and <37 weeks (Level of Certainty = 1) OR 3. Birth weight ≥1000 g but <2500 g AND 4. Death of infant in first 28 days of life AND 5. Medically-confirmed death
2	1. Live born infant AND 2. Gestational age/size of newborn assesses as one or more of: a. Gestational age ≥28 and <37 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight ≥1000 g but <2500 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death
3	(MAY apply to LMIC- or may be non-viable in LMIC) 1. Live born infant AND 2. Gestational age ≥7 months but <9 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death
Neonatal death in a term live birth	
Level	**Description**
1	1. Live born infant AND 2. Gestational age ≥37 weeks (GA Level of Certainty = 1) AND 3. Birth weight >2500 g OR 4. Documented intra-uterine growth retardation if ≤2500 g AND 5. Death of infant in first 28 days of life AND 6. Medically-confirmed death

Neonatal death in a term live birth (continued)	
Level	**Description**
2	1. Live born infant AND 2. Gestational age/size of newborn assesses as one or more of: a. Gestational age ≥37 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight ≥2500 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death which is confirmed by examination by (by at least) non-medically-trained attendant (e.g. undertaker, community member)
3	(apply to LowerMiddleIncomeCountries) 1. Live born infant AND 2. Gestational age ≥9 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death

Reference: Pathirana J, Muñoz FM, Abbing-Karahagopian V, et al. Neonatal death: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6027-6037.

Table 37 Neonatal Infections

Neonatal bacteraemia and sepsis (of early or late onset), meningitis, pneumonia and other respiratory infections such as bronchiolitis, caused by bacteria, parasites, viruses or fungi. Localised eye and ear infections, encephalitis, urinary tract infections and intestinal infections were excluded from these guidelines

Neonatal invasive blood stream infections: bacterial/fungal/viral	
Level	**Description**
1	Recognised pathogen identified using a validated method and from a normally sterile site.
2	Not meeting Level 1 of evidence AND Meeting 3 or more of the following criteria: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachycardia or new or more frequent episodes of bradycardia •New or more frequent episodes of apnea or increased oxygen requirement or increased requirement for ventilatory support • Lethargy or moving only when stimulated or hypotonia or irritability • Difficulty in feeding or abdominal distention • Pallor or poor perfusion or hypotension •Abnormal White Cell Count or I/T ratio >0.2 • Abnormal platelet count •Increased inflammatory markers (CRP, procalcitonin) • Metabolic acidosis as defined by a base excess

Neonatal invasive blood stream infections: bacterial/fungal/viral (continued)	
Level	**Description**
3	Not meeting Level 1 or 2 of evidence AND Meeting 2 or more of the following criteria: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachypnea or severe chest in drawing or grunting or cyanosis • Change in level of activity • History of feeding difficulty • History of convulsions
Bacterial/fungal/viral meningitis	
Level	**Description**
1	Recognised pathogen identified using a validated method from cerebrospinal fluid (CSF)
2	CSF pleocytosis OR positive IgM antibodies to a specific pathogen in the CSF AND Recognised pathogen identified using a validated method from a normally sterile site (other than CSF) AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 1 or more criteria below: • History of convulsions •Lethargy or irritability •Coma •Apnea •Bulging fontanel •Neck stiffness
3a	CSF pleocytosis AND No pathogen identified using a validated method from a normally sterile site AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 3 or more criteria below: • History of convulsions • Lethargy or irritability • Coma • Apnea • Bulging fontanel • Neck stiffness
3b	No lumbar puncture done or no sample available AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 4 or more criteria below: • History of convulsions • Lethargy or irritability • Coma • Apnea • Bulging fontanel • Neck stiffness

Respiratory bacterial/fungal/viral infection	
Level	**Description**
1	New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND Recognised virus identified using a validated assay from an upper respiratory sample OR Recognised pathogen identified using a validated method and from a normally sterile site AND 3 or more criteria below: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachypnea or Nasal flaring or Chest in-drawing or Grunting • Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% • Apneas • Increased respiratory secretions or Increased suctioning requirements • Cough or wheeze or crepitations • Increased CRP or procalcitonin
2	New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND 4 or more criteria below: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachypnea or Nasal flaring or Chest in-drawing or Grunting • Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% • Apneas • Increased respiratory secretions or Increased suctioning requirements • Cough or wheeze or crepitations • Increased CRP or procalcitonin
3	2 or more criteria below: • Difficulty in breathing/Tachypnea • Severe chest in-drawing • Nasal flaring • Grunting • Wheezing • Stridor • Fever

Reference: Vergnano S, Buttery J, Cailes B, et al. Neonatal infections: Case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34 (49):6038-6046

Table 38 Respiratory Distress in the Neonate

Constellation of clinical findings that support the presence of breathing difficulty in the neonate (0-28 days of life), independent from etiology or severity, and independent from the infant's gestational age or circumstances at the time of delivery

Level	Description
1	Newborn 0 to 28 days of life AND Abnormal respiratory rate: Measurement of number of breaths per minute consistent with: – Tachypnea = respiratory rate of more than 60 breaths per minute OR – Bradypnea = respiratory rate of less than 30 breaths per minute OR – Apnea = cessation of respiratory effort (no breaths) for at least 20 seconds AND Clinical symptoms consistent with labored breathing: – Nasal flaring (dilatation of alae nasi) OR – Noisy respirations in the form of expiratory grunting, stridor, or wheeze OR – Retractions or increased chest in-drawings on respiration (subcostal, intercostal, sternal, suprasternal notch) OR – Central cyanosis (whole body, including lips and tongue) on room air OR – Low Apgar Score (< 7 points) at 10 min, with respiration score <2 AND Examination and documentation by qualified, trained, health care provider appropriate for the clinical setting.
2	Newborn 0 to 28 days of life AND Abnormal respiratory rate: Not measured, but reported as "rapid breathing", "slow breathing", having periods of "no breathing", or "abnormal breathing" AND Clinical symptoms consistent with labored breathing: – Nasal flaring (dilatation of alae nasi) OR – Noisy respirations in the form of expiratory grunting, stridor, or wheeze OR – Retractions or increased chest in-drawings on respiration (subcostal, intercostal, sternal, suprasternal notch) or seesaw respirations OR – Central cyanosis (whole body, including lips and tongue) on room air OR – Low Apgar Score (< 7 points) at 10 min, with respiration score <2 AND – No medical record documentation, but reporting through either a non-medical observer (e.g. mother, father, community worker) or via standard census mechanisms (e.g. Demographic and Health Surveillance System) OR – Collection of information from medical record review or billing codes.
3	No need for a level 3 per working group.
4	Not enough information to ascertain case of respiratory distress.
5	Not a case of respiratory distress in the neonate.

Reference: Leigh R. Sweet, Cheryl Keech, Nicola P. Klein, et al. Respiratory distress in the neonate: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35: 6506-6517.

Table 39 Preterm Birth

Birth in less than 37 gestation-completed weeks (less than 259 days).

Prematurity and assessment of gestational age	
Level	**Description**
1	Certain last menstrual period date (LMP) LMP or intrauterine insemination (IUI) date or embryo transfer (ET) date with confirmatory 1st trimester scan (≤13 $^{6/7}$ weeks). OR 1st trimester scan (≤13 $^{6/7}$ weeks)
2a	Certain LMP* with 2nd trimester scan (14 $^{0/7}$ weeks to 27 $^{6/7}$weeks). *Note: If LMP and U/S do not correlate, default to U/S GA assessment.* OR Certain LMP* with 1st trimester physical examination.
2b	Uncertain LMP with 2nd trimester scan (14 $^{0/7}$ weeks to 27 $^{6/7}$ weeks).
3a	Certain LMP with 3rd trimester scan ≥ 28 $^{0/7}$ weeks OR Certain LMP with confirmatory 2nd trimester Fundal Height (FH) OR Certain LMP with birth weight OR Uncertain LMP with 1st trimester physical examination.
3b	Uncertain LMP with FH. OR Uncertain LMP with newborn physical assessment. OR Uncertain LMP with Birth weight
*	Definitions of LMP, birth weight and physical assessment in referenced article.

Reference: Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34(49):6047-6056.

Table 40 Failure to Thrive

Failure to Thrive (FTT) can be broadly defined as a faltering of growth from a previously established pattern of growth. It is universally established that a diagnosis of failure to thrive should be based on anthropometric data. However no consensus exits as to which measurements achieve the highest specificity and sensitivity. Weight is generally regarded is the indicator of choice, particularly a change in growth velocity, and as such has been selected as the standard for this case definition with a weight for age deceleration as the primary indicator of failure to thrive. The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Level	Description
1	Infant age[1] determined by a documented birth date AND Weights obtained using an electronic scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration[2] through at least 2 centile spaces on growth chart[3]
2a	Infant age determined by a documented birth date AND Weights obtained using a beam balance scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration through at least 2 centile spaces on growth chart OR Infants with an undocumented birth date, where age is determined based on Mothers recall to nearest month AND Weights obtained using electronic scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration through at least 2 centile spaces on growth chart
2b	Infant age determined by a documented birth date AND Weights obtained using a spring balance scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration through at least 2 centile spaces on growth chart OR Weight measured using electronic scale or beam balance scale AND Length taken using Infantometer AND Weight for length less than or equal to the 3rd centile on the appropriate growth chart

Level	Description
3a	Infants with an undocumented birth date, where age is determined based on Mothers recall to nearest month AND Weight obtain using either beam balance or spring balance scale AND At least 2 weights, measured as least 4 weeks apart AND Weight for age deceleration through at least 2 centile spaces on growth chart
3b	Infants with no weight available AND Physical examination consistent with FTT[4] AND MUAC[5] indicative of severe wasting

[1]This case definition is limited to infants up to 12 months of age.

[2] Weight should be documented on the appropriate growth chart at the time of assessment. A fall through 2 centile spaces may be demonstrated at any point in the first 12 months of life, using any two weights as long as they are taken at least 4 weeks apart. Details of use of the weight balances allowable under this case definition and use of the Infantometer for length assessment are presented in the reference given below.

[3] For infants born at 37 weeks gestation or above, the WHO growth charts should be applied. When using weight for age use the growth chart most accurate for the infants age. The birth to 6 months age range should be used where data is available for this range only, the birth to 2 years chart should be used where data is available beyond 6 months of life. When using weight for length, use the chart for birth to 2 years. For infants born less than 37 completed weeks gestation, the Intergrowth charts for postnatal growth standards in preterm infant should be used. All infants should be plotted on their respective growth chart using their corrected age. Links to relevant growth charts are presented in the reference given below.

[4] Physical examination with signs of Failure to Thrive (must include at least 2 findings, with at least one major finding) Major findings: Reduced subcutaneous fat stores; poor muscle mass; loose skin folds; prominent ribs; thin limbs Other less specific signs include: sparse hair; rashes; pallor; miserable; lethargy/fatigue.

[5] Mid Upper Arm Circumference (MUAC): For infants 0–6 months, a MUAC of 6 110 mm is indicative of severe wasting. For infants 6–12 months, a MUAC of 6 115 mm is indicative of severe wasting. Instructions on performing MUAC are presented in the reference given below.

Reference: Ross E, Munoz F, Edem B et al. Failure to thrive: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35:6483-6491.

Table 41 Standard Definitions for Neonatal Events of interest not defined as events in GAIA

Event of Interest	Definition
Large for gestational age	Birth weight > 90% for newborns of same gestational age in same population (>4000g at term).
Macrosomia	BW >4000 g (*8 lb, 13 oz*).

APPENDIX E AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccines R & D Protocol Amendment 1	
eTrack study number and Abbreviated Title	207636 (EPI-RSV-008 BOD)
Amendment number:	Amendment 1
Amendment date:	12-FEB-2018
Co-ordinating author:	PPD, Lead Science Writer

Rationale/background for changes:

The protocol has been amended to reflect the following changes and provide the following clarifications / corrections.

- A separate screening visit has been added.
- Evaluations of GBS rectovaginal colonization of pregnant women, and the occurrence of GBS bacteremia/septicemia in their newborn infants, have been removed as study objectives.
- The Study Procedures Table and Detailed Descriptions of Study procedures have been updated both for consistency with these changes, and for improved consistency with the content of the electronic Case Report Forms for the study.
- Parents / LARs/designates are to contact the study site whenever:
  - the infant has developed symptoms of respiratory tract infection (RTI),
  - the infant has developed symptoms of difficulty in breathing or wheezing,
  - the infant's RTI symptoms have worsened,
  - the parent(s)/LAR(s) (or their designate(s)) are concerned about the infant's RTI signs and/or symptoms (parental concern).
- Text describing the content and use of the maternal health memory aid and the infant health and RTI memory aid has been updated and clarified.
- Additional editorial changes have been made to ensure consistency with the modifications noted above, and typographical errors have been corrected.

Text that has been moved or added is presented in ***bold italics*** and deleted text in ~~strikethrough~~ in the following sections.

Contributing Authors:

- PPD, ***Clinical Research and Development Lead***
- PPD, PPD, PPD, Epidemiologists

List of Abbreviations

~~GBS~~	~~Group B Streptococcus~~
ICH	International ~~Conference on~~ Council for Harmonisation

Glossary

Level 2 ultrasound ***(or fetal morphology ultrasound)***	Definition is unchanged. Only the label has been adjusted, as noted on the left.
Neonatal events of interest	***Events as described in Section 11.1 that occur from birth through 28 days of age.***
Pregnancy related events of interest	Events as described in Section 11.1 that occur from ~~post-enrolment~~***Visit 1*** through Visit 6 (Day 42).
Protocol amendment:	The International ~~Conference on~~ ***Council for*** Harmonisation (ICH) ……
~~Respiratory tract infection (RTI) with parental concern:~~	~~Any RTI for which the parents/ LAR(s) have visited or plan to visit a medical health care practitioner.~~
End of Study (Synonym of End of Trial)	~~For studies without collection of human biological samples or imaging data, EoS is the Last Subject Last Visit (LSLV).~~

Synopsis

Number of subjects	~~Up~***Approximatey 4000 pregnant women (up*** to approximately 400 pregnant women ~~≥~~$24^{0/7}$ ~~weeks and < $28^{0/7}$ weeks of gestation are planned to be enrolled~~ per country.) Neonates of enrolled pregnant women who consent to the infant's continued study participation will also be enrolled.
Sampling schedule for neonates/infants	During the 1-year post-birth surveillance period, for each RTI with suspicion of difficulty in breathing, or wheezing, or with parental concern, a nasal swab will be collected ~~at the LRTI study visit~~ ***a visit to assess potential LRTIs***

Background and Rationale (Section 1.1 and Synopsis "Rationale for the Study and Study Design")

…… There are also a number of maternal vaccines in development that aim to protect neonates and infants from additional pathogens, including respiratory syncytial virus (RSV) ~~and group B streptococcus (GBS).~~ GlaxoSmithKline (GSK)~~ will enter Phase II with its~~ ***is developing an*** investigational vaccine for use in pregnant women, against RSV disease.~~ GBS vaccines are also being developed by GSK. Of note, these vaccines are developed solely for immunization in pregnancy.~~

Maternal immunization is implemented worldwide and has the potential to make a major contribution to reducing RSV lower respiratory tract infections (LRTI) ~~GBS~~ and other disease burden in infants globally.

Whilst there is good documentation of the global burden of RSV disease, incidence of RSV-LRTI according to the World Health Organization (WHO) 2015 case definitions [Modjarrad, 2016] is lacking in the literature. Hence, this study will also estimate the incidence of infant RSV-LRTI using WHO case definitions across geographically distinct locations to support incidence rate assumptions for planning of future efficacy trials. ~~There are limited data on the prevalence of GBS rectovaginal colonization in pregnant women, by serotype, in different global settings and this study will aim to address this gap.~~

To achieve these goals, GSK will be guided by the WHO recommendations on antenatal care for a positive pregnancy experience [WHO, 2016] and the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) case definitions [~~Bonhoeffer, 2016~~]. ~~Standardisation of surveillance methodology and case definitions (applicable to maternal immunization AEs) may support comparison of data across different countries~~ [~~Jones , 2016~~ ***Bauwens 2016; Bonhoeffer 2016; Kochhar 2017***].

Rationale for the Study Population (Section 1.1.1 and Synopsis)

……Regardless of enrolment location, healthy pregnant women aged 18 to 40 years with normal, uncomplicated, singleton pregnancies, who have had a ~~second trimester~~***level 2 (fetal morphology)*** ultrasound without any significant findings will be eligible for possible study participation. Inclusion / exclusion criteria have been structured in a way that resembles those of Phase ***II***/III ~~exclusion~~ criteria to ensure good comparability

Pregnant women ~~will be enrolled starting at~~ ***24$^{0/7}$*** ~~and~~ ***up to (but not including) 28$^{0/7}$ weeks of gestation*** will ***be enrolled***, to ensure that they are followed as of the time of potential vaccination in a clinical trial.

Rationale for the Surveillance System for the detection of pregnancy related events of interest (Section 1.1.2)

…... ~~Study~~ ***Information obtained from*** study-specific procedures and laboratory ~~testing~~ ***tests*** (e.g. blood sampling, ~~vaginal swabs,~~ urine dipstick) ~~will be performed for epidemiological purposes only; the information obtained from these procedures and tests~~ is not to be relied upon for clinical management of study subjects.

~~**Rationale for the inclusion of GBS serotyping and surveillance**~~

~~In addition to RSV, GSK is developing a GBS maternal vaccine. GBS is the leading cause of neonatal sepsis globally, and disease can occur from the time of birth through 3 months of age. There is a need to address some of the GBS knowledge gaps and if possible prepare sites to detect GBS invasive disease. Aligned with this strategy, this study may collect vaginal swabs and blood samples to assess GBS colonization and serotypes, and antibody levels in maternal and cord blood. Data regarding occurrence of GBS invasive disease (sepsis, pneumonia and meningitis) may be collected through 90 days after birth, if possible. In case of suspected neonatal sepsis, pneumonia or~~

~~meningitis, GBS culture results will be documented if performed by a local healthcare provider. Because GBS testing results from study vaginal swabs will be performed only for epidemiological purposes and will not be available in time to inform clinical management, the GBS portion of this protocol will only be implemented in settings that have ongoing routine implementation of risk based intrapartum antibiotic prophylaxis for GBS. Vaginal swabs will only be performed in settings that adhere to this risk based approach for intrapartum antibiotic prophylaxis.~~

Rationale for the use of Global Alignment of Immunization safety Assessment in pregnancy (GAIA) case definitions (Section 1.1.3)

GAIA, a Brighton collaboration project, aims to develop standardized case definitions and criteria for diagnostic certainty of maternal and neonatal outcomes in the context of immunization trials [~~Bonhoeffer, 2016~~]***Bauwens 2016, Bonhoeffer 2016, Kochhar 2017***].

Risk Assessment (Section 2.1)

~~Vaginal~~ ***Nasal swab*** ~~sample~~ ***collection from infant subjects may cause discomfort***	***Spontaneous data***	***Sample collection will only be performed by appropriately trained personnel.*** ~~Sample collection will only performed if amniotic membranes are intact~~ ~~Subjects~~ ***Subjects' parent(s)/LAR(s) will be notified of this risk in the informed consent form***.

Benefit Assessment (Section 2.2)

….. Data collected during the study may enhance understanding of the incidence of maternal events of interest in women with low risk pregnancies, neonatal events of interest, ~~GBS colonization and serotype distribution in pregnant women, GBS invasive disease in neonates and infants,~~ and lower respiratory tract infections associated with RSV infection in neonates and infants.

Overall Benefit / Risk Conclusion (Section 2.3)

Potential risks to subjects participating in this study are limited to those associated with the collection of biological specimens ~~for analysis by the sponsor~~.

Primary Objectives (Section 3.1 and Synopsis)

In healthy pregnant women with uncomplicated pregnancies ~~at the time~~ ***as of*** ~~enrolment~~ ***Visit 1:***

Secondary Objectives (Section 3.2 and Synopsis)

In healthy pregnant women with uncomplicated pregnancies ~~at the time~~***as of*** ~~enrolment~~***Visit 1***:

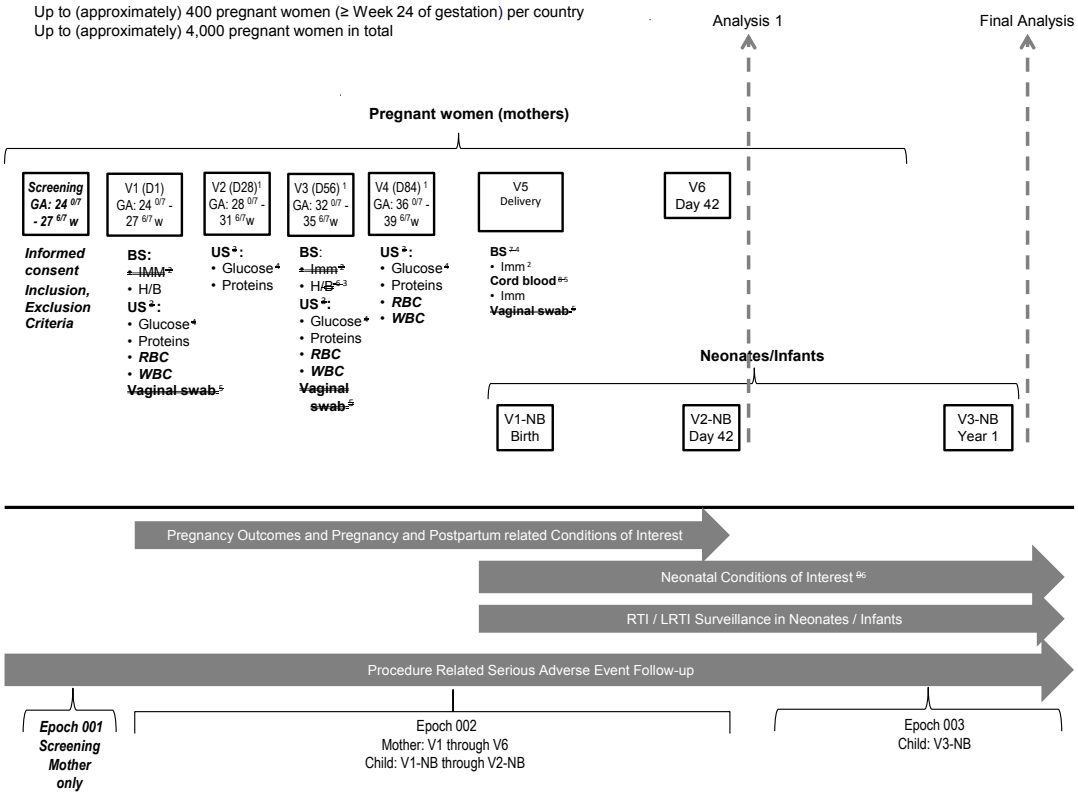
Tertiary Objectives (Section 3.3 and Synopsis)

- To ~~explore~~***describe*** the association of other respiratory viruses with the occurrence of RSV-LRTI in infants.

- To ~~evaluate~~***describe*** the association between RSV-LRTI in infants and the level of RSV neutralizing antibodies in cord blood.
- ~~To describe the prevalence of GBS vaginal colonization and serotype distribution in pregnant women in the 2nd and 3rd trimester and at delivery (if possible).~~
- ~~To describe GBS serotype specific antibody concentrations in pregnant women in the 2nd and 3rd pregnancy trimester and at delivery (if possible)~~
- ~~To describe GBS serotype specific antibody concentrations in cord blood (if possible)~~
- ~~To describe the occurrence of GBS invasive disease in infants (if possible).~~
- ~~To describe occurrences of hospitalization and death due to GBS invasive disease (if possible).~~

Study Design Figure 1 and accompanying footnotes (Section 4.0)

These have been adjusted to include a screening visit, to clarify that urine dipstick testing will be done at study site visits 1 through 4, to remove references to sample collection for GBS testing, and to remove the reference to oral glucose challenge/tolerance testing. Footnotes have been renumbered for consistency with these changes.



Study Design Footnotes

D = day; M = month; V = visit; W = week; Y = year. NB = newborn; GA = Gestational age; BS = blood sample; US = urine sample ***for dipstick testing***; IMM = immune response; HB = hematology/biochemistry; ***RBC = red blood cell(s); WBC = white blood cell(s)***; RSV = respiratory syncytial virus; RTI = respiratory tract infection; LRTI = lower respiratory tract infection;

[1] ~~Visits may be replaced by V5 depending on the date of~~***. If delivery occurs prematurely, skip to Visit 5 ("at delivery").***

[2] At Delivery, RSV-A antibody titers for all women

[3] ~~Red blood cells, white blood cells will be recorded when available.~~ ***~~Record positive results of any urine culture(s), if performed.~~***

[4] ~~Results of Oral glucose challenge / oral glucose tolerance test(s) should be recorded~~***~~, if performed by local healthcare provider and available.~~***

[5] At V3, only hemoglobin testing.

[6] Blood sample should be collected within 72 hours after delivery.

[7] RSV-A antibodies in cord blood

[8] Neonatal conditions of interest occur (by definition) between 0 and 28 days after birth. They will be reported once site staff become aware of them (whether this occurs during the first 28 days after birth, or at a later time).

Study population (Section 4.0 and Synopsis)

- ~~Study population (per country): Up to (approximately) 400 pregnant women ≥24$^{0/7}$ and < 28$^{0/7}$ weeks of gestation (at the first study visit) will be enrolled; neonates of consenting parent(s) / LAR(s) will be enrolled at birth. The study will be conducted in up to approximately 10 countries.~~***Study population: The study will be conducted in multiple countries, in pregnant women and their neonates***.
- ~~Thus the total study population will consist of up to (approximately) 4000 pregnant women and their neonates.~~

Table 1 and Synopsis Table 1 Sampling schedule for pregnant women/mothers

		Visit				
Sample	**Parameter(s) evaluated**	**1**	**2**	**3**	**4**	**Delivery**
Maternal Blood	Hematology/ biochemistry[1,4] Antibody titer (RSV-A) ~~Antibody concentration (GBS)~~	x ~~x~~ ~~x[4]~~		x[2,3] ~~x~~ ~~x[4]~~		 ≤ 72 hours after delivery[3,5] ~~≤ 72 hours after delivery[3]~~
Cord Blood	Antibody titer (RSV-A) ~~Antibody concentration (GBS)~~					x ~~x~~
Urine	Protein~~, glucose[1]~~***glucose***, ***RBC***, ***WBC*** [2, 4]	x	x	x	x	
~~**Vaginal swab**~~	~~GBS vaginal colonization and serotypes~~	~~x[4]~~		~~x[4]~~		~~Before rupture of membranes~~

[1] ~~Haematology/biochemistry and urine protein/glucose testing will~~ ***To*** be performed preferentially by local healthcare providers~~The~~, ***as per local practice***. ***To be performed by the*** investigator/study staff ~~will collect biological samples~~***ONLY*** if not done by the local healthcare provider ~~as per local practice. When available~~***, within 2 weeks before the study visit***.

[2] ***The investigator/site staff will perform a urine*** ~~dipstick results for red blood cells (RBC) and white blood cells (WBC) will also be collected~~***test using supplies provided by GSK***.

[3] Haemoglobin only

[4] ~~This~~***If results are abnormal, subjects will be referred per local standard of care.***

[5] ***This*** sample may ~~also~~ be collected as from start of labor (e.g. when the mother arrives at the hospital to deliver and an intravenous line is inserted).

~~[4] only in countries with routine implementation of risk based intrapartum antibiotic prophylaxis for GBS~~

- Sampling schedule for **neonates/infants**: During the 1-year post-birth surveillance period, for each RTI with suspicion of difficulty in breathing, or wheezing, or with parental concern, a nasal swab will be collected at ~~the LRTI study visit~~ ***a visit to assess potential LRTIs***.

- Primary Completion Date (PCD): 42 days post-delivery/birth (i.e. Visit 6 for the mothers and Visit 2-NB for the infants) or last visit of Epoch ~~1~~***002***.
- Duration of the study: Approximately 4.5 to 6 months for ~~all~~ ***participating pregnant*** women ~~enrolled~~; approximately 1 year for ~~all~~ ***participating*** infants ~~enrolled~~.
  - Epoch 001: ***Screening***
  - Epoch 002: ***Primary starting at Visit 1 and ending 42 days post-delivery/birth (Visit 6 for the mothers and Visit 2-NB for the infants).****
  - Epoch ~~002~~***003: Follow-up of infants starting 43 days post-delivery/birth and ending at Visit 5-NB (1 year post-birth).***

*Any safety and disease surveillance data collected after Visit 2-NB will be collected in Epoch ~~002~~ ***003***.

Table 2 and Synopsis Table 2 Study groups and epochs foreseen in the study

Study Groups	Number of subjects enrolled	Age (Min/Max)	Epochs		
			Epoch 001	Epoch 002	*Epoch 003*
Mothers	Up to ~ 400 (~~by~~ ***per*** country)	18 years - 40 years	●	●	
Infants	Up to ~ 400 (~~by~~ ***per*** country)	NA		●	●
To achieve the enrolment targets noted above, the number of pregnant women SCREENED in each country may exceed 400					

- Surveillance for pregnancy outcomes and pregnancy-related events of interest …..from ~~enrolment~~ ***Visit 1*** up to 42 days after delivery.
- Surveillance for neonatal events of interest ….. ***that occur*** from birth up to 28 days of age.
- ~~Surveillance for GBS invasive disease (refer to Section 8.6) in infants, from birth through 90 days of age.~~

Case Definitions – Neonatal Events of Interest (Section 5.2)

~~**Invasive GBS disease**~~

~~GBS invasive disease is a serious bacterial infection that requires urgent referral to a hospital. A lack of prompt diagnosis and treatment may lead to infant death. Diagnosis of a case of GBS invasive disease requires routine collection of blood/cerebrospinal fluid for culture, and a subsequent GBS positive local laboratory result.~~

~~Signs and symptoms of potentially serious bacterial infection that may be caused by GBS and lead to the routine collection of blood/cerebrospinal fluid for culture may include:~~

- ~~not able to feed since birth or stopped feeding well (confirmed by observation)~~
- ~~convulsions~~
- ~~fast breathing (60 breaths per minute or more) among infants less than 7 days old~~
- ~~severe chest in-drawing~~
- ~~fever (38°C or greater)~~

- ~~low body temperature (less than 35.5 °C)~~
- ~~movement only when stimulated or no movement at all.~~

Case Definitions – Respiratory Tract Infection (RTI) / Lower respiratory tract infection (LRTI) (Section 5.3)

During ~~the~~ ***data*** analysis ~~of the study data~~, cases of respiratory tract infection (RTI) identified from birth up to 1 year of age will be classified according to the case definitions in Table 3.

Footnote to Table 3: SpO_2 = blood oxygen saturation ***by pulse oximetry***.

Study Population - Number of Subjects / Centres (Section 6.1)

- ~~Up~~ ***The study will be conducted at multiple centres in multiple countries. The total enrolled study population will consist of up to (approximately) 4004000 pregnant women ≥ and their neonates***.
- ***In each participating country, up to (approximately) 400 pregnant women ≥24$^{0/7}$ ~~weeks~~ and <28$^{0/7}$ weeks of gestation*** ~~are planned to~~ ***will be enrolled*** ~~per country~~. . Neonates of enrolled pregnant women who consent to their child's study participation will also be enrolled.

Inclusion Criteria for Enrolment (Section 6.2)

Pregnant Women

- Healthy pregnant women 18-40 years of age who are ≥ 24 0/7 weeks GA ***at screening and < 28 0/7 weeks GA at Visit 1***, as established by ultrasound examination and/or last menstrual period (LMP) date
- Women whose pregnancy is considered low risk ***at the time of*** ~~enrolment~~, based on medical history, obstetric history, and clinical findings during the current pregnancy
- Women who had no significant findings (such as abnormal fetal morphology, amniotic fluid levels, placenta, or umbilical cord) observed during a Level 2 ultrasound ***(fetal morphology assessment)*** after ~~18 0~~***24***$^{0/7}$ weeks and ~~prior to enrolment~~ .
- HIV uninfected women who have been tested within the past year and have documented HIV negative test results ~~at the time of enrolment~~.
- Individuals ***(mother or mother and father)*** who, at the time of ~~enrolment~~***their informed consent*** t, express willingness to enroll their infant in the study at the time of birth.
- Individuals who, at ~~the time of enrolment~~, are in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator;
- Individuals who, in the opinion of the investigator ~~at enrolment~~ can and will comprehend and comply with all study procedures (e.g., return for study follow-up visits, be contactable and available on a regular basis for surveillance).

Exclusion Criteria for Enrolment (Section 6.3)

Pregnant Women

- Individuals determined ~~at the time of enrolment~~ to have one of the following conditions associated with increased risk for a serious obstetrical complication (specify any/all that apply in the eCRF)
  - Gestational diabetes uncontrolled by diet and exercise ~~as per American College of Obstetricians and Gynecologists guidelines (ACOG Practice Bulletin 2013~~);
- Individuals determined to have (during the current pregnancy, ~~prior to enrolment~~) one of the following infections or conditions associated with risk of adverse outcome (specify any/all that apply in the eCRF):
- Individuals who ~~at the time of enrolment~~ have any underlying condition or infection that would predispose them to increased risk for a serious obstetrical complication that is not mentioned above
- Individuals who ~~at the time of enrolment~~ have behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, could interfere with the subject's ability to participate in the study;
- Individuals ***who*** ~~at the time of enrolment~~ have known or suspected impairment of the immune system, an active autoimmune disorder that is not well-controlled, or who are receiving systemic immunosuppressive therapy;

Subject Identification (Section 8.1)

Subject numbers for ~~both~~ pregnant women (mothers) ~~consenting~~ ***who consent*** to participate in the study ~~and~~***will be assigned at screening. Subject numbers for*** their (yet to be born) neonates will be assigned at Visit 1. ~~They~~***Subject numbers*** will be assigned sequentially according to the range of ~~subject~~ numbers allocated to each study centre. Subject numbers of mother –infant pairs will be clearly linked.

General Study Aspects (Section 8.2)

Supplementary study conduct information not mandated to be present in this protocol is provided in the ~~accompanying~~ Study Procedures Manual (SPM).

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207636 (EPI-RSV-008 BOD)
Protocol Amendment 4 Final

Outline of Study Procedures (Section 8.3)

Potential study participants (pregnant women) are to be screened at ≥ 24 0/7 weeks gestational age. Pregnant women for whom eligibility has been confirmed are to complete Visit 1 not later than at 27 6/7 weeks gestational age.

Table 4, List of Study Procedures (a new column – for the screening visit was added, and text was adjusted. Both the original Table and the revised Table are reproduced below.)

List of study procedures for pregnant women/ mothers (original protocol)

~~Gestational age~~	~~24 0/7 - 27 6/7~~	~~28 0/7 - 31 6/7~~	~~32 0/7 - 35 6/7~~	~~36 0/7 - delivery~~	~~-~~	~~-~~	
~~Epoch~~	~~Epoch 001~~						
~~Type of contact~~	~~Visit 1~~	~~Visit 2[1]~~	~~Visit 3[1]~~	~~Visit 4[1]~~	~~Visit 5~~	~~Visit 6[2,3]~~	~~Additional antenatal/medical evaluations (external to study visits/procedures)~~
~~Timepoints~~	~~Day 1~~	~~Day 28~~	~~Day 56~~	~~Day 84~~	~~At Delivery~~	~~Post-Delivery Day 42~~	
~~Eligibility Review and Confirmation~~							
~~Informed consent~~	~~●~~						
~~Check inclusion/exclusion criteria~~	~~●~~						
~~Assign subject study number (mother)~~	~~●~~						
~~Assign subject study number (child)~~	~~O~~						
~~Inform study paediatrician and/or staff of subject's participation~~	~~O~~				~~O~~		
~~Medical History / Examinations~~							
~~Distribute maternal health card~~	~~O~~						
~~Record demographic and lifestyle characteristics data~~	~~●~~						
~~Collect medical history~~	~~●~~						
~~Collect obstetric history from current and past pregnancies~~	~~●~~						
~~Travel history to, or living in, Zika virus endemic countries/regions~~	~~●~~					~~●~~	
~~Inquire whether mother would have agreed to take part in the study if an investigational vaccine were given~~	~~●~~						
~~Record outcome of 2d trimester Level 2 ultrasound~~	~~●~~						

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~~Gestational age~~	~~24 0/7 - 27 6/7~~	~~28 0/7 - 31 6/7~~	~~32 0/7 - 35 6/7~~	~~36 0/7 - delivery~~	-	-	
~~Epoch~~	~~Epoch 001~~						
~~Type of contact~~	~~Visit 1~~	~~Visit 2[1]~~	~~Visit 3[1]~~	~~Visit 4[1]~~	~~Visit 5~~	~~Visit 6[2, 3]~~	~~Additional antenatal/medical evaluations (external to study visits/procedures)~~
~~Timepoints~~	~~Day 1~~	~~Day 28~~	~~Day 56~~	~~Day 84~~	~~At Delivery~~	~~Post-Delivery Day 42~~	
~~Record outcome(s) of subsequent ultrasounds if performed~~	~~●~~	~~●~~	~~●~~	~~●~~			~~●~~
~~Record gestational age, expected date of delivery and method of EDD estimation~~	~~●~~						
~~Record height~~	~~●~~						
~~Record weight~~	~~●~~	~~●~~	~~●~~	~~●~~		~~●~~	~~●~~
~~Record results of antenatal physical examination~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
~~Check and record medications, vaccinations, folate and/or iron (independently or included in a multivitamin) beginning the month before the estimated date of conception and while on study~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
~~Biological Specimens / Laboratory Test Results~~							
~~Collect blood sample for antibody assessment by sponsor (~5 ml)~~	~~●[5]~~		~~●[5]~~		~~●~~		
~~Collect cord blood for antibody assessment by sponsor (~5 to 10 ml)~~					~~●~~		
~~Collect vaginal swab to send to sponsor for analysis, where relevant~~	~~●[5]~~		~~●[5]~~		~~●~~		~~●~~
~~Record results of blood sampling for local hematology/ biochemical analysis (~10 ml)[4]~~	~~●~~		~~●[6]~~				~~●~~
~~Record results of urine dipstick to check for presence of proteins, glucose[4, 7]~~	~~●~~	~~●~~	~~●~~	~~●~~			~~●~~
~~Record results of oral glucose tolerance test if performed by local healthcare provider and available~~	~~●~~	~~●~~	~~●~~	~~●~~			~~●~~
~~Record outcome of urine bacterial culture if performed by local healthcare provider and available~~	~~●~~	~~●~~	~~●~~	~~●~~			~~●~~

Gestational age	**24 0/7 - 27 6/7**	**28 0/7 - 31 6/7**	**32 0/7 - 35 6/7**	**36 0/7 - delivery**	-	-	
Epoch	**Epoch 001**						
Type of contact	**Visit 1**	**Visit 2**[1]	**Visit 3**[1]	**Visit 4**[1]	**Visit 5**	**Visit 6**[2, 3]	**Additional antenatal/medical evaluations (external to study visits/procedures)**
Timepoints	**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Record results of any peri-natal laboratory tests pertinent to assess maternal safety if performed by local healthcare provider and available	●	●	●	●	●	●	●
Labor / Delivery							
Record date and time of rupture of membranes					●		
Record type of delivery					●		
Record gestational age determined at delivery					●		
Outcomes and Events of Interest							
Record Pregnancy/Delivery outcome(s)					●		
Record pregnancy-related events of interest (and hospitalisations / other clinically significant events or diagnoses that could impact the pregnancy		●	●	●	●	●	●
Serious Adverse Events							
Record SAEs related to study participation	●	●	●	●	●	●	●
Study Conclusion							
Study conclusion						●	
Investigator sign-off on eCRF before analysis						●	

eCRF = electronic case report form; **SAE** = serious adverse event; **WHO** = World Health Organization.

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

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

[1] The visit may be replaced by Visit 5 depending on the date of delivery.

[2] Visit 6 (Day 42) may take place in the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.

[3] To coincide with Visit 2-NB (Day 42) for infants.

[4] To be performed preferentially by local healthcare providers, in which case the information will be collected and recorded in the eCRF. The investigator/study staff will provide these procedures if not done by the local healthcare provider as per local practice. If abnormal, subjects will be referred per local standard of care.

[5] Only in countries with routine implementation of risk based intrapartum antibiotic prophylaxis for GBS

[6] At Visit 3, only hemoglobin testing.

[7] When available, urine dipstick results for red blood cells (RBC) and white blood cells (WBC) will also be collected

List of study procedures for pregnant women/ mothers *(Amended 12 February 2018)*

Gestational age	≥ 24 0/7 - 27 6/7	24 0/7 – 27 6/7	28 0/7 - 31 6/7	32 0/7 - 35 6/7	36 0/7 - delivery			
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	Screening	**Visit 1**	**Visit 2** [1]	**Visit 3** [1]	**Visit 4** [1]	**Visit 5**	**Visit 6** [2, 3]	**Additional antenatal/medical evaluations (external to study visits/procedures)** [4]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Eligibility Review and Confirmation								
Informed consent	●							
Check inclusion/exclusion criteria	●	O						
Assign subject study number (mother)	●							
Assign subject study number (child)		O						
Inform study paediatrician and/or staff of subject's participation		O				O		
Medical History / Examinations								
Distribute maternal health ***memory aid***		O	O	O	O	O		
Record demographic data	●							
Record lifestyle characteristics		●						
Record outcome of Level 2 ultrasound (fetal morphology scan) [7]	●							
Record outcome(s) of subsequent ultrasounds if clinically significant [4]		O	O	O	O	O		●
Review and collect medical history	O	●						
Review and collect obstetric history from past pregnancies	●							
Review and collect obstetric history from current pregnancy, including: gestational age, expected date of delivery and method of EDD estimation	●							
Travel history to, or living in, Zika virus endemic countries/regions	O	●						

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Gestational age	≥ 24 0/7 - 27 6/7	24 0/7 – 27 6/7	28 0/7 - 31 6/7	32 0/7 - 35 6/7	36 0/7 - delivery			
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	Screening	**Visit 1**	**Visit 2** [1]	**Visit 3** [1]	**Visit 4** [1]	**Visit 5**	**Visit 6** [2, 3]	**Additional antenatal/medical evaluations (external to study visits/procedures)** [4]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Where authorized by the local Ethics Committee, inquire whether mother would have agreed to take part in the study if an investigational vaccine were given		●						
Record outcome of HIV test [9]	●							
Record results of ***General and Obstetric*** *examination* [10]	●	●	●	●	●		●	● [13]
Check and record prescription medications, vaccinations, folate and/or iron (independently or included in a multivitamin) [12]		●	●	●	●	●	●	
Biological Specimens / Laboratory Test Results								
Collect blood sample for antibody assessment by sponsor (~5 ml)						●		
Collect cord blood for antibody assessment by sponsor (~5 to 10 ml)						●		
Record results of local hematology/ biochemical analysis (up to 10 ml) [5]		●		● [8]				● [13]
Record results of urine dipstick to check for presence of proteins, glucose, RBC, WBC [6]		●	●	●	●			● [13]
Record results of oral glucose challenge / tolerance test(s) if performed by local healthcare provider and available [4]	●	O	O	O	O			●
Record results of any clinically significant abnormal laboratory tests (including positive urine culture) if performed by local healthcare provider and available [4]		O	O	O	O	O	O	●
Labor / Delivery								
Collect and record labor and delivery information [11]						●		

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Gestational age	≥ 24 0/7 - 27 6/7	24 0/7 – 27 6/7	28 0/7 - 31 6/7	32 0/7 - 35 6/7	36 0/7 - delivery			
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	Screening	**Visit 1**	**Visit 2** [1]	**Visit 3** [1]	**Visit 4** [1]	**Visit 5**	**Visit 6** [2, 3]	**Additional antenatal/medical evaluations (external to study visits/procedures)** [4]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Outcomes and Events of Interest								
Record Pregnancy/Delivery outcome(s)						●		
Record pregnancy-related events of interest and other clinically significant events or diagnoses that could impact the pregnancy		●	●	●	●	●	●	
Record all hospitalizations (except hospitalization for delivery), and all extensions of hospitalizations (including extension of hospitalization for delivery).		●	●	●	●	●	●	
Serious Adverse Events								
Record SAEs related to study participation		●	●	●	●	●	●	
Screening/Study Conclusion								
Screening conclusion	●							
Study conclusion							●	
Investigator sign-off on eCRF before analysis	●						●	

SAE = serious adverse event; ● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF)
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

[1] ***If delivery occurs prematurely, skip to Visit 5 ("at delivery").***

[2] Visit 6 (Day 42) may take place in the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator.

[3] To coincide with Visit 2-NB (Day 42) for infants.

[4] Information from additional antenatal / medical evaluations (external to study visits/procedures) may be collected during, before or after a scheduled study visit but should only be recorded in the additional antenatal/medical evaluations eCRF.

[5] To be performed preferentially by local healthcare providers ***as per local practice***. ***To be performed by*** the investigator/site staff ***ONLY*** if not done by the local healthcare provider ***within 2 weeks before the study visit. If results are abnormal, subjects will be referred per local standard of care.***

[6] ***The Investigator/ site staff will perform a urine dipstick test to detect the presence of proteins, glucose, RBC and WBC.***

[7] ***If ultrasound results are not available at time of screening, the ultrasound can be performed as a study procedure under certain conditions. Refer to SPM for further details. If abnormal, subjects will be referred per local standard of care. [Table 4 Footnotes continue on the next page]***

Table 4 Footnotes Continued

[8] At Visit 3, only hemoglobin testing.

[9] If HIV test results are not available at time of screening, the HIV test can be performed as a study procedure under certain conditions. Refer to SPM for further details. If results are positive, subject will be referred per local standard of care.

[10] Height at screening. Weight, vital signs, fetal heart tones, fetal movement, and fundal height at Screening and Visits 1 – 4. Vital signs at Visit 6.

[11] Includes date and time of rupture of membranes, date and time of delivery, type of delivery, and other delivery information related to the health and safety of the mother and fetus.

[12] Beginning the month before the estimated date of conception and while on study. (Routine concomitant medications administered during labor and delivery need not be collected.)

Table 5, List of Study Procedures (both the table from the original protocol and the amended table are reproduced below).

List of study procedures for neonates/ infants (original protocol)

~~Epoch~~	~~Epoch 001~~		~~Epoch 002~~	~~Epoch 002~~	
~~Age~~	~~0-10 days~~	~~42 Days~~	~~12 months~~	~~0-12 months~~	
~~Type of contact~~	~~Visit 1-NB~~	~~Visit 2-NB [a]~~	~~Visit 3-NB [a]~~	~~Contact for active/ passive surveillance [b]~~	~~LRTI Assessment visit [a, c]~~
~~Timepoints~~	~~Birth~~	~~Day 42~~	~~Y1~~		
~~Check inclusion/exclusion criteria~~	~~●~~				
~~Obtain informed consent of parent(s)/LAR(s)~~	~~●~~				
~~Record infant's subject number~~	~~●~~				
~~Record Apgar assessment~~	~~●~~				
~~Record demographic and lifestyle characteristics data~~		~~●~~			
~~Distribute child health card~~	~~O~~				
~~Distribute RTI episode card (memory aid) to record disease symptoms~~	~~O~~				~~O~~
~~Physical examination including weight, length and head circumference~~	~~●~~	~~●~~	~~●~~		
~~Record medications / vaccinations / vitamins~~	~~●~~	~~●~~	~~●~~		
~~Record neonatal events of interest~~	~~●~~	~~●~~	~~●~~		
~~Nasal swab~~					~~●~~
~~Record occurrences of GBS invasive disease (sepsis, pneumonia and meningitis)~~	~~●~~	~~●~~	~~●~~	~~●~~	
~~Record outcome of GBS blood or cerebrospinal fluid testing, if performed by a local healthcare provider~~	~~●~~	~~●~~	~~●~~	~~●~~	

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207636 (EPI-RSV-008 BOD)
Protocol Amendment 4 Final

Epoch	Epoch 001		Epoch 002	Epoch 002	
Age	0-10 days	42 Days	12 months	0-12 months	
Type of contact	Visit 1-NB	Visit 2-NB [a]	Visit 3-NB [a]	Contact for active/ passive surveillance [b]	LRTI Assessment visit [a,c]
Timepoints	Birth	Day 42	Y1		
Record all hospitalizations and/or clinically significant events	●	●	●	●	● [d]
Record SAEs related to study participation	●	●	●	●	●
Study conclusion			●		
Investigator sign-off on eCRF before analysis		●	●		

eCRF = electronic case report form; **GBS** = Group B Streptococcus; **LAR** = legally acceptable representative; **LRTI** = lower respiratory tract infection; **M** = month; **NB** = newborn; **RTI** = respiratory tract infection; **SAE** = serious adverse event; **Y** = year

Grey shaded columns represent study procedures to be performed for active/passive surveillance of RTIs which are applicable throughout the entire study period (from birth up to study end).

Note: The double-line borders indicate primary analyses.

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

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

[a] Visit 2-NB (Day 42), Visit 3-NB (Year 1) and LRTI assessment visits may take place in the subject's home or at the investigator's clinical facility as appropriate to the circumstances in the judgment of the investigator, and if the standard of care allows home visits

[b] Supplemental information about invasive GBS disease and hospitalization will be solicited during select RTI active surveillance contacts in order to capture GBS events that occur within the first 90 days of life. Relevant medical record abstraction should be performed for identified occurrences.

[c] If an LRTI assessment visit is conducted, a nasal swab is collected, and the parents return for a follow-up LRTI assessment visit at which symptoms have diminished / resolved, no additional nasal swab need be collected. If an LRTI assessment visit is conducted, a nasal swab is collected, and the parents return for a follow-up LRTI assessment visit because symptoms have worsened, an additional nasal swab may be collected at the discretion of the investigator.

[d] If not previously communicated during a surveillance contact

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207636 (EPI-RSV-008 BOD)
Protocol Amendment 4 Final

List of study procedures for neonates/ infants *(Amended 12 February 2018)*

Epoch	***Epoch 002***		***Epoch 003***	***Epoch 002 and Epoch 003***	
Age	**0-10 days**	**42 Days**	**12 months**	**0-12 months**	
Type of contact	**Visit 1-NB**	**Visit 2-NB [a]**	**Visit 3-NB [a]**	**Contact for active/ passive surveillance**	**Visit to assess potential LRTI [a]**
Timepoints	**Birth**	**Day 42**	**Y1**		
Check inclusion/exclusion criteria	●				
Obtain informed consent of parent(s)/LAR(s)	●				
Record infant's subject number	●				
Record Apgar assessment	●				
Record demographic data	●				
Record lifestyle characteristics		●			
Distribute ***infant health and RTI memory aid***	○	○			○
Weight, length, head circumference, results of targeted medical history, and results of physical examination	●	●	●		
Record ***prescription*** medications / vaccinations	●	●	●		●
Record neonatal events of interest	●	●	●		
Clinical evaluation of potential LRTI					●
Nasal swab [b]					● [b]
Record all hospitalizations and/or clinically significant events	●	●	●	●	●
Record SAEs related to study participation	●	●	●	●	●
Study conclusion			●		
Investigator sign-off on eCRF before analysis		●	●		

LAR = legally acceptable representative; **LRTI** = lower respiratory tract infection; **NB** = newborn; **RTI** = respiratory tract infection; **SAE** = serious adverse event; **Y** = year. Grey shaded columns represent study procedures to be performed for active/passive surveillance of RTIs/LRTIs which are applicable throughout the entire study period (from birth up to study end). **Note:** The double-line borders indicate primary analyses. ***Footnotes to Table 5 continue on the next page.Table 5 footnotes continued***

● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF).

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

[a] Visit 2-NB (Day 42), Visit 3-NB (Year 1) and LRTI assessment visits may take place in the subject's home ***(if the standard of care allows for home visits),*** at the investigator's clinical facility ***or at another facility*** per the investigator's judgment.

[b] If more than one assessment visit is conducted to evaluate a potential LRTI episode, additional nasal swabs may be collected at the discretion of the Investigator.

Intervals Between Study Visits/Contacts (Section 8.4)

Table 6: Intervals between study visits/contacts/observations

Interval	Optimal interval~~***~~	Allowed interval**
Screening → Visit 1	***1 days***	***0 – 28 days***

If a subject returns for the visit outside the ~~recommended~~ allowed time interval, he/she ~~will~~ ***may still* be considered for ~~the~~ analysis.

Investigators should make at least 3 documented attempts (through telephone call(s) or any other convenient procedure) to contact (as relevant) the pregnant woman/mother or the child's parents/ LAR(s) (or their designates) if they do not return for scheduled visits or follow-up. Additional details can be found in the SPM.

Eligibility Review and Confirmation (Section 8.5.1)

- Check all applicable inclusion and exclusion criteria as described in Sections 6.2 and 6.3 before enrolment and record results~~for each criterion in the eCRF~~.
- Assign / record subject study number (~~mother~~***pregnant woman***)
- Assign subject study number (infant) ***for eligible pregnant women who complete Visit 1.***
- Inform study paediatrician and/or staff of ~~subject's~~ the ***pregnant woman's*** participation
  - A copy of the informed consent should be forwarded to the study paediatrician and/or staff ***as soon as possible*** after ~~the subject's~~ ***a pregnant woman's*** enrolment to ensure the study paediatrician is informed in a timely manner of the approximate date of delivery and ***potential*** enrolment of the neonate.

History and Examinations *for pregnant women/mothers* (Section 8.5.2)

- Distribute ~~maternal health card~~ ***the Maternal Health Memory Aid. It is intended to serve as a reference during study visits/contacts, to help the subject provide the investigator/ study staff with protocol-specified data (and contact information for other healthcare providers, so medical records may be requested if required). (Refer to the SPM for details).***
- Record demographic ~~and lifestyle characteristics data. Demographic~~ ***data, which may include (but is not limited to) information such as race, month and year of birth, ethnicity, and geographic location.*** ~~Lifestyle characteristics (exposures) may include data on factors such as smoking status/exposures, household environment and other factors that could place subjects at risk of study outcomes.~~
- ***Record information about*** lifestyle characteristics ***(exposures)***, ***which*** may include ***(but are not limited to)*** data on ***highest level of education***, factors such as smoking status/exposures, household environment, and other factors that could place subjects at risk of study outcomes.

- Record outcome of ~~2d trimester (~~Level 2 ultrasound ***(fetal morphology assessment).*** Please see GLOSSARY OF TERMS for description. ***If Level 2 ultrasound results are not available at screening, then the ultrasound can be performed as a study procedure under certain conditions. Refer to the SPM for further details.***
- ***Record outcome(s) of any subsequent*** ~~ultrasounds~~***ultrasound(s) ONLY if clinically significant***.~~Record gestational age along with GAIA level of certainty using priorities defined in APPENDIX C~~
- ~~Record expected date of delivery (EDD) and method of estimation~~
- Record medical / obstetric history
  - Obtain the subject's medical history by interview and/or review of her medical records; record any pre-existing conditions or signs and/or symptoms present before participation in the study.~~ Targeted questions may be asked about allergies, respiratory diseases (including asthma) and other conditions that may be related to study outcomes.~~
  - Obtain the subject's obstetric history by interview and/or review of her medical records~~record any data from current~~ and~~-~~.
  - ***For past pregnancies, record:***
    - ***number of past pregnancies and their outcome(s),***
    - ***presence of caesarian section scars (if any).***
  - ***For the current pregnancy, record:***
    - ***number of prenatal visits attended up to the date of the study Screening visit,***
    - ***approximate date of first prenatal visit,***
    - ***results of any clinically significant, abnormal pregnancy screening laboratory tests,***
    - ***results of any procedures intended to screen for congenital anomalies.***

    ~~Inquire~~ ***Where authorized by the local Ethics Committee***, inquire whether mother would have agreed to take part in the study if an investigational vaccine were given and record the answer
- Record height at ~~baseline~~ ***screening*** and weight at ***screening and*** Visits 1~~-4 and 6~~. ~~Measurements~~ ***Height*** measurements should be performed……..
- Record results of ~~antenatal~~ ***General and Obstetric examination***

  Unless the study visit is performed concurrently with a routine ~~antenatal~~ care visit ~~in~~***at*** which the below data are collected, the investigator/study staff should perform ~~an antenatal physical examination:~~ ***General and Obstetric examinations as follows***:
  - ~~All visits through~~ ***Screening, Visits 1 – 4, and*** Visit 6 should include assessment of vital signs (systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest);
  - ~~All visits through Visit 5~~ Screening and Visits 1 - 4 should include assessment of fetal heart tones, fetal movement, and fundal height;

- ~~Visit 1 should include assessment of any scars from prior deliveries.~~

- ***If the Screening Visit and Visit 1 occur on the same day, only one General and Obstetric examination will be performed.***

- ~~Record medications / vaccinations / folate and iron supplements beginning the month before the estimated date of conception and while on study(this includes medications administered during labor and delivery).~~

  - ~~***ONLY medications that are NOT routine should be recorded during labor and delivery.***~~

Biological Specimens / Laboratory Data ***for pregnant women/mothers*** **(Section 8.5.3)**
Blood samples for assessment of antibody titers/concentrations: An overall volume of approximately ~~15~~5 mL

- ~~Vaginal Swabs:~~

- ~~In countries with routine implementation of risk based intrapartum antibiotic prophylaxis for GBS, vaginal swabs should be collected at Visits 1, 3, and 5 (prior to rupture of membranes). In countries without routine implementation of risk based intrapartum antibiotic prophylaxis for GBS, vaginal swabs should ONLY be collected at Visit 5 (prior to rupture of membranes).~~

- ~~WHO does not currently recommend the use of vaginal swabs to screen for GBS colonization.~~

- ~~The vaginal swabs collected in this study will be used solely for epidemiological purposes. Samples will be analyzed by a central testing laboratory and results will not be available for diagnostic purposes. Thus, vaginal swabbing conducted as a study procedure is not intended to replace local standard of care practices or to inform clinical management.~~

- ***The Investigator/site staff will arrange for collection of maternal blood and cord blood samples at delivery.***

- ***The Investigator/site staff will perform urine dipstick tests using supplies provided by GSK.***

- ***If HIV test results are not available at time of screening, the HIV test can be performed as a study procedure under certain conditions. Refer to the SPM for further details. If results are positive, the subject will be referred per local standard of care.***

- ***It is preferred that local healthcare providers perform haematology and biochemistry tests per local practice; the investigator/site staff will*** ~~perform these procedures~~ ***then collect and record the results. The investigator/site staff will only perform haematology/biochemistry tests if not done by the local healthcare provider*** ~~as per local practice~~ ***within 2 weeks before a study visit***.

  - ~~Perform dipstick test for presence of proteins and glucose in urine. When available, red blood cell (RBC) and white blood cell (WBC) results will also be collected.~~

  - ~~Perform HIV test at Screening (to assess eligibility)~~

- If performed ~~record~~ ***by local healthcare provider and available, the investigator/site staff will also:***
  - ***Record*** oral glucose ***challenge / oral glucose*** tolerance test results
  - ~~If performed, record~~***Record any positive*** urine bacterial culture results
  - Record abnormal and clinically significant laboratory test ***results***
  - ***Record results of*** ~~any laboratory tests pertinent to assess maternal safety~~***Group B Streptococcus screening test(s).***

Labor and Delivery (Section 8.5.4)

Record information related to labor and delivery~~; should include the following:~~, ***including***:

- Medications administered during labor and delivery ***(if not routine)***
- ~~Gestational age as determined at delivery~~

Additional ~~antenatal/medical evaluations~~ *General and Obstetric examinations (Section 8.5.7)*

For any additional ~~antenatal/medical evaluations~~***General and Obstetric examinations*** at which a pregnancy related event of interest is identified, record information that supports the diagnosis of the event.

Medications, Vaccinations, and Supplements for pregnant women/mothers (Section 8.5.5)

- ***Record medications / vaccinations / folate and iron supplements beginning the month before the estimated date of conception and while on study.***
  - ***Folic acid and/or iron supplements should be reported when taken independently and/or when included in a multivitamin mineral supplement.***
  - ***ONLY medications that are NOT routine should be recorded during labor and delivery.***

~~**Surveillance for**~~ ***Outcomes and*** **Events of Interest** ***in pregnant women/mothers (Section 8.5.6)***

- Maternal events of interest (including, but not limited to, those described in Section 11.1.1) occurring up to Visit 6 (Post-delivery Month 1.5) should be recorded in the eCRF along with additional details pertinent to the diagnosis, GAIA assessment and level of diagnostic certainty (Appendix D), ***when applicable.***

- ***Record all hospitalizations and/or clinically significant events.***
- ***Record all study participation related SAEs as specified in Section 9.***

Eligibility Review and Confirmation for Neonates / Infants **(Section 8.6.1)**

- Check all applicable inclusion and exclusion criteria as described in Sections 6.2 and 6.3. ~~A pre-selected child~~A ***neonate*** who does not meet the eligibility criteria should be considered ineligible.
- Obtain informed consent from parent(s) / LAR(s) at Visit 1-NB, ~~and update~~ as per local requirements.

History and Examinations for Neonates / Infants (Section 8.6.2)

- Record demographic data~~ and lifestyle characteristics at birth, and any changes in this information at subsequent visits: Data includes~~, ***including date of birth, gender, race and ethnicity***~~; living environment and household composition, breastfeeding, passive smoking and day-care attendance~~
- ***Record lifestyle characteristics. Data may include (but are not limited to) passive smoking and day-care attendance.***
- Record weight, length, ~~ and~~ head circumference ~~at birth and at subsequent study visits.~~***and results of*** ~~age~~***-targeted medical history, and results of physical examination(s).***
- Record ***prescription*** medications/ vaccinations~~ vitamins~~
- ~~Record all hospitalizations and/or clinically significant events. For hospitalizations where an RSV infection is suspected, refer to Section 8.6.6.~~
- Distribute ~~Child~~ ***the-Infant*** Health ~~CardA child health card will be distributed~~***and RTI Memory Aid to the parent(s)/LAR(s)/designate(s)*** ~~at Visit 1-NB if one is not already provided by~~). Health ***and RTI Memory Aid to the parent(s)/LAR(s)/designate(s). The memory aid is intended to serve as a reference during study visits/contacts, to help parent(s)/LAR(s)/designate(s) provide the investigator/ study staff with protocol-specified data (and contact information for other healthcare providers, so medical records may be requested if required). Refer to the*** ~~healthcare provider.~~ ***SPM for additional details.***
- ***Record all hospitalizations and/or clinically significant events. For hospitalizations where an RSV infection is suspected, refer to Section 8.6.6.***
- ***Record all study participation related SAEs (Section 9).***

~~**Surveillance for Invasive GBS disease (Deleted Section)**~~

- ~~To ensure that all GBS cases are captured, data regarding occurrence of GBS invasive disease (sepsis, pneumonia~~***lifestyle characteristics and*** ~~meningitis) will be collected within the first year of life, with a particular emphasis being placed on the first 90 days. Instructions will be given to mothers and local health care providers (through child health cards) to contact the study staff~~ ***any subsequent changes in*** ~~case of occurrence of GBS invasive disease. Information regarding GBS blood testing in the neonates/infants will be collected if performed by a local healthcare provider. In order to identify potential GBS cases that occur beyond Visit 2-NB,~~***this information*** ~~about potential GBS invasive disease in the first 90 days of life will be solicited during LRTI active surveillance contacts (described in Section 8.5.5).~~

~~During the initial months of LRTI surveillance, supplemental questions related to invasive GBS disease~~.***Data includes living environment and household composition, breastfeeding, passive smoking and*** ~~hospitalization will be included with the LRTI script.~~

- ~~In case of suspected neonatal sepsis, pneumonia or meningitis, the outcome of blood or cerebrospinal fluid test results for GBS should be documented in the infant's eCRF if performed by a local healthcare provider~~ ***day-care attendance***.

Surveillance for Neonatal events of interest (Section 8.6.3)

- ~~Investigators should make at least 3 documented attempts (through telephone call(s) or any other convenient procedure) to contact the child's parents/ LAR(s) (or their designates) if they do not return for scheduled visits or follow-up. Additional details can be found in the SPM.~~

Surveillance for *episodes of potential Lower Respiratory Tract Infection (LRTI)* (Section 8.6.4)

Definitions (Section 8.6.4.1)

- ***Symptoms of Respiratory Tract Infection (RTI) include:***
  - ***regular bursts of cough,***
  - ***nasal discharge running freely out of the infant's nose (runny nose), or***
  - ***breathing through the mouth because the infant's nose is blocked (blocked nose).***
- ***An episode of potential lower respiratory tract infection (LRTI) is one in which the infant has one or more of the RTI symptoms listed above AND at least one of the following:***
  - ***Difficulty in breathing (fast breathing, poor feeding, working hard to breathe, or making unusual sounds when breathing);***
  - ***Wheezing (a whistling sound when the infant breathes out);***
  - ***Parental concern (the parent(s)/LAR(s) or their designate(s) are concerned about the infant's respiratory tract illness or general health and intend to seek medical care).***
  - ***An RTI episode starts on the day when (per parental report) the first RTI symptom started.***
  - ***An RTI episode ends on the day when (per parental report) the last RTI symptom resolved.***
  - ***There must be at least 7 symptom-free days between 2 consecutive RTI episodes.***

Overview (Section 8.6.4.2)

It will be accomplished via two types of contact. ***Both may be made with/ by either the Parent(s)/ LAR(s), or a person designated by the parent(s)/LAR(s), such as grandparents or a nanny (as long as the parent(s)/LAR(s) have given approval).***

- ***In an*** Active~~, wherein~~ ***contact***, site personnel contact the subject's parent(s) / LAR(s) ***or their designate(s).*** Active contacts will occur at regular intervals and will be scripted.
- ***In a*** Passive~~, wherein~~ ***contact***, the subject's parent(s) / LAR(s) ***or their designate(s)*** notify site personnel. ***Site personnel will use a script to guide data collection once a passive contact has been made.***

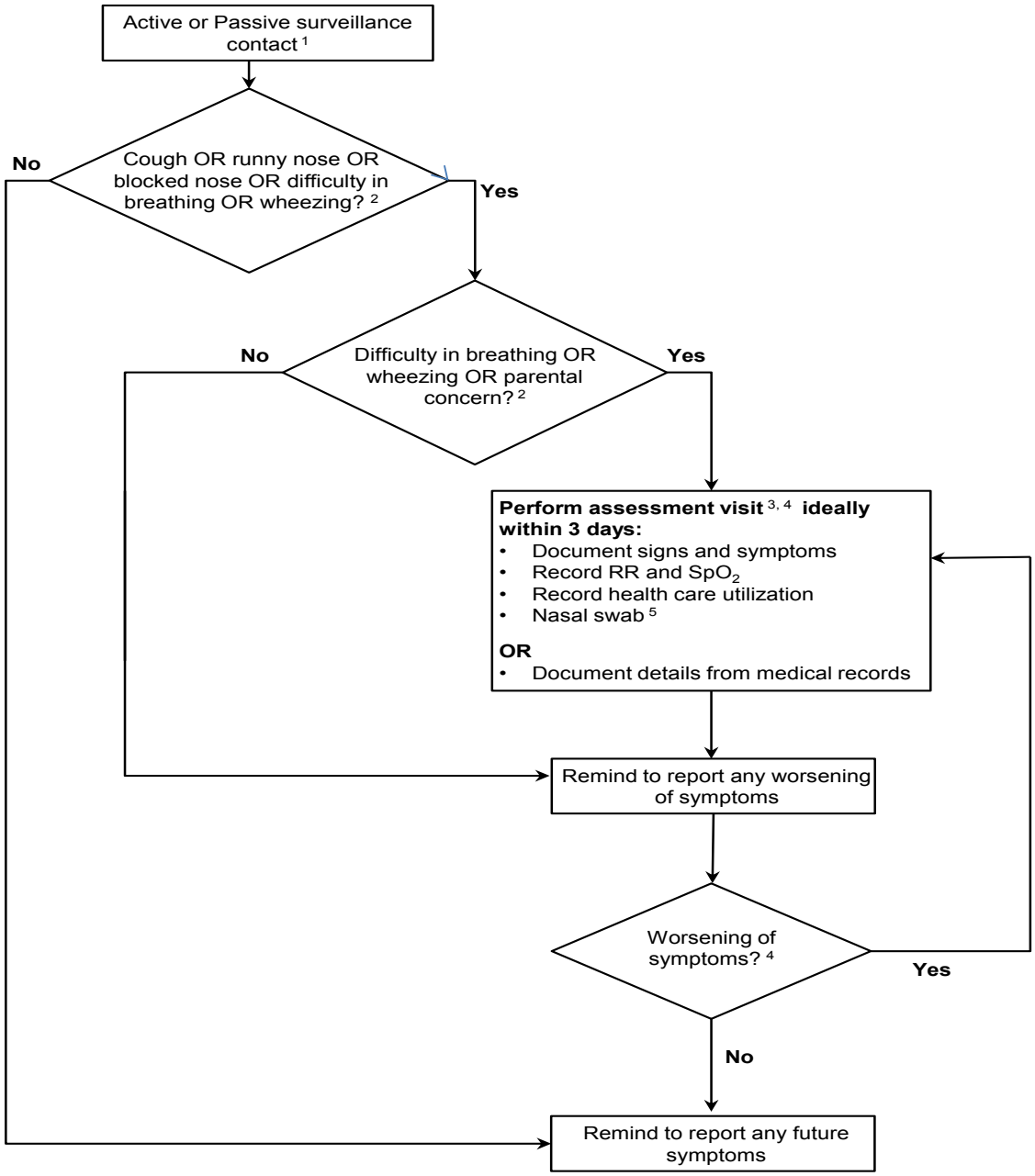
~~Active and passive surveillance contacts can also be made with/by a person designated by the parent(s)/LAR(s) (e.g. grandparents, nanny) as long as the parent(s)/LAR(s) have given approval.~~

Site staff will use information gathered during each active or passive surveillance contact to determine whether a visit to assess a potential LRTI …..should be scheduled.

For all interactions between parent(s)/LAR(s)/designates **and study staff, the safety of the infant is paramount. For any reported illness, the investigator/study staff should assess the need for any intervention and ~~provide this as part of regular healthcare or instruct~~/advise the parent(s) / LAR(s) ~~where~~ to ~~obtain this~~seek care as necessary.** ***This study is not intended to replace local standards of care.***

Figure 2

Two footnotes have been deleted, and 4 footnotes have been added to the figure. Revisions to the footnotes are presented on this page. The figure itself is presented on the next page. In the figure, the phrase "Perform assessment visit within 3 days" has been changed to read "Perform assessment visit ideally within 3 days."



RR: Respiratory rate: **SpO_2**: Blood oxygen saturation ***by pulse oximetry***..

~~Refer to the GLOSSARY OF TERMS for a definition of RTI with parental concern.~~

~~[1] Refer to the Study Procedures Manual (SPM) for signs and symwardhanptoms to be collected.~~

[1]Details regarding Active and Passive Surveillance are provided in Sections 8.6.4.3, 8.6.4.4, and the SPM.

[2]Cough, runny nose, blocked nose, difficulty in breathing, wheezing and parental concern are defined in Section 8.6.4.1.

[3]Details regarding the assessment visit to evaluate a potential LRTI are provided in Section 8.6.5and the SPM.

[4] Post-visit follow up is described in Section 8.6.6 and in the SPM.

[5]If a follow-up assessment visit is conducted, collection of additional nasal swabs are at the Investigator's discretion.

Active surveillance (Section 8.6.4.3)

The purpose of the contact is to check with the infant's parent(s)/LAR(s) or their designate(s) if, ***as defined in Section 8.6.4.1:***

- ***the infant has developed (new*** ~~RTI symptoms (cough, runny nose or blocked nose),~~
- ~~the infant has developed new~~) ***symptoms of RTI, difficulty in breathing, or wheezing***

~~the parent(s)/LAR(s) (or their designate(s)) are concerned about the infant's RTI signs and/or symptoms~~ ***(there is parental concern*** ~~During active surveillance contacts, Parent(s) /LAR(s) (or their designates) will be reminded to record RTI symptoms, their start and stop dates, and any medications taken, on the RTI episode card.~~

Passive Surveillance (Section 8.6.4.4)

Infants' parents/LAR(s) or their designate(s) will be instructed to contact the site whenever:

- ~~their~~***the infant has developed (new) symptoms of RTI, difficulty in breathing, or wheezing as defined in Section 8.6.4.1,***
- ~~they (the parent(s) / LAR(s) or their designate(s)) are concerned about~~ ***the infant's*** ~~RTI signs and/or~~ ***symptoms worsen***
- ***there is parental concern as defined in Section 8.6.4.1.***
- ~~During passive surveillance contacts, Parent(s) /LAR(s) (or their designates) will be reminded to record RTI symptoms, their start and stop dates, and any medications taken, on the RTI episode card.~~

Decision to conduct a *visit to assess a potential LRTI* (Section 8.6.4.5)
If there is NO suspicion of difficulty in breathing, nor wheezing, nor parental concern:

- No ~~LRTI~~ assessment visit will be conducted.

If there IS difficulty in breathing, or wheezing (both based on parental assessment), or there is parental concern:

- ~~The parent(s)/LAR(s) will be informed that their infant potentially has a(n) (new) LRTI,~~
- An~~LRTI~~ assessment visit will be conducted as soon as possible, ideally within 3 calendar days after learning of the potential LRTI case ***(Section 8.6.5).***

~~If it is not possible to perform the clinical evaluation and collect a nasal swab during an assessment visit (for example, if the child develops a potential LRTI while the family is travelling), then the LRTI assessment visit page of the eCRF should be filled in as completely as possible using available medical records.~~

Visit *to assess a potential LRTI* (Section 8.6.5)

Overview (Section 8.6.5.1)

The visit may take place in the subject's home ***(if allowed per standard of care),*** the investigator's clinical facility or another medical facility, as appropriate ~~to the circumstances in~~***per*** the judgment of the investigator.

Note that if the reported symptoms are ~~of a level of severity that warrants~~*severe enough to* warrant urgent care, the parent(s)/LAR(s)/designates should be advised to seek ~~urgent~~ *such* care (e.g. Emergency Room).

Clinical evaluation (Section 8.6.5.2)

The investigator/study staff will evaluate the clinical signs and symptoms of the RTI. ~~Signs and symptoms~~ ***Data to be collected and*** recorded ~~in the eCRF will be listed in the Study Procedures Manual (SPM).~~***include (but are not limited to):***

- ***Temperature***
- ***Respiratory rate***
- ***Blood oxygen saturation (measured by pulse oximetry in room air, if feasible)***
- ***Signs of difficulty in breathing (including wheezing, tachypnoea, nasal flaring, chest in-drawing and apnoea)***

Refer to the Study Procedures Manual (SPM) ***for additional details***.

Nasal Swab (Section 8.6.5.3)

~~Follow up assessment~~

A nasal swab will be collected ***using sponsor-provided supplies and sent to the sponsor laboratory*** for detection of RSV-A/B using quantitative RT-qPCR.

If ~~an LRTI~~ ***more than one assessment visit is conducted to evaluate a*** ~~nasal swab is collected, and the parents return for a follow-up LRTI assessment visit at which symptoms have diminished / resolved, no~~***potential LRTI episode, additional nasal*** ~~swab need be collected.~~

~~If an LRTI assessment visit is conducted, a nasal swab is collected, and the parents return for a follow-up LRTI assessment visit because symptoms have worsened, an additional nasal swab~~***swabs may be collected at the discretion of the*** ~~investigator~~***Investigator***.

Note: If other nasal swabs are collected and tested locally as per routine standard of care, results will be entered into the eCRF. However, only the sponsor laboratory results will be used when applying the case definitions for data analysis in Table 3.

Missed assessment visit (Section 8.6.5.4)

Note that the visit may be conducted, and a nasal swab collected, as long as symptoms are ongoing.

If it is truly not possible to perform an assessment visit (for example, if the child develops a potential LRTI while the family is travelling, and all symptoms have resolved by the time the family returns), then the LRTI assessment visit page of the eCRF should be filled in as completely as possible using available medical records.

Follow-up after an assessment visit to evaluate a potential LRTI (Section 8.6.6)
After an assessment visit (Section 8.6.5) the infant will be followed with at least weekly active surveillance contacts, until the RTI/LRTI episode has resolved. During these active contacts, worsening of symptoms will be assessed. Parent(s) / LAR(s) / designate(s) will be reminded to call/contact/visit the site if symptoms worsen.

If parent(s)/LAR(s)/designates report during an active or passive contact that symptoms have worsened, the site should perform a follow-up visit.

During the follow-up visit, collection of a nasal swab is at the Investigator's discretion.

Additional details can be found in the SPM.

RSV Hospitalization (Section 8.6.7)

- ~~Study staff will collect~~ ***If possible***, a nasal swab ***will be collected*** from any subject who ~~has been~~***is*** hospitalized with a RTI (or soon after release, ***as long as symptoms are ongoing***, per SPM specifications). The nasal swab should be collected using sponsor-provided supplies, for transmission to and testing by the sponsor laboratory.
- ~~In order to establish a fast and accurate diagnosis, collection (using locally providedlocal supplies) of an additional nasal swab for testing at a local laboratory is recommended.~~
- ***If other specimens are collected and tested locally as per routine standard of care, results will be entered into the eCRF. However,*** only the sponsor laboratory results will be used when applying the case definitions for data analysis in Table 3.

~~Baseline~~ *Screening* failures (Section 8.9)

~~Baseline~~***Screening*** failures are defined as subjects who withdraw or are withdrawn from the study after giving informed consent, but before study eligibility (presence of all inclusion and absence of all exclusion criteria) is confirmed. ~~The Day 1 discovery~~Discovery ***during screening*** of any pregnancy related-event of interest or other condition that violates the ***requirements for*** study ~~enrolment~~***eligibility*** should be considered ~~to be~~ a ~~baseline~~***screening*** failure. ***Discovery during Visit 1 of any condition that violates the requirements for study eligibility should also be considered a screening failure.***

The ~~subsequent~~ development of such conditions (after ~~Day~~***Visit 1***) ~~are~~***does*** not ~~baseline failures~~***constitute*** screening failure and should be captured on the eCRF, as applicable.

Limited data for ***screening*** failures ***will be*** reported to the eCRF. ***This limited data set is specified in the eCRF***. ~~for screening failures will be limited to:~~

- ~~ICF information~~
- ~~Demographic data~~
- ~~Inclusion/Exclusion criteria~~
- ~~Level II /Fetal Morphology Ultrasound~~
- ~~Screening conclusion data~~
- ~~Study conclusion data.~~

~~Medical history and OB/GYN physical assessment data (including height, weight and vital signs) do not need to be reported to the eCRF.~~

Table 7 Biological samples

Sample Type†	Quantity	Unit	Timepoint	Group
Samples collected by Investigator / site staff				
Maternal Blood for antibody titers	~~~ 5~~ ~~~ 5~~	~~ml~~ ~~ml~~	~~Visit 1 (Day 1)[1]5 (Delivery)~~ ~~Visit 3 (Day 56)[1]~~	~~All mothers in selected countries~~
	~ 5	ml	Visit 5 (Delivery)	All ***pregnant women (mothers)***
~~Vaginal swab~~	~~-~~ ~~-~~ ~~-~~	~~-~~ ~~-~~ ~~-~~	~~Visit 1 (Day 1)[1]~~ ~~Visit 3 (Day 56)[1]~~ ~~Visit 5 (Delivery)[2]~~	~~All mothers in selected countries~~ ~~All mothers~~
~~Nasal swab~~	~~-~~	~~-~~	~~LRTI Assessment visit~~	~~All infants, event-driven~~
Urine (dipstick)1	-	-	***Visit 1 (Day 1)*** ***Visit 2 (Day 28)*** ***Visit 3 (Day 56)*** ***Visit 4 (Day 84)***	***All pregnant women (mothers)***
Cord blood	~ 5 up to 10	ml	Visit 5 (Delivery)	All ***pregnant women (mothers)*** (provides infant antibody levels)
Nasal swab	-	-	LRTI Assessment visit	All infants, event-driven
Samples preferentially collected by local health care provider per local practice[1]				
Maternal Blood for haematology/ biochemistry	Up to 10 Up to 10	ml ml	Visit 1 (Day 1) Visit 3 (Day 56)[2]	All ***pregnant women*** (mothers)
~~Urine (dipstick)~~	~~-~~	~~-~~	~~Visit 1 (Day 1)~~ ~~Visit 2 (Day 28)~~ ~~Visit 3 (Day 56)~~ ~~Visit 4 (Day 84)~~	~~All (mothers)~~
			~~Visit 5 (Delivery)~~	

[1] ~~Only in countries where routine implementation of risk based intrapartum antibiotic prophylaxis for GBS is the standard of care~~

[2] ~~Vaginal swab at delivery will only be collected prior to rupture of membranes.~~

[3] ~~Performed~~ [1] To be performed preferentially by local healthcare providers, as per local practice. **To be performed by** the investigator/study staff ***ONLY*** if not done by the local healthcare provider ***within 2 weeks before the study visit***.

[2] Hemoglobin only

Antibody determination (Section 8.10.3.1)

- ~~Testing for GBS antibody concentrations will be performed upon availability of assay.~~

Table 8 Humoral immunity (Antibody determination)

System	Component	Method**	Kit / Manufacturer	Unit	Cut-off*	Laboratory**
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALISATION	In house	ED60	To be defined	GSK Biologicals or GSK designated lab***
~~SERUM~~	~~GBS antibody~~	~~To be defined~~	~~To be defined~~	~~To be defined~~	~~To be defined~~	~~GSK Biologicals or GSK designated lab***~~

~~GBS assessment of vaginal swabs~~

~~GBS vaginal colonization will be assessed by culture and/or molecular biology methodologies (GSK Biologicals or GSK designated laboratory) upon assay availability. If available, local laboratory results on GBS colonization will also be recorded in the eCRF.~~

~~The method that will be used to perform GBS serotyping remains to be determined (will be done at GSK Biologicals or by a GSK designated laboratory).~~

~~Table **10** GSB assessment of vaginal swabs*~~

~~Vaginal swab sampling timepoint Type of contact (timepoint)~~	~~Component~~	~~Method~~	~~Scale~~	~~Laboratory~~
~~Visit 1 (Day 1)*** Visit 3 (Day 56)*** Visit 5 (Delivery)**~~	~~GBS~~	~~To be determined~~	~~To be determined~~	~~GSK Biologicals or GSK designated lab**~~

~~* Laboratory assays for GBS assessment of vaginal swabs to be confirmed (may be assessed by culture and/or molecular biology).~~

~~** Vaginal swab at delivery will only be collected prior to rupture of membranes.~~

~~*** Only in countries where routine implementation of risk based intrapartum antibiotic prophylaxis for GBS is the standard of care~~

Haematology, biochemistry and urinalysis (Section 8.10.3.3)

Haematology and biochemistry ~~and urinalysis will~~ ***tests are to be performed preferentially*** ~~requested~~ ***by local*** ~~health care~~***healthcare providers***~~.~~ ~~Information will~~, ***as per local practice. They are to be*** ~~collected and recorded in the eCRF.~~ ***If performed by the investigator/study staff ONLY if not done by the local healthcare provider*** ~~as per local practice~~***within 2 weeks before the*** ~~investigator~~ study ~~staff~~ ***visit***.

The investigators will perform a urine dipstick test to detect for the ~~tests specified in Table 10~~ ***presence of proteins, glucose, RBC and/or WBC.***

Table 10 Hematology, biochemistry, urine tests

System	Discipline	Component	Time point	Method	Scale	Laboratory
Whole blood	Hematology	Hemoglobin	Visit 1	As per local practice	Quantitative	Local laboratory
			Visit 3			
		Leukocytes (White Blood Cells)	Visit 1			
		Platelets	Visit 1			
Serum	Biochemistry	Alanine Aminotransferase (ALT)	Visit 1	As per local practice	Quantitative	Local laboratory
		Aspartate Aminotransferase (AST)	Visit 1			
		Creatinine	Visit 1			
		Urea Nitrogen	Visit 1			
Urine	-	Protein	***Visit 1***	As per local practice, dipsticks provided by GSK Biologicals	Ordinal	Local laboratory
			Visit 2			
			Visit 3			
			Visit 4			
		Glucose	***Visit 1***			
			Visit 2			
			Visit 3			
			Visit 4			
		Hemoglobin	***Visit 1***			
		(RBC)	***Visit 2***			
			Visit 3			
			Visit 4			
		Leukocyte esterase	***Visit 1***			
		(WBC)	***Visit 2***			
			Visit 3			
			Visit 4			

~~[1] When available, urine dipstick results for RBC and WBC will also be collected.~~
~~[2] Culture results will be obtained, if performed~~

Table 11 Immunological read-outs

Blood sampling timepoint Type of contact and time point	Group	No. subjects	Component	Component priority rank
Maternal Blood				
~~Visit 1 (Day 1)**~~	~~All mothers in selected countries~~	~~~400 maximum by country~~	~~GBS*~~	~~1~~
~~Visit 3 (Day 56)**~~	~~All mothers in selected countries~~	~~~400 maximum by country~~	~~GBS*~~	~~1~~
Visit 5 (Delivery)			~~GBS*~~	~~2~~
Cord Blood				
Visit 5 (Delivery)			~~GBS*~~	~~2~~

~~**GBS** = group B streptococcus;~~ **RSV-A/B** = Respiratory syncytial virus subtype A/B.
~~* Testing for GBS antibody concentrations will be performed upon availability of assay.~~
~~** Only in countries where routine implementation of risk based intrapartum antibiotic prophylaxis for GBS is the standard of care~~

~~In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to the priority ranking provided in Table 11.~~

Table 12 Molecular biology for nasal swab specimen analysis

Nasal swab sampling timepoint		Group	No. subjects
Type of contact (timepoint)	Sampling timepoint		
Visit to assess potential LRTI ~~Assessment visit~~	Unscheduled	All infants*	Event-driven**

Footnotes

~~* For each RTI with suspicion of difficulty in breathing, wheezing or parental concern reported during an active or passive surveillance contact a nasal swab will be collected. A nasal swab will also be collected at the examination visit performed in case parents/ LAR(s) come to the study site without previous surveillance contact (if RTI with suspicion of difficulty in breathing, wheezing or parental concern, and visit within 3 days after the start of symptoms).~~

**** Refer to Section 8.6.5.***

Table 13 Hematology/blood chemistry tests (footnotes only)

* Number of subjects depending on country. ~~Prenatal screening will~~Tests to be performed preferentially by local healthcare providers and information will be collected and recorded in the eCRF. The investigator/study staff will collect biological samples for ~~prenatal screening~~***the specified testing*** if not done by the local healthcare provider as per local practice.

~~GBS assessment of vaginal swabs (Deleted Section)~~

~~Table **15** GSB assessment of vaginal swabs*~~

~~Vaginal swab sampling timepoint~~ ~~Type of contact (timepoint)~~	~~Group~~	~~No. subjects~~	~~Component~~
~~Visit 1 (Day 1)***~~	~~All mothers, selected countries***~~	~~~400 maximum by country~~	~~GBS*~~
~~Visit 3 (Day 56)***~~	~~All mothers, selected countries***~~	~~~400 maximum by country~~	~~GBS*~~
~~Visit 5 (Delivery)**~~	~~All mothers~~	~~~400 maximum by country~~	~~GBS*~~

~~* Laboratory assays for GBS assessment of vaginal swabs to be confirmed (may be assessed by culture and/or molecular biology).~~

~~** Vaginal swab at delivery will only be collected prior to rupture of membranes.~~

~~*** Only in countries where routine implementation of risk based intrapartum antibiotic prophylaxis for GBS is the standard of care~~

Event Identification (Section 9.2)

Blood~~, urine~~ ***and*** ~~vaginal swab~~urine samples will be collected from pregnant women enrolled in the study. Nasal

Subject withdrawal (Section 10.2)

Investigators will make ~~an attempt~~at least 3 attempts to contact ~~those subjects~~ ***asubject who*** ~~do~~***does*** not return for a scheduled ~~visits~~visit ~~or follow-up~~ ***as described in Section 8.4 and in the SPM.***

A subject will be defined as lost to follow-up if there is no contact with the subject /subject's parent(s) / LAR(s) over a period of ***at least 3 months after a planned visit*** (see SPM for details). Efforts to contact the subject/subject's parents should be recorded in the

source documents. The subject's data will be censored at the time of last contact once this definition is met.

Information ~~relative~~ ***relevant*** to the withdrawal will be documented in the eCRF. …….as well as which of the following possible reasons was responsible for withdrawal:

- Study ~~procedure~~ ***participation*** related SAE.
- Neonatal event of interest (specify). Note: includes death in infants ***from*** birth – 28 days old
- Death in infants > 28 days old (specify cause). Note that death in neonates ***from*** birth – 28 days old is captured as a neonatal event of interest).

Subjects who are withdrawn from the study because of ***study participation related SAEs*** must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of ~~an~~a ***study participation related*** SAE until resolution of the event (see Section 9.6.2).

Primary endpoints (Section 11.1.1), Primary Objectives Analysis (Section 11.6) and Synopsis

- Hypertensive disorders of pregnancy:
  - gestational hypertension, ***and***
  - Pre-eclampsia, ***and***
  - ***Pre-eclampsia with severe features (including*** eclampsia),
- Neonatal ~~Acute neonatal~~ encephalopathy

Secondary endpoints (Section 11.1.2), Secondary Objectives Analysis (Section 11.7) and Synopsis

- Occurrence of nneonatal events of interest from birth through ~~Day~~ ***28 days of age*** (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible)

Tertiary endpoints (Section 11.1.3), Tertiary Objectives Analysis (Section 11.8) and Synopsis

~~Human respiratory syncytial virus A (RSV A)~~

~~Human respiratory syncytial virus B (RSV B)~~

Exposed Set (ES) – pregnant women (mothers) (Section 11.3.1.1)

The ES will include all pregnant women (mothers) with a valid informed consent~~form who were enrolled in the study~~.

Per Protocol Sets (PPS) – pregnant women (mothers) and Neonates/Infants (Sections 11.3.2)

The ***maternal*** PPS will include all pregnant women (mothers)

The ***infant*** PPS will include all enrolled neonates / infants

Derived and transformed data (Section 11.4)

Age of the ***infant*** subject at time of the LRTI case will be expressed in months and will be computed as the difference between the start date of the LRTI case and the date of birth

~~Age of the subject at time of blood sample collection will be expressed in months and will be computed as the difference between the sample collection date and the date of birth.~~

Analysis of demographic *and baseline characteristics* (Section 11.5)

- For the ~~ES and~~ ***maternal*** PPS ~~cohorts, the~~ ***cohort, analyses of*** demographic ~~analyses for pregnant women~~ ***and baseline characteristics at Visit 1*** will ~~describe~~ ***be described***.
- ***For the infant PPS cohort, analyses of*** demographic ~~characteristics of women at visit 1~~ ***at Visit 1-NB will be described. Analyses of lifestyle characteristics will be described at Visit 2 NB***.
- ~~For the ES and PPS cohorts, the overall demographic analyses for neonate / infants will describe the demographic characteristics of the neonate / infants at visit 1-NB.~~
- ***For Screening Failures, reasons for non-eligibility will be described.***

Analysis of primary objectives (Section 11.6)

The primary objectives analyses will be performed on the PPS cohorts by country, and possibly by region or other relevant grouping~~In case more than 5% of the subjects are excluded from the PPS cohort then the analyses may be performed on the ES cohort.~~

Analysis of secondary objectives (Section 11.7)

The secondary objectives analyses will be performed on the PPS cohorts (***maternal or infant as applicable***) *overall by country and possibly by region or other relevant grouping~~. In case more than 5% of the subjects are excluded from the PPS cohort then the analyses may be performed on the ES cohort~~.*

Analysis of tertiary objectives (Section 11.8)

The following tertiary objectives analyses will be performed on infants within the PPS cohort overall by country, region, or other relevant grouping. ~~In case more than 5% of the subjects are excluded from the PPS cohort then the analyses may be performed on the ES cohort:~~

The following tertiary objectives analyses will be performed on the PPS cohorts (maternal or infant as applicable) *by country, region, or other relevant grouping~~. In case more than 5% of the subjects are excluded from the PPS cohort then the analyses may be performed on the ES cohort:~~*

~~**To describe GBS serotype specific antibody concentrations in cord blood (if possible).**~~

- Geometric mean titers (GMTs) will be tabulated with 95% CI.
- Percentage of subjects above thresholds will be tabulated.

The following tertiary objectives analyses will be performed on pregnant women (mothers) within the PPS cohort overall by country, region, and/or other relevant grouping:

- **To describe the prevalence of GBS vaginal colonization and serotypes distribution in pregnant women in the 2nd and 3rd trimester and at delivery (if possible).**
  - The proportion of women colonized with GBS by serotype at each timepoint will be calculated. The proportion of colonized women will be calculated as the number of women having a positive result for GBS divided by the number of women for whom a vaginal swab has been taken. This will be presented overall and by serotype.
- **To describe GBS serotype specific antibody concentrations in pregnant women in the 2nd and 3rd trimester and at delivery (if possible).**
  - For each serotype-specific GBS Concentration in serum of mothers and in cord blood the following analysis will be performed:
    - The proportion of women with serotype specific antibody concentrations above various thresholds will be calculated overall and by colonization status.
    - GMCs for each serotype will be calculated overall and by colonization status
    - Variation in colonization status and antibody titers will be calculate for each timepoint, when feasible.

The following tertiary objectives analyses will be performed on neonates / infants within the PPS cohort overall by country, region, or other relevant grouping:

- **To describe the occurrence of GBS invasive disease in infants (if possible).**
  - Incidence proportions will be calculated as the number of new invasive GBS disease cases occurring from birth up to 90 days of life (if feasible) divided by the number of infants included in the study.
  - Incidence proportions will be categorized as follows: early onset disease (during days 1-7) and late onset disease (during days 8-90) (if data available; i.e., depending on whether GBS blood and / or CSF testing is done as per local practice).
- **To describe occurrences of hospitalization and death due to GBS invasive disease (if possible).**
  - Incidence proportions will be calculated as the number of new hospitalizations due to GBS disease cases occurring from birth up to 1 year of life (if feasible) divided by the number of infants included in the study.

~~Incidence proportions will be calculated as the number of new deaths due to GBS disease cases occurring from birth up to 1 year of life (if feasible) divided by the number of infants included in the study.~~

~~Incidence proportion will categorized as follows: early onset disease (during days 1-7), late onset disease (during days 8-90), and post-late onset disease (≥91 days) (if data available; i.e., depending on whether GBS blood and / or CSF testing is done as per local practice).~~

Conduct of analyses (Section 11.11)

Analyses will be performed in a stepwise manner after each country / group of countries / countries in a region have completed all study visits in Epoch 001 *002* and again after completion of all study visits in Epoch ~~002~~ ***003***.

Analyses of pregnancy outcomes, pregnancy related events of interest, and neonatal events of interest will be performed when all data up to 42 days post-delivery are available (Epoch ~~001~~***002***).

Final analyses will be performed when all data up to study end are available (Epoch ~~001~~***002*** and Epoch ~~002~~***003***).

~~Interim~~ ***Additional*** analyses may be performed if deemed necessary to inform the design or implementation of future clinical trials

References (Section 14)

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APPENDIX D: Definitions Of Maternal, Fetal And Neonatal Events Of Interest As Per Gaia D

The 2 tables presented in the original protocol have been replaced with 21 separate tables (one for each of the 19 events of interest defined per GAIA, and two for events of interest – maternal and neonatal – not defined as such per GAIA). Definitions and levels of diagnostic certainty have been updated (where applicable) per the reference cited (beneath each table) for each event of interest.

The 2 tables in the original protocol, for reference, follow.

Maternal events of interest – TABLE FROM PROTOCOL VERSION 01

Event of interest	Description	Levels of diagnostic certainty	Reference
Maternal death	The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. (As ICD-10 terminology). In the context of immunization: "Death of a woman during pregnancy, childbirth and the puerperium that is closely related temporally to an immunization event of the mother which is likely the single or contributory cause"	Level 1 Diagnosis of pregnancy established by any of the following documented criteria: a. Ultrasound examination b. Fetal heart tones c. Positive serum or urine human chorionic gonadotropin pregnancy test d. Delivery of a neonate or other products of conception (abortus, stillborn) And Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy And Documentation of Cause of death as: a. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric com-plications, unanticipated complications b. Indirect: non obstetric complications c. Death during pregnancy, childbirth and the puerperium: other or coincidental Level 2 Diagnosis of pregnancy established by any of the following criteria in the absence of Level 1 criteria: a. LMP date b. Serial Symphysio Fundal Height examinations And Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy And Documentation of Cause of death as: a. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications b. Indirect: non-obstetric complications c. Death during pregnancy, childbirth and the puerperium: other or coincidental d. Unspecified: unknown or undetermined Level 3 Absence of Level 1 or 2 criteria for establishing diagnosis of pregnancy and: a. Unsure LMP b. No clinical examination documented And Death of the mother temporal to pregnancy, childbirth or the postpartum period when exact timing of death is unknown, And Documentation of cause of death as:	[Patwardhan, 2016]

Event of interest	Description	Levels of diagnostic certainty	Reference
		a. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric com-plications, unanticipated complications b. Indirect: non-obstetric complications c. Death during pregnancy, childbirth and the puerperium: other or coincidental d. Unspecified: unknown or undetermined.	
Hypertensive disorders of pregnancy Gestational hypertension / Preeclampsia / Eclampsia	Gestational Hypertension is a clinical syndrome characterized by pregnancy ≥20 weeks AND new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h WITHOUT severe features (see preeclampsia with severe features category) and WITHOUT proteinuria Preeclampsia has conventionally been defined as the development of gestational hypertension and proteinuria after 20 weeks gestation. Proteinuria can be quantified by 24 h urine collection, a spot protein: creatinine ratio, or with urinary dipstick. Proteinuria of≥300 mg in a 24 h urine specimen (the gold standard for measurement of proteinuria), or ≥0.30 on a spot protein: creatinine ratio, or ≥1+ on a dipstick meets the criteria for preeclampsia. Preeclampsia diagnose with severe features •Vascular: ◦ Severely elevated blood pressures, with systolic blood pressure≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only	<u>Preeclampsia</u> For All Levels of Diagnostic Certainty Clinical syndrome characterized by pregnancy ≥20 weeks AND new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND new onset proteinuria Level 1 proteinuria diagnosed with ≥300 mg of protein on 24 h urine collection OR≥0.3 on spot protein: creatinine ratio Level 2 proteinuria diagnosed with ≥1+ protein on urine dipstick Insufficient evidence blood pressure cannot be measured OR no proteinuria evaluation is available (note diagnosis of preeclampsia with severe features does not require proteinuria, see definition below) <u>Preeclampsia with severe features</u> For All Levels of Diagnostic Certainty Clinical syndrome characterized by pregnancy ≥20 weeks AND new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND At least one of the criteria for severe disease: Level 1 At least one of the following: Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110mmHg, which is confirmed after only minutes OR Development of severe, persistent headache OR Development of visual changes OR Eclampsia OR New onset thrombocytopenia (platelets <100,000/L) OR New onset unremitting epigastric pain ORAST and ALT elevated to twice upper limit of normal OR	[Rouse, 2016]

Event of interest	Description	Levels of diagnostic certainty	Reference
	minutes (to facilitate timely anti-hypertensive treatment) •Neurologic: ◦ Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen/paracetamol) ◦ Development of visual changes (including photopsia, scotomata,cortical blindness) ◦ Eclampsia, or new-onset grand mal seizures in a patient with pre-eclampsia, without other provoking factors (such as evidence of cerebral malaria or preexisting seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status •Hematologic: ◦ New onset thrombocytopenia, with platelet count <100,000/L •Gastrointestinal: ◦ New onset of nausea, vomiting, epigastric pain ◦ Transaminitis (AST and ALT elevated to twice the upper limit of normal) ◦ Liver capsular hemorrhage or liver rupture •Renal: ◦ Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine(absent other renal disease) ◦ Oliguria (urine output <500 mL/24 h)	Evidence of liver capsular hematoma or liver rupture (diagnosed on clinical exam or with imaging) OR Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease) or oliguria (<500 cc/24 h) OR Pulmonary edema (confirmed on imaging with chest X-ray, or on clinical exam) Level 2 new onset nausea and vomiting Insufficient evidence blood pressure cannot be measured <u>Gestational Hypertension</u> For All Levels of Diagnostic Certainty Clinical syndrome characterized by pregnancy ≥20 weeks AND new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h WITHOUT severe features (see preeclampsia with severe features category) and WITHOUT proteinuria Level 1 of diagnostic certainty no proteinuria (as defined by 24 h urine collection < 300 mg, spot protein: creatinine ratio <0.3) Level 2 of diagnostic certainty no proteinuria (as defined by urine dipstick negative or trace) Insufficient evidence blood pressure cannot be measured OR no proteinuria evaluation is available	

Event of interest	Description	Levels of diagnostic certainty	Reference
	•Respiratory: ◦ Pulmonary edema (confirmed on clinical exam or imaging)		
Antenatal Bleeding	Antenatal bleeding is a clinical syndrome characterized by bleeding in the second or third trimester of pregnancy. Pathologic etiologies attributable to the pregnant state include placenta previa, morbidly adherent placenta, vasa previa, placental abruption, cesarean scar pregnancy, intra-abdominal pregnancy, and uterine rupture. For both levels of diagnostic certainty for each etiology of antenatal bleeding: Bleeding is either documented vaginally or suspected to be occurring intrauterine, intraperitoneally, or (rarely) retroperitoneally, based on clinical signs and symptoms. In the case of ultrasound-based diagnosis, transvaginal ultrasound is more specific than transabdominal ultrasound, and transvaginal ultrasound is recommended where available.	<u>Placenta Previa</u> Level 1 Second or third trimester ultrasound (and/or MRI) evidence of placental tissue overlying or abutting the internal cervical os. Level 2 Painless vaginal bleeding in the second or third trimester, AND a high presenting part or abnormal fetal lie. AND pelvic exam with fullness palpable in the fornices (avoiding digital cervical exam). <u>Morbidly Adherent Placentation</u> Level 1 Second- or third-trimester ultrasound or MRI evidence of placenta previa, AND one of the following ultrasound features: Greyscale: loss of the retroplacental sonolucent zone, irregular retroplacental sonolucent zone, thinning or disruption of the hyperechoic serosa–bladder interface, presence of focal exophytic masses invading the urinary bladder, abnormal placental lacunae Color Doppler: diffuse or focal lacunar flow, vascular lakes with turbulent flow (peak systolic velocity over 15 cm/s), hypervascularity of serosa–bladder interface, markedly dilated vessels over peripheral subplacental zone 3D Power Doppler: numerous coherent vessels involving the whole uterine serosa–bladder junction (basal view), hypervascularity (lateral view), inseparable cotyledonal and intervillous circulations, chaotic branching, detour vessels (lateral view) AND one of the risk factors: prior cesarean delivery, prior uterine surgery (including endometrial ablation) or cesarean scar pregnancy OR Morbidly adherent placentation found on histology in a hysterectomy or partial wedge resection specimen. Level 2 Ultrasound evidence of placenta previa, AND hypervascularity of the lower uterine segment, diagnosed at laparotomy. OR Difficulty with placental separation after delivery of the infant, at either a vaginal or cesarean delivery with resultant hemorrhage due to partial separation.	Prabhu M, Eckert LO, Belfort M, et al. Antenatal Bleeding: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty	Reference
		Vasa Previa Level 1 Second trimester ultrasound evidence of fetal vessels (vessel with fetal heart rate identified by color flow Doppler) running through the membranes and overlying the internal cervical os, AND post-delivery examination of the placental specimen with unsupported fetal vessels within the membranes. Level 2 Vaginal bleeding in the second or third trimester at the time of ruptured amniotic membranes, AND fetal heart rate changes ultimately resulting in sinusoidal rhythm/terminal bradycardia, AND delivery of a pale, anemic infant or recent stillbirth or neonatal death, AND post-delivery examination of the placental specimen with unsupported fetal vessels within the membranes. Placental Abruption Level 1 In the absence of placenta previa on ultrasound, vaginal bleeding in the second or third trimester, AND uterine irritability or labor, AND clinical signs of hypovolemic shock or coagulopathy. OR Placental pathology with histologic findings of a chronic abruption. Level 2 Vaginal bleeding in the second or third trimester, AND uterine irritability or labor, without clinical signs of hypovolemic shock or coagulopathy, OR Vaginal bleeding in the second or third trimester, AND clinical evidence of retroplacental clot or visually evident placental infarcts at the time of delivery. Cesarean Scar Pregnancy Level 1 Transvaginal ultrasound with the following characteristics: empty uterine cavity, AND empty cervical canal, without contact with the gestational sac, AND presence of gestational sac, +/- fetal pole, +/- cardiac activity, in the anterior uterine segment adjacent to the cesarean scar, AND absence or defect in myometrium between bladder and gestational sac, AND gestational sac well perfused on Doppler ultrasound (to differentiate from an expulsing, avascular gestational sac).	

Event of interest	Description	Levels of diagnostic certainty	Reference
		OR Hysterectomy specimen with evidence of pregnancy implanted into the cesarean scar. There is no Level 2 definition for this event. <u>Intra-abdominal Pregnancy</u> Level 1 At laparotomy, a fetus found within the abdominal cavity, without evidence of uterine rupture, and with placentation not within the uterine cavity. There is no Level 2 definition for this event. <u>Uterine Rupture</u> Level 1 Complete uterine disruption at the time of laparotomy in the context of vaginal or intra-abdominal bleeding. There is no Level 2 definition for this event.	
Postpartum haemorrhage	Genital tract bleeding after delivery (up to 42 days) of a foetus or infant that leads to an adverse clinical outcome. Such as hypovolemia or anaemia e.g. exertional dyspnoea, postural presyncope, tiredness or reduced consciousness. At the furthest extreme uncorrected hypovolaemic shock can lead to organ-dysfunction and maternal death. ICD-10 definition: “heamorrhage after delivery of a foetus or infant”	Level 1 Genital bleeding after delivery leading to severe maternal out-come (maternal death or maternal near miss) as defined by WHO[28]. Level 2 Genital bleeding after delivery with at least one of the following: measured abnormal bleeding (1000 ml or more), or any bleeding leading to hypotension or blood transfusion. Level 3 Genital bleeding after delivery estimated at 1000 ml or more	[Kerr, 2016]
Fetal Growth Restriction	A fetus with a sonographic estimation of fetal weight below the tenth percentile for a given gestational age with increasing specificity for adverse perinatal outcomes below the third percentile.	Level 1a Level 1 evidence of pregnancy dating AND Estimated fetal weight below 3% using locally-accepted growth curve OR Estimated fetal weight below 10% using locally-accepted growth curve AND Absent or reversed end-diastolic flow of the umbilical artery Doppler OR Oligohydramnios as defined by amniotic fluid index (AFI) < 8 or deepest vertical pocket (DVP) < 2. Level 1b Level 1 evidence of pregnancy dating AND Estimated fetal weight below 10%ile using locally-accepted growth curve AND	Easter SR, Eckert OL, Boghossian N, et al. Fetal Growth Restriction: Case Definition & Guidelines for Data Collection, Analysis, and

Event of interest	Description	Levels of diagnostic certainty	Reference
		Lack of absent or reversed end-diastolic flow of the umbilical artery OR oligohydramnios as defined by AFI <8 or DVP <2. Level 2a Level 2 evidence of pregnancy dating AND Estimated fetal weight below 3% using locally-accepted growth curve OR Estimated fetal below 10% using locally-accepted growth curve AND Absent or reversed end-diastolic flow of the umbilical artery Doppler. OR Oligohydramnios as defined by AFI < 8 or DVP < 2. Level 2b Level 2 evidence of pregnancy dating AND Estimated fetal weight below 10%ile using locally-accepted growth curve AND No findings of absent or reversed end-diastolic flow of the umbilical artery or oligohydramnios as defined by AFI <8 or DVP <2. OR Level 1 evidence of pregnancy dating AND Estimated fetal weight below 10% using locally-accepted growth curve with no findings of oligohydramnios as defined by AFI <8 or DVP <2 with inability to assess umbilical artery Doppler. Insufficient Evidence Absence of ultrasound for use in assessment of estimated fetal weight.	Presentation of Immunization Safety Data. Unpublished manuscript.
Dysfunctional Labor	Prolonged labor at or after 37 weeks and before 42 weeks of gestational age	First Stage of Labor For both levels of diagnostic the woman is in established labor defined by regular contractions and cervical dilation of at least 4cm. Level 1 Progress of less than 0.5 cm cervical dilation per hour, for at least 4 hours, in women in established labor (i.e. have regular contractions and cervical dilation of at least 4cm) and with confirmed ruptured membranes. Level 2 Progress of less than 0.5cm cervical dilation per hour in women, for at least 4 hours, with established labor, (i.e. that is, regular contractions and cervical dilation of at least 4cm) without certainty of ruptured membranes. Second Stage of Labor The definitions below are applicable in cases with or without regional analgesia. Level 1 Full dilation of the cervix AND onset of the active stage (active maternal effort (i.e. pushing) OR visible baby) AND	Boatin AA, Eckert LO, Boulvain M, et al. Dysfunctional Labor: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty	Reference
		greater than 2 hours of pushing in nulliparous women OR greater than 1 hour of pushing in multiparous women OR use of instrument OR caesarean delivery for the indication of dystocia. Level 2 Full dilation of the cervix in any phase of the second stage AND no delivery within 3 hours of full dilation in the nulliparous woman OR within 2 hours in multiparous women OR use of instrument OR caesarean delivery for the indication of dystocia.	
Gestational Diabetes Mellitus	Pregnancy induced hyperglycemia	For All Levels of Diagnostic Certainty Gestational diabetes mellitus (GDM) is a clinical syndrome characterized by the absence of pre-gestational diabetes diagnosis defined by Previous diagnosis of diabetes while not pregnant OR First trimester hemoglobin A1c level of ≥ 6.5% (47.5 mmol/mol) OR First trimester fasting blood glucose 126 mg/dL / ≥ 7mmol/L AND Identification of sustained hyperglycemia during pregnancy not due to other known causes (i.e. corticosteroids, beta-mimetics, etc.) Level 1 Absence of pre gestational diabetes mellitus diagnosis in the first trimester as defined above with level 1-2 certainty for gestational age using GAIA definition for gestational age AND Diagnosis of gestational diabetes based on a positive internationally recognized oral glucose tolerance test (see below “major criteria”) using venous blood sample/samples Level 2 Absence of pre gestational diabetes mellitus diagnosis in the first trimester as defined above with at least level 3 certainty for gestational age using GAIA definition for gestational age AND Diagnosis of gestational diabetes based on positive internationally recognized oral glucose tolerance test (see below “major criteria”) using capillary blood sample/samples Level 3 Absence of pregestational diabetes mellitus diagnosis in the first trimester as defined above with at least level 3 certainty for gestational age using GAIA definition for gestational age AND Diagnosis of gestational diabetes based on fasting plasma glucose of 5.1-6.9 mmol/l (92-125 mg/dL) using venous or capillary blood samples. Insufficient evidence for diagnosis Blood glucose cannot be measured OR	Kachikis A, Eckert LO, Walker C, et al. Gestational Diabetes Mellitus: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty	Reference
		Use of Hemoglobin A1c alone for the diagnosis of GDM without a diagnostic oral glucose tolerance test (OGTT) or elevated fasting plasma glucose level. OR Clinical and laboratory findings such as glucosuria, fundal height greater than dates, obesity, prior history of GDM or family history for the diagnosis of gestational diabetes mellitus without a diagnostic test.	
Non-reassuring fetal status	Indicator of underlying event resulting in temporary or permanent oxygen deprivation to the fetus which may lead to fetal hypoxia and metabolic acidosis	Level 1 Category III fetal heart rate tracings detected via continuous cardiotocography as defined by NICHD Absent baseline fetal heart rate variability AND any of the following: - recurrent late decelerations - recurrent variable deceleration - bradycardia (<110 bpm) OR Sinusoidal pattern AND Umbilical cord blood analysis consistent with metabolic acidosis (pH < 7.0 and Base deficit >12 mmol/L) Level 2 Category III fetal heart rate tracings detected via continuous cardiotocography as defined by NICHD Absent baseline fetal heart rate variability AND any of the following: - recurrent late decelerations - recurrent variable deceleration - bradycardia (<110 bpm)OR◦ Sinusoidal pattern Level 3 Fetal heart pattern detected via intermittent auscultation suggestive of fetal hypoxia Baseline FHR <110 bpm or >160 bpm Presence of repetitive or prolonged (>3 min) decelerations More than 5 contractions in a 10 min period	[Gravett, 2016]
Pathways to preterm birth	Premature preterm rupture of membranes Preterm labor Insufficient cervix Provider-initiated preterm birth	Premature preterm rupture of membranes All levels of certainty Patient is determined to be preterm as defined by GAIA On presentation, patient is determined to not be in preterm labor, having ≤4 contractions per hour documented clinically or on tocodynometer, with <2 cm cervical dilation (greater than 4 contractions per hour would qualify the patient as having preterm labor) Fluid can be noted to be clear, blood-tinged, meconium-tinged (fetal stool), purulent-tinged (yellowish, suggesting infection) Level 1	[Harrison, 2016]

Event of interest	Description	Levels of diagnostic certainty	Reference
		Clinical history of rupture of membranes AND Visible leakage of fluid on vaginal speculum exam AND Visible arborization (ferning) on microscopy of amniotic fluid OR Ultrasound with oligohydramnios (AFI <5 or MVP <2) AND Documented membrane rupture by a diagnostic test (one of the below options): Positive intra-amniotic dye-injection method Positive result on amniotic fluid alpha-fetoprotein test kit Amniotic fluid pH measurement (nitrazine paper test) Amniotic fluid placental alpha macroglobulin-1 protein assay (PAMG-1) test (AmniSure test) Amniotic fluid insulin-like growth factor binding protein(IGFBP-1) test (Actim PROM test) Level 2 Clinical history of rupture of membranes AND Visible leakage of fluid on vaginal speculum examination AND Visible arborization (ferning) on microscopy of amniotic fluid OR document membrane rupture by a diagnostic test (one of those listed above) OR Ultrasound with oligohydramnios (AFI <5 or MVP <2) Level 3 Clinical history of rupture of membranes AND Visible leakage of presumed amniotic fluid; this may be on vaginal speculum examination (pooling in vagina), on inspection of the perineum (wet perineum due to leakage of fluid from the vagina), or fluid soaked cloth/clothes/sanitary pad. <u>Preterm labor</u> For all levels of diagnostic certainty Patient is determined to be have delivered preterm as defined by the Brighton Collaboration definition Level 1 On presentation, >4 documented uterine contractions per hour as determined by a tocodynometer AND Documented change in length or dilation of cervix by physical examination or transvaginal ultrasound over a two hour period, with clinical criteria for documenting cervical change by exam including: a. Cervical dilation 2 cm or greater at the internal os by digital examination b. Cervical length of 1 cm or less by digital examination c. 50% or greater effacement by digital examination	

Event of interest	Description	Levels of diagnostic certainty	Reference
		Level 2 Greater than 4 uterine contractions per hour as determined by a tocodynometer or clinical assessment AND Documented change in length or dilation of cervix by physical examination, with clinical criteria including: a. Cervical dilation 2 cm or greater at the internal os by digital examination b. Cervical length of 1 cm or less by digital examination c. 50% or greater effacement by digital examination Level 3 1. Greater than 4 documented uterine contractions per hour determined by clinical assessment AND 2. Documented change in cervical examination (change in dilation or effacement) over a two hour period <u>Insufficient cervix</u> For all levels of diagnostic certainty Patient is determined to be ≥16 weeks and <24 weeks gestation as defined by the Brighton Collaboration definitions of gestational age Patient is determined to have advanced cervical dilation (>2 cm) resulting in either treatment with a cerclage (cervical stitch) or preterm delivery Patient is determined to not be in preterm labor, having ≤4 con-tractions per hour documented clinically or on tocodynometer (with anything >4 contractions per hour falling into the category of preterm labor) Level 1 Internal cervical os dilation (>2 cm) with ≤4 contractions/h, as determined by transvaginal ultrasound AND digital examination Level 2 Internal cervical os dilation (>2 cm) with ≤4 contractions/h, as determined by digital examination Level 3 Patient reports fetal delivery without any painful contractions History excludes other causes of mid-trimester delivery <u>Provider-initiated preterm birth</u> For all levels of diagnostic certainty Patient is determined to be preterm as defined by the Brighton Collaboration definition	

Event of interest	Description	Levels of diagnostic certainty	Reference
		Level 1 Documentation in the healthcare record by a patient's delivering provider that there were no signs or symptoms of the spontaneous onset of preterm labor AND Documentation in the healthcare record by a patient's delivering provider that the patient needed to undergo induction of labor or cesarean delivery which led to the preterm delivery Level 2 From recall, delivering provider confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND Delivering provider reports from recall that he or she decided that the patient needed to undergo induction of labor or cesarean delivery Level 3 From recall, patient confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND Patient reports from recall that the healthcare provider indicated that she needed to undergo induction of labor or cesarean delivery	

Neonatal events of interest - –TABLE FROM PROTOCOL VERSION 01

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
Small for gestational age	Weight below 10th percentile for gestational age as assessed against a validated global, regional or local standard.	Level 1 Weight below 10th percentile for gestational age AND The following used in assessment of weight: Newborn weighed within 24 hours of birth Weight assessed using a calibrated electronic scale with 10 g resolution AND The following for assessment of gestational age: Certain LMP or IUI or embryo transfer date AND confirmatory ultrasound in first trimester OR The following for assessment of gestational age: First trimester ultrasound Level 2A Weight below 10th percentile for gestational age AND The following used in assessment of weight: Newborn weighed within 24 hours of birth on any scale with a < 50 g resolution, tared to zero and calibrated AND The following for assessment of gestational age: Certain LMP with first or second trimester ultrasound OR Certain LMP with first trimester physical exam2 Level 2B Weight below 10th percentile for gestational age AND The following used in assessment of weight: Newborn weighed within 24 hours of birth on any scale with a < 50 g resolution, tared to zero and calibrated AND The following assessment of gestational age: Uncertain LMP with second trimester ultrasound Level 3A Weight below 10th percentile for gestational age AND The following used in assessment of weight: Infant weighed within the first 48 hours of life, Newborn weighed on any scale with a < 50 g resolution, tared to zero and calibrated AND The following assessment of gestational age: Certain LMP with third trimester ultrasound OR Certain LMP with confirmatory 2nd trimester fundal height OR Certain LMP with birthweight OR Uncertain LMP with first trimester physical exam Level 3B Weight below 10th percentile for gestational age AND	Schlaudecker EP, Munoz FM, Bardají A, et al. Small for Gestational Age: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Maternal Immunisation Safety Data. unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		The following used in assessment of weight: Infant weighed within the first 48 hours of life, Newborn weight assessed by measuring the difference between an adult holding the infant and the adult being weighed alone on any scale AND The following assessment of gestational age: Uncertain LMP with fundal height OR Uncertain LMP with newborn physical assessment OR Uncertain LMP with birthweight Level 4 Baby noted to be small, but no actual weight Baby with GA assessed only by infant examination Diagnosis extracted from billing codes or chart, with no documentation of actual birth weight or GA	
Low birth weight (LBW)	LBW <2500 grams. Very low birth weight (VLBW) <1500 grams and extremely low birth weight (ELBW) is <1000grams.	Level 1 1. Newborn infant weighed within 24 hours of birth AND 2. Use electronic scale which is graduated to 10 grams AND 3. Scale is calibrated at least once a year AND 4. Scale placed on level, hard surface AND 5. Scale tared to zero grams AND 6. Weight recorded as <2500 grams OR 7. Birth weight recorded as <2500 grams AND 8. Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 5 Level 2 1. Newborn infant weighed within 24 hours of birth AND 2. Scale (electronic/spring) is graduated to at least 50 grams AND 3. Scale is calibrated at least once a year, or more often if moved AND 4. Scale tared to zero grams or 0.00kg AND 5. Weight recorded as <2500 grams OR 6. Birth weight recorded as <2500 grams AND 7. Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 4 (Scale used could be electronic or spring scale, including colour-coded scale) Level 3 1. Newborn infant weighed on day 1 or 2 of life (first 48 hours of life) AND 2. Weight measured using dial/spring/colour-coded scale AND	Cutland CL, Lackritz E, Alonso AB, et al. Low Birth Weight: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Maternal Immunisation Safety Data. Unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		3. Weight assessed as <2500 grams Level 4 1. Newborn weight assessed between 3 and 7 days of age AND 2. Weight assessed using dial/ spring/ colour-coded scale OR 3. Proxy measure (Table 1 of reference) of birth weight used AND 4. Weight CATEGORY assessed as <2500 grams	
Acute Neonatal Encephalopathy	Is a clinical syndrome presenting with abnormal functioning of the central nervous system, in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by an abnormal level of alertness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone that may be due to a variety of etiologies including hypoxia/ischemia, metabolic disturbance, or infection.	Level 1 Abnormal level of alertness AND Clinical Seizures with electroencephalographic correlation AND Difficulty with initiating and maintaining respiration AND Depression of tone Level 2 Abnormal level of alertness AND Clinical Seizures with or without electroencephalographic correlation AND Difficulty with initiating and maintaining respiration OR Depression of tone Level 3 Abnormal level of alertness AND Clinical Seizures OR Difficulty with initiating and maintaining respiration OR Depression of tone	Sell E, Munoz FM, Soe A, et al. Acute Neonatal Encephalopathy: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Maternal Immunization Safety Data. Unpublished manuscript.
Congenital Microcephaly	Congenital microcephaly, also referred to as primary microcephaly due to its presence in utero or at birth, is a descriptive term for a structural defect in which a fetus or infant's head (cranium) circumference is smaller than expected when compared to other fetuses or infants of the same gestational age, sex and ethnic background.	<u>Postnatally diagnosed Congenital Microcephaly Case Definition</u> Level 1 Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of Gestational Age (GA) AND HC 2 SD below mean or <3% according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured between 24–36 hours after birth or end of pregnancy. Level 2A Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA AND HC 2 SD below mean or <3% according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured within the first 24 hours OR	DeSilva M, Munoz FM, Sell E, et al. Congenital Microcephaly: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Safety Data after Maternal Immunisation.

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Measured >36 hours and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly Level 2B Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA AND HC 2 SD below mean or <3% according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured within the first 24 hours OR Measured >36 hours and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly Level 3 Live birth, stillbirth, or spontaneous or therapeutic abortion AND Case meets criteria for microcephaly using a validated algorithm: 1 inpatient diagnosis OR 2 outpatient diagnoses OR 1 outpatient diagnosis AND death in first year using the following diagnostic codes ICD-9-CM code 742.1 or ICD-10-CM code Q02 Level 4 Live birth, stillbirth, or spontaneous or therapeutic abortion AND Diagnosis of congenital microcephaly based on physical inspection without HC measurement OR Diagnosis of congenital microcephaly based on ICD-9-CM or ICD-10-CM code that does not meet validated algorithm criteria above. <u>B. Prenatally diagnosed Congenital Microcephaly Case Definition</u> Level 1A Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester (<14 weeks) or 2nd trimester US scan IUI, or embryo transfer date AND HC 2 SD below mean or <3% according to fetal ultrasound (US) examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) in fetus by at least one additional US after 24 weeks and at least one week after first US OR Confirmation of microcephaly by HC measurement with standard tape measure at birth or autopsy	Unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Level 1B 1. Fetus of at least 24 weeks GA based on uncertain LMP with 2nd trimester US AND 2. HC 2 SD below mean or <3% according to fetal ultrasound (US) examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) in fetus by at least one additional US after 24 weeks and at least one week after first US OR Confirmation of microcephaly by HC measurement with standard tape measure at birth or autopsy Level 2 Fetus of at least 24 weeks GA based on LMP with fundal height and no confirmatory US scan AND HC 2 SD below mean or <3% according to fetal US examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) in fetus with at least one additional US after 24 weeks and at least one week after first US OR Confirmation of microcephaly by HC measurement with standard tape measure at birth or autopsy Level 3 Fetus of at least 24 weeks GA AND HC 2 SD below mean or <3% according to fetal US examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND No confirmation of microcephaly with any additional US or by HC measurement at birth or autopsy Level 4 Fetus of at least 24 weeks GA AND No available measurement of HC in utero by US, but documentation on medical record review suggesting microcephaly based on US imaging AND No confirmation of microcephaly with any additional US or by HC measurement at birth or autopsy	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Level 5 Fetus of at least 24 weeks GA AND HC 2 SD below mean or <3% according to fetal US examination using appropriate standardized reference charts according to GA and gender for the population (eg. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND HC at birth or autopsy is in the normal range using appropriate standardized reference charts according to GA and gender for the population, which means that this is NOT a case of prenatally diagnosed congenital microcephaly	
Congenital anomalies	Congenital anomalies, also commonly referred to as birth defects, congenital disorders, congenital malformations, or con-genital abnormalities, are events of prenatal origin that a represent at birth, potentially impacting an infant's health, development and/or survival.	For all levels of diagnostic certainty A major congenital anomaly is a structural or functional defect with the following three characteristics: 1. Of prenatal origin 2. Present at the time of live birth or fetal demise, or in utero 3. Affecting (or has the propensity to affect) the health, survival, or physical or cognitive functioning of the individual Major External Structural Defects Level 1 •Alterations in external anatomy visible at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR •Alterations in external anatomy visible in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND •Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of morphology training for the specific setting Level 2 •Alterations in external anatomy visible at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR •Alterations in external anatomy visible in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND •Confirmed by documentation of a diagnosis made by a clinician with some experience diagnosing congenital anomalies Level 3 •Alterations in external anatomy visible at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR	[DaSilva, 2016]

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		•Alterations in external anatomy visible in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND •Confirmed by documentation of a diagnosis made by a trained maternal or child health care provider with at least minimal experience diagnosing congenital anomalies OR •For live births, confirmed using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated Level 4 (insufficient evidence to confirm) •Alterations in external anatomy visible at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR •Alterations in external anatomy visible in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND •Confirmed by medical record review OR •Confirmed in claims data (ICD-9/ICD-10 diagnoses) Internal Structural Defects Level 1 •Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND •Confirmed by definitive imaging study or intraoperative diagnosis OR •Alterations in internal anatomy detected during autopsy for a stillbirth, spontaneous or therapeutic abortion confirmed by documentation by a pathologist or other relevant subspecialist Level 2 •Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND •Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of morphology training for the specific setting without definitive imaging or intraoperative evaluation OR •For stillbirth, spontaneous or therapeutic abortion, internal structural defect is visible by ultrasound or other imaging modality prenatally Level 3 •Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		•Confirmed by documentation of a diagnosis made by a clinician with some experience diagnosing congenital anomalies OR •Confirmed using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated Level 4 insufficient evidence to confirm •Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR •Alterations in internal anatomy present at time of stillbirth, spontaneous abortion, or induced abortion AND •Confirmed through medical record review, with the medical record demonstrating that the anomaly was present at the time of live birth or time of fetal demise, and that the anomaly was diagnosed by a trained maternal or child health care provider with minimal experience diagnosing congenital anomalies OR •Confirmed by claims data (ICD-9/ICD-10 diagnoses) Functional Defects Level 1 •For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at the time of birth (or propensity to develop alteration present at live birth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed by definitive diagnostic study Level 2 •For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at livebirth (or propensity to develop alteration present at live birth),and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of training in the diagnosis of functional defects for the specific setting Level 3	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		•For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at livebirth (or propensity to develop alteration present at live birth),and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed by documentation of a diagnosis made by a clinician with some experience diagnosing functional defects OR •Confirmed using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome(individual code or algorithm) has been validated Level 4 (insufficient evidence to confirm) •For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at the time of live birth (or propensity to develop alteration present at livebirth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR •For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND •Confirmed through medical record review, with the medical record demonstrating that the anomaly was present at the time of live birth or time of fetal demise, and that the anomaly was diagnosed by a trained maternal or child healthcare provider who is not a qualified geneticist, neonatologist, pathologist, subspecialist, pediatrician, obstetrician, or family medicine practitioner OR •Confirmed by claims data (ICD-9/ICD-10 diagnoses)	
Neonatal death	Death of a live born infant regardless of gestational age at birth, within the first 28 completed days of life.	Neonatal death in a non-viable live birth Level 1 1. Live born infant AND 2. Gestational age <22 weeks (GA level of certainty = 1) OR 3. Birth weight <500 g AND 4. Death of infant in first 28 days of life AND 5. Medically-confirmed death Level 2 1. Live born infant AND 2. Gestational age/size of newborn assessed as at least one of: a. Gestational age <22 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight <500 g AND	[Pathirana, 2016]

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death Level 3 1. Live born infant AND 2. Gestational age <5 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death <u>Neonatal death in an extremely preterm live birth</u> Level 1 1. Live born infant AND 2. Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1) OR 3. Birth weight ≥500 g but <1000 g AND 4. Death of infant in first 28 days of life AND 5. Medically-confirmed death Level 2 1. Live born infant AND 2. Gestational age/size of newborn assesses as one or more of: a. Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight ≥500 g but <1000 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death Level 3 1. Live born infant AND 2. Gestational age ≥5 months but <7 months according to neonate's parent (mother/father)/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death <u>Neonatal death in a preterm live birth (gestational age ≥28to <37 weeks)</u> Level 1 1. Live born infant AND 2. Gestational age ≥28 and <37 weeks (Level of Certainty = 1)OR 3. Birth weight ≥1000 g but <2500 g AND 4. Death of infant in first 28 days of life AND	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		5. Medically-confirmed death Level 2 1. Live born infant AND 2. Gestational age/size of newborn assesses as one or more of: a. Gestational age ≥28 and <37 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight ≥1000 g but <2500 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death Level 3 (MAY apply to LMIC- or may be non-viable in LMIC) 1. Live born infant AND 2. Gestational age ≥7 months but <9 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death <u>Neonatal death in a term live birth</u> Level 1 1. Live born infant AND 2. Gestational age ≥37 weeks (GA Level of Certainty = 1) AND 3. Birth weight >2500 g OR 4. Documented intra-uterine growth retardation if ≤2500 g AND 5. Death of infant in first 28 days of life AND 6. Medically-confirmed death Level 2 1. Live born infant AND 2. Gestational age/size of newborn assesses as one or more of: a. Gestational age ≥37 weeks (GA Level of Certainty = 1 OR 2) b. Birth weight ≥2500 g AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death which is confirmed by examination by (by at least) non-medically-trained attendant (e.g. undertaker, community member)	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Level 3 (apply to LMIC) 1. Live born infant AND 2. Gestational age ≥9 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death	
Neonatal infections	Neonatal bacteraemia and sepsis (of early or late onset), meningitis, pneumonia and other respiratory infections such as bronchiolitis, caused by bacteria, parasites, viruses or fungi. Localised eye and ear infections, encephalitis, urinary tract infections and intestinal infections were excluded from these guidelines.	<u>Neonatal invasive blood stream infections: bacterial/fungal/viral</u> Level 1 Recognised pathogen identified using a validated method and from a normally sterile site. Level 2 Not meeting Level 1 of evidence AND 3 or more criteria: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachycardia or new or more frequent episodes of bradycardia •New or more frequent episodes of apnea or increased oxygen requirement or increased requirement for ventilatory support • Lethargy or moving only when stimulated or hypotonia or irritability • Difficulty in feeding or abdominal distention • Pallor or poor perfusion or hypotension •Abnormal White Cell Count or I/T ratio >0.2 • Abnormal platelet count •Increased inflammatory markers (CRP, procalcitonin) • Metabolic acidosis as defined by a base excess Level 3 Not meeting Level 1 or 2 of evidence AND 2 or more of the following criteria: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachypnea or severe chest in drawing or grunting or cyanosis • Change in level of activity • History of feeding difficulty • History of convulsions <u>Bacterial/fungal/viral meningitis</u> Level 1 Recognised pathogen identified using a validated method from cerebrospinal fluid (CSF)	[Vergnano, 2016]

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Level 2 CSF pleocytosis OR positive IgM antibodies to a specific pathogen in the CSF AND Recognised pathogen identified using a validated method from a normally sterile site (other than CSF) AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 1 or more criteria: • History of convulsions •Lethargy or irritability •Coma •Apnea •Bulging fontanel •Neck stiffness Level 3a CSF pleocytosis AND No pathogen identified using a validated method from a normally sterile site AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 3 or more criteria: • History of convulsions • Lethargy or irritability • Coma • Apnea • Bulging fontanel • Neck stiffness Level 3b No lumbar puncture done or no sample available AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 4 or more criteria: • History of convulsions • Lethargy or irritability • Coma • Apnea • Bulging fontanel • Neck stiffness Respiratory bacterial/fungal/viral infection	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Level 1 New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND Recognised virus identified using a validated assay from an upper respiratory sample OR Recognised pathogen identified using a validated method and from a normally sterile site AND 3 or more criteria: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachypnea or Nasal flaring or Chest in-drawing or Grunting • Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% • Apneas • Increased respiratory secretions or Increased suctioning requirements • Cough or wheeze or crepitations • Increased CRP or procalcitonin Level 2 New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND 4 or more criteria: • Temperature ≥37.5 ◦C or <35.5 ◦C • Tachypnea or Nasal flaring or Chest in-drawing or Grunting • Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% • Apneas • Increased respiratory secretions or Increased suctioning requirements • Cough or wheeze or crepitations • Increased CRP or procalcitonin Level 3 2 or more criteria: • Difficulty in breathing/Tachypnea • Severe chest in-drawing • Nasal flaring • Grunting • Wheezing • Stridor	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		• Fever	
Respiratory distress in the neonate	Constellation of clinical findings that support the presence of breathing difficulty in the neonate.	Level 1 Newborn 0 to 28 days of life AND Abnormal respiratory rate: Measurement of number of breaths per minute consistent with: Tachypnea = respiratory rate of more than 60 breaths per minute OR Bradypnea = respiratory rate of less than 30 breaths per minute OR Apnea = cessation of respiratory effort (no breaths) for at least 20 seconds AND Clinical symptoms consistent with labored breathing Nasal flaring (dilatation of alae nasi) OR Noisy respirations in the form of expiratory grunting, stridor, or wheeze OR Retractions or increased chest in-drawings on respiration (subcostal, intercostal, sternal, suprasternal notch) OR Central cyanosis (whole body, including lips and tongue) on room air OR Low Apgar Score (< 7 points) at 10 min, with respiration score <2 AND Examination and documentation by qualified, trained, health care provider appropriate for the clinical setting. Level 2 Newborn 0 to 28 days of life AND Abnormal respiratory rate: Not measured, but reported as “rapid breathing”, “slow breathing”, having periods of “no breathing”, or “abnormal breathing” AND Clinical symptoms consistent with labored breathing Nasal flaring (dilatation of alae nasi) OR Noisy respirations in the form of expiratory grunting, stridor, or wheeze OR Retractions or increased chest in-drawings on respiration (subcostal, intercostal, sternal, suprasternal notch) or seesaw respirations OR Central cyanosis (whole body, including lips and tongue) on room air OR Low Apgar Score (< 7 points) at 10 min, with respiration score <2 AND No medical record documentation, but reporting through either a non-medical observer (e.g. mother, father, community worker) or via standard census mechanisms (e.g. Demographic and Health Surveillance System) OR Collection of information from medical record review or billing codes.	Sweet LR, Keech C, Klein NP, et al. Respiratory Distress in the Neonate: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Maternal Immunization Safety Data. Unpublished manuscript.

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		Level 3 No need for a level 3 per working group. Level 4 Not enough information to ascertain case of respiratory distress.	
Stillbirth	Fetal death occurring before birth after a 20 to 28 weeks of gestation (variation due to country definitions).	Antepartum Stillbirth Fetal death occurs prior to the evidence of labor. Level 1 •Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined by physical examination after delivery (with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry). AND •Prenatal ultrasound examination documenting lack of fetal cardiac activity or movement before the onset of labor. OR •Auscultation for fetal heart tones (using electronic devices or non-electronic devices) documenting lack of fetal heartbeat. AND •Maternal report of lack of fetal movement for 24 h or more. OR •Maternal physical examination confirming lack of fetal movement. OR •Radiology findings consistent with intrauterine fetal death. AND •Attended delivery followed by fetal physical examination afterbirth consistent with antepartum death, by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, or pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, mid-wife, nurse practitioner, a physician's assistant or other qualified trained practitioner). OR •Fetal/placental pathology report consistent with antepartum death. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1 or 2 in GA assessment algorithm). Level 2 •Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined physical examination after delivery. AND •Maternal report of lack of fetal movement for 24 h or more. OR •Maternal physical examination confirming lack of fetal movement. OR •Auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND	[DaSilva, 2016]

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		•Attended delivery followed by physical examination after birth consistent with antepartum death, by specialist or qualified trained practitioner appropriate to the health care setting. OR •Fetal/placental pathology report consistent with antepartum death. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm). Level 3 •Delivery of an infant reported to have no of signs of life at birth(No spontaneous movements, no umbilical cord pulse, no heart-beat, no cry or spontaneous respirations, no chest movement, and whole body cyanosis). AND •Maternal report of lack of fetal movement for 24 h or more prior to delivery. OR •Report of auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND •Non-attended delivery followed by physical examination of the fetus after birth consistent with antepartum death by a healthcare professional appropriate to the level of standard of care in the health care setting. OR •Verbal history by a trained health care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth and with physical features consistent with antepartum death. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level2–3 in GA assessment algorithm).Level 4•Report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made) •Maternal information insufficient to assess gestational age <u>Intrapartum stillbirth</u> Fetal death occurs during labor and before delivery Level 1 •Delivery of an infant with no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and Apgar score of 0 at 1 and 5 min .•Determination of the absence of signs of life is made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry. AND •Evidence of live fetus prior to onset of labor (documentation of fetal movement and of fetal heart tones by ultrasound prior to onset of labor) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth).AND	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		•Attended delivery followed by physical examination afterbirth consistent with intrapartum death by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, midwife, or other qualified trained practitioner).AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal-neonatal parameters (Level 1 in GA assessment algorithm) Level 2 •Delivery of an infant with no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and Apgar score of 0 at 1 and 5 min. •Determination of the absence of signs of life is made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry OR documentation of lack of response to resuscitation efforts. AND •Evidence of live fetus prior to onset of labor (maternal report of fetal movement prior to onset of labor and documentation of fetal heart tones by auscultation or hand held Doppler) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND •Attended delivery followed by physical examination after birth consistent with intrapartum death by a health care professional appropriate to the level of standard of care in the health care setting. AND •Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm). Level 3 •Delivery of an infant reported to have no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no cry, no spontaneous respirations or chest movement, and whole body cyanosis. AND •Evidence of live fetus prior to onset of labor (maternal report of fetal movement prior to onset of labor OR auscultation of fetal heart tones) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND •Non-attended delivery followed by physical examination of the fetus after birth consistent with intrapartum death by a healthcare professional appropriate to the level of standard of care in the health care setting OR verbal history by a trained health care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth. AND	

Event of interest	Description	Levels of diagnostic certainty (1 highest level to 4 lowest level of certainty)	Reference
		•Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level2–3 in GA assessment algorithm). Level 4 •Report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made). •Maternal information insufficient to assess gestational age.	
Preterm birth	Birth in less than 37 gestation completed weeks (less than 259 days).	Prematurity and assessment of gestational age Level 1 Certain LMP or intrauterine insemination (IUI) date or embryo transfer (ET) date with confirmatory 1st trimester scan (≤13 6/7 weeks). OR 1st trimester scan (≤13 6/7 weeks) Level 2A Certain LMP* with 2nd trimester scan (14 0/7 weeks to 27 6/7weeks). If LMP and U/S do not correlate, default to U/S GAassessment.OR2. Certain LMP* with 1st trimester physical examination. Level 2B Uncertain LMP with 2nd trimester scan (14 0/7 weeks to 276/7 weeks). Level 3A Certain LMP with 3rd trimester scan – 28 0/7 weeks + OR Certain LMP with confirmatory 2nd trimester FH OR Certain LMP with birth weight OR Uncertain LMP with 1st trimester physical examination. Level 3B Uncertain LMP with FH. OR Uncertain LMP with newborn physical assessment. OR Uncertain LMP with Birth weight Definitions of LMP, birth weight and physical assessment in article.	[Quinn, 2016]

GlaxoSmithKline Biologicals **Vaccines R & D** **Protocol Amendment 2**	
eTrack study number and Abbreviated Title	207636 (EPI-RSV-008 BOD)
Amendment number:	Amendment 2
Amendment date:	03-JUL-2018
Co-ordinating author:	PPD, Lead Science Writer

Rationale/background for changes:

The protocol has been amended to reflect the following changes and provide the following clarifications / corrections.

- The title and detailed title have been re-phrased in an effort to improve their clarity.
- The Glossary of terms has been updated.
- Objectives and endpoints have been re-phrased for improved consistency with epidemiological terminology.
- In the inclusion criteria for pregnant women, language regarding informed consent has been clarified.
- Language describing inclusion criteria for infants has been clarified.
- For infants, a Month 6 visit has been added.
- Memory aids have been replaced with Diary cards.
- Subject cards have been added.
- An interim analysis has been added.
- Laboratory assays described in Appendix B have been updated.
- Laboratory addresses in Appendix B have been updated.
- Additional editorial changes have been made to ensure consistency with the modifications noted above, and typographical errors have been corrected.

Text that has been moved or added is presented in bold italics and deleted text in ~~strikethrough~~ in the following sections.

Global changes:

Global additions/replacements are displayed in boldface italics in the document but are not enumerated word by word here.

US spellings replace UK spellings of terms such as hospitali~~s~~***z***ation, p~~ae~~diatric, h~~ae~~matology, enrol***l***ment, labo~~u~~r, and tit***e***r~~e~~.

"~~Maternal/fetal~~" has been replaced throughout with the term "***maternal***."

"Difficulty breathing" has been replaced with "Difficulty ***in*** breathing."

Where reference is made to specifically to the first 28 days of life, the term "~~neonate/infant~~" has been replaced with the term "***neonate***."

Title:

A ~~Prospective Epidemiological~~ prospective epidemiological study of ~~Outcomes~~ ***pregnancy outcomes*** and ***of*** events of interest in pregnant women, ~~Neonates~~ neonates and ~~Infants~~ infants (PE***P***NI)

Detailed Title:

A prospective epidemiological study of women ~~as of~~ ***between 24-27*** weeks of pregnancy~~and their infants up to 1 year of age,~~ to describe ~~maternal, fetal and neonatal~~ ***pregnancy outcomes***~~, pregnancy-related and /infant~~ ***and events of interest*** ~~and~~ ***in*** the ~~occurrence~~ ***mother and neonate, as well as determine incidence in*** ~~neonates~~ infants of RSV LRT***I and RSV hospitalization***.

Contributing Authors:

Two lists are now provided. The first is a list of authors who contributed to Amendment 2. The second is a list of authors who contributed to previous versions of the document. Persons who appear as contributing authors for the first time are:

- PPD ***, Clinical Research and Development Lead***
- PPD ***, Expert Epidemiology Biostatistician***
- PPD , Clinical Trial Supply manager
- PPD ***, Clinical Read-Out Team Leader***
- PPD ***, Safety Physician***
- PPD , Study Delivery Lead

PPD **replaces** PPD as the CEPL**.**

Glossary

Child	A young human being below the legal age of majority (generally ≤ < 18 years of age).
Enrollment	***Pregnant woman who meet all eligibility criteria at the Screening visit and return to the study site for Visit 1 are considered enrolled. Live born neonates who meet all eligibility criteria and complete Visit 1-NB are considered enrolled.***

GAIA	***Global Alignment of Immunization Safety Assessment in pregnancy. A project that aims to improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in low to middle income countries .***
Local healthcare provider	***A healthcare provider who provides subjects with medical care per local standards. This individual may or may not be a member of the study staff.***
Neonatal events of interest	~~Events as described in~~ ***Clinically significant events that occur from birth through 28 days of age and may be considered adverse events if they occur after vaccination. They are listed in*** Section 11.1 ~~that occur from birth through 28 days of age.~~***and described in detail in APPENDIX D.***
Parental concern	***The parent(s) / Legally Acceptable Representative(s) or their designates are concerned about the infant's respiratory tract illness or general health and intend to seek medical care***
Pregnancy related events of interest	~~Events as described in Section 11.1 that occur from ***Visit 1*** through Visit 6 (Day 42).~~***Clinically significant events that occur up to 42 days after delivery and may be considered adverse events if they occur after vaccination. They are listed in Section 11.1 and described in detail in APPENDIX D***.

Synopsis:

Rationale for the study:

This multi-country study will enroll pregnant women ≥ $24^{0/7}$ weeks and <$28^{0/7}$ weeks gestational age (GA). ***Study procedures in this protocol are defined to ensure that maternal and neonatal events of interest are captured. They are not intended to replace procedures performed by local healthcare providers as part of standard care.*** Prenatal screening and care will be provided by local healthcare providers ~~as much as possible and information will be collected and recorded in this study's electronic case report form (eCRF~~***(in accordance with local standards***).

- End of Study (EoS): … samples collected up to ***Visit*** ~~3~~ ***4-NB.***.
- Epoch 003: … ending at ***Visit*** ~~3~~ ***4-NB*** (1 year post-birth).

Background and Rationale (Section 1.1 and Synopsis "Rationale for the Study and Study Design")

…Several marketed vaccines are already recommended for and routinely administered to pregnant women, including influenza, tetanus and Tdap vaccines (~~MMWR 2013, ACIP 2012).~~***CDC 2013a, CDC 2013b***). There are also a number of maternal vaccines in development that aim to protect neonates and infants from ~~additional~~ pathogens~~including~~ ***in addition to*** respiratory syncytial virus (RSV). GlaxoSmithKline (GSK) is developing an investigational vaccine for use in pregnant women, against RSV disease. Of note ~~these vaccines are~~ ***this vaccine is*** developed solely for immunization in pregnancy.

Maternal immunization is implemented worldwide and has the potential to make a major contribution to reducing RSV lower respiratory tract infections (LRTI) and ~~other disease~~ ***the*** burden ***of other diseases*** in infants globally.… GSK is proactively addressing potential challenges of conducting clinical trials in pregnant women in low- and middle income countries ***(LMIC)***.

~~Understanding~~ ***Before conducting clinical trials it is important to understand*** the ***frequency of pregnancy outcomes and the*** maternal ~~, fetal,~~ and neonatal outcomes and events of interest ***(i.e. clinically significant events that may be considered adverse events if they occur after vaccination) in each setting*** ~~prior to conducting~~ ***where clinical trials*** ~~is critical~~ ***may be conducted*** for ***better*** interpretation of safety data. Also, to ensure safety of the participating women, and to characterize the safety profile of the product, adverse events (AEs) in pregnancy should be appropriately detected and managed. This study addresses gaps in understanding of anticipated rates of pregnancy outcomes ~~and~~ ***as well as*** events of ***interest***~~Further~~***in pregnant women and neonates***. ***Furthermore***, this study will be conducted at potential sites for future maternal immunization trials and will help assure the capacity of sites to detect and manage clinically significant events of interest in pregnant women and their neonates. ~~It will also establish surveillance mechanisms for infections and events of interest.~~

Secondarily, the study will establish surveillance mechanisms for RSV infections ***in the neonate/infant(through the first 12 months of life.*** Whilst there is good documentation of the global burden of RSV disease, incidence of RSV-LRTI according to the World Health Organization (WHO) 2015 case definitions [Modjarrad , 2016] is ~~lacking~~ ***limited*** in the literature***, particularly in many LMIC settings***. Hence, this study will also estimate the incidence of infant RSV-LRTI using WHO case definitions across geographically distinct locations to support incidence rate assumptions for planning of future efficacy trials.

Section 1.1 only: ***Standardization of surveillance methodology and case definitions (applicable to maternal immunization AEs) may support comparison of data across different countries*** [Jones , 2016].

Rationale for the Study Population (Section 1.1.1 and Synopsis)

The intention of this ~~trial~~ ***epidemiological study*** is to obtain an estimate of the background rate of adverse pregnancy outcomes ***and events*** that ~~will~~ ***may*** be seen in future vaccine trial populations and, ***separately***, to assess whether sites are suitable for Phase II/III vaccine trials.

Rationale for the Surveillance ~~System for the detection~~ of pregnancy related events of interest (Section 1.3)

There are particular challenges in conducting clinical trials in pregnant women, among them limited data on background rates of ***pregnancy outcomes as well as what may be observed in clinical trials as*** maternal and neonatal ~~outcomes and~~ adverse events.

~~This study is not intended to provide comprehensive antenatal care or to replace local antenatal standard of care, but rather to leverage the data (e.g., clinical findings, diagnoses, laboratory results) captured in local antenatal standard of care.~~ ***~~Information obtained from~~ s***~~tudy specific procedures and laboratory~~ ***~~tests~~*** ~~(e.g. blood sampling, urine dipstick) is not to be relied upon for clinical management of study subjects.~~

To achieve these goals, GSK will be guided by the WHO recommendations on antenatal care for a positive pregnancy experience [WHO, 2016] ***and the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) case definitions*** [Bonhoeffer , 2016; Bauwens , 2016; Kochhar , 2017]. ***Standardization of surveillance methodology and case definitions (applicable to maternal immunization AEs) may support comparison of data across different countries*** [Jones , 2016].

The number and timing of study visits was informed by WHO recommendations on antenatal care [WHO, 2016]. However, local standards of care differ ***from*** country-~~by~~-***to*** country. Women should follow the local standard of care. Study ~~visits~~ ***data*** will be ~~used to collect and record~~ ***collected***, ***in part, from records of*** the data obtained during the locally recommended antenatal care visits.

In this study, best effort***s*** will be made to work with local healthcare providers to collect the key data on maternal, fetal ~~and~~, neonatal ***and infant*** health from routine health records to avoid duplication and an undue burden on the trial subjects.

Rationale for the use of Global Alignment of Immunization safety Assessment in pregnancy (GAIA) case definitions (Section 1.4)

GAIA, a Brighton collaboration project, aims to develop standardized case definitions and criteria for diagnostic certainty of maternal ***outcomes and events of interest*** and neonatal ~~outcomes~~ ***events of interest*** in the context of immunization trials [Bauwens 2016, Bonhoeffer 2016, Kochhar 2017].

Rationale for the active and passive surveillance for RSV associated respiratory tract infections (RTI) with suspicion of difficulty in breathing/wheezing or with parental concern in neonates/ infants (Section 1.5)

~~As part~~ ***The implementation of*** ~~the RSV maternal program, this study aims to set up the~~ ***surveillance will also assist in establishing robust infrastructure and*** processes for RSV-LRTI and RSV hospitalization detection~~, for site preparedness~~ ***in future vaccine trials.***

Benefit Assessment (Section 2.2)

Study procedures aim to ensure ~~adequate~~ surveillance for maternal ~~and neonatal~~ ***outcomes*** ~~of pregnancy~~ and events of interest ***and neonatal events of interest***. The attention to ~~adequate~~ surveillance ~~of these events~~ may enhance the ability to detect these ***safety*** events and to refer subjects for management according to local standard of care. The protocol also includes procedures that may enhance surveillance for ***RSV, and possibly other*** lower respiratory tract infections, in neonates and infants. Thus, the procedures described in this protocol may enhance the ability to detect these events ***or infections*** and to refer subjects for management according to local standard of care.

Data collected during the study may enhance understanding of the ~~incidence~~ ***frequency*** of maternal events of interest in women with low risk pregnancies, neonatal events of interest, and ***RSV-associated*** lower respiratory tract infections ~~associated with RSV infection~~ in neonates and infants.

Overall Benefit:Risk Conclusion (Section 2.3)

…….and by the knowledge gained about the ~~incidence~~ ***frequency*** of ~~medical~~ events of interest.

Primary Objectives (Section 3.1 and Synopsis)

- ***To determine the frequencies*** of ~~*Visit 1*~~: ~~To~~ ~~detect and describe~~ pregnancy outcomes.
- To ~~detect and describe~~ ***determine the frequencies of*** pregnancy related events of interest.

  from enrollment (Visit 1) through 42 days after delivery (Visit 6).

  (Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.)
- To ~~detect and describe~~ ***determine the frequencies of*** neonatal events of interest.

Neonatal AEs of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study.

Secondary Objectives (Section 3.2 and Synopsis)

In healthy pregnant women with uncomplicated pregnancies ~~as of Visit *1* at enrollment~~:

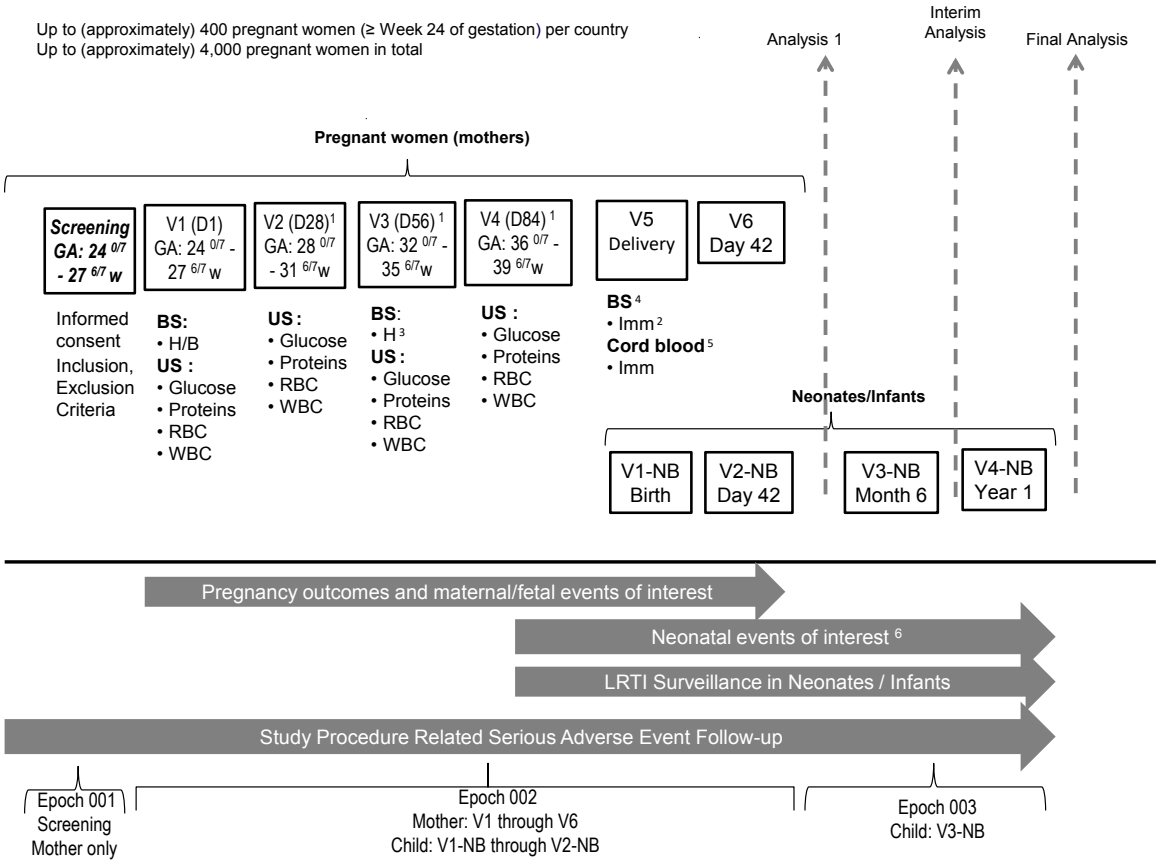
- To ~~detect and describe~~ ***determine frequencies*** of pregnancy related events of interest according ~~(where these are specified)~~ to GAIA levels of diagnostic certainty ***(where these are specified)*** (APPENDIX D) ***from enrollment (Visit 1) through 42 days after delivery (Visit 6). (Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.)***
- To describe ***the distribution of*** RSV-A antibody titers in maternal blood at delivery
- To ~~detect and describe~~ ***determine frequencies of*** neonatal events of interest according ~~(where these are specified)~~ to GAIA levels of diagnostic certainty ***(where these are specified).***(APPENDIX D).
  Neonatal AEs of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study.
- To describe ***the distribution of*** RSV-A antibody titers in cord blood ***at delivery***.
- To ~~describe occurrences of~~ ***determine the incidence*** of ***all, of severe, and of very severe*** RSV-lower respiratory tract infections (LRTI***s***).
- To ~~describe occurrences~~ ***determine the incidence*** of RSV hospitalization.
- ***Refer to the GLOSSARY OF TERMS for the definition of enrollment.***

Tertiary Objectives (Section 3.3 and Synopsis)

- To ***describe*** ~~the association~~ ***co-infections*** of ***RSV-LRTI with*** other respiratory viruses ~~with the occurrence of RSV-LRTI~~ in infants.
- To ~~describe~~ ***estimate*** the association ~~between~~ ***of*** RSV-LRTI in ***neonates/***infants and the level of RSV neutralizing antibodies in cord blood.
- To ~~describe~~ ***determine*** risk factors for ***pregnancy-related*** and neonatal events of interest
- If deemed necessary, to further characterize the immune responses to ~~the diseases under study~~ ***RSV and other infections*** in pregnant women/mothers and infants~~, and / or to explore further parameters in pregnant women (mothers) or their infants.~~***(based on maternal serum and cord blood)***.

Study Design Figure 1 and accompanying footnotes (Section 4.0)

The design figure has been adjusted to add a 6-month visit in infants and to indicate that an interim analysis will be performed. The entire figure is reproduced below.



Study Design Footnotes

Refer to Section 11.11 for additional information about the analyses indicated above.

[4] ~~Blood~~ ***Allowed interval for blood*** sample ~~should be collected within~~ ***collection begins with start of labor (e.g. when the mother arrives at the hospital to deliver and an intravenous line is inserted) and ends*** 72 hours after delivery.

[6]Neonatal ~~conditions~~ ***events of*** interest occur (by definition) between 0 and 28 days after birth. They will be reported once site staff become aware of them (whether this occurs during the first 28 days after birth, or at a later time).

Study population (Section 4.0 and Synopsis)

- Study population: The study will be conducted in multiple countries, in pregnant women and their ~~neonates~~***infants***.

Sampling schedule for pregnant women/mothers, Table 1 and Synopsis Table 1, footnote 5:

[5]This sample may be collected ~~as~~ from start of labo~~u~~r (e.g. when the mother arrives at the hospital to deliver and an intravenous line is inserted)) ***through 72 hours after delivery***.

- Sampling schedule for **neonates/infants**: ***Surveillance for RSV LRTI will be conducted in infants through the 12 month study period.*** During ~~the~~ ***this*** 1-year post-birth surveillance period, for each RTI with suspicion of difficulty in breathing, or wheezing, or with parental concern, a nasal swab will be collected at a visit to assess potential ***RSV associated RTIs/***LRTIs.
- Epoch 003: Follow-up of infants starting 43 days post-delivery/birth and ending at Visit ~~3~~ ***4***-NB (1 year post-birth).
- Surveillance for pregnancy outcomes and pregnancy-related events of interest (Section 8.5.8) ***that occur*** from Visit 1 up to 42 days after delivery ***(Visit 6).***

Footnotes to Table 3:

[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. ***In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.***

[5] RSV sampling and testing is based on ~~medical~~ judgment of medical practitioner or driven by algorithm.

[6] ***Hospitalization is defined as*** ~~a medical decision that the child requires~~ ***admission for observation or treatment based on the judgement of a health care provider***.

Pregnancy related events of interest (Section 5.1)

Pregnancy related events of interest are ***briefly defined in the GLOSSARY OF TERMS*** …….

Neonatal events of interest (Section 5.2)

Neonatal events of interest are ***briefly defined in the GLOSSARY OF TERMS***…

Inclusion Criteria for Enrolment (Section 6.2)

Pregnant Women (Section 6.2.1)

- ***Individuals who*** ~~gave~~ ***give written or witnessed/thumb printed informed consent after the study*** ~~had~~ ***has been explained according to local regulatory requirements.*** ~~Informed~~
  - ***The informed consent given at screening should either include*** consent for ~~study~~ ***both the mother's*** participation ***and participation*** of the ~~mother should be obtained from the mother or~~ ***infant after*** the ***infant's birth (if consistent with local regulations/guidelines), or consent for the mother's participation and expressed willingness to consider permitting the infant to take part after the infant has been born (if local regulations/guidelines require parent(s) to provide an additional informed consent after the infant's birth).***
  - ***Both*** mother and father~~, as applicable by local law, prior to performance of any study specific procedures;~~ ***should consent if local regulations/guidelines require it.***
- ~~Individuals ***(mother or mother and father)*** who, at the time of ***their informed consent***, express willingness to enroll their infant in the study at the time of birth.~~

Infants (Section 6.2.2):

- ~~Infants live-born to enrolled women that resulted from the enrolled pregnancy~~Infants who were ***in utero at the time maternal (and paternal, if required***) informed consent ***was given, and*** who are live-born.
- ***If local law requires it:***Written or witnessed/thumb printed informed consent for study participation of the infant obtained ~~from the infant's mother and/or father, as applicable by local law, or~~ ***parent(s)/LAR(s)*** within 10 days of birth.

General Study Aspects (Section 8.2)

~~Supplementary~~ ***Critical*** study conduct information not mandated to be present in this protocol is provided in the Study Procedures Manual (SPM). ***As such, the SPM should be viewed as a companion document that should be read carefully to fully understand the study protocol.*** The SPM provides the investigator and the site personnel with ~~administrative and~~ detailed ~~technical~~***operational*** information that ***is essential for correct study execution and*** does not impact the safety of the subjects.

Study ***visits and*** procedures in this protocol are defined to ensure that maternal~~, fetal~~ and neonatal events of interest, ***as well as RSV-associated LRTIs and RSV hospitalization in infants,*** are captured. Prenatal screening and care will be provided by local healthcare providers ~~and information will be collected and recorded in the eCRF.~~***(in accordance with local standards).***

Study visits are not intended to replace local standard of care antenatal visits. If local standard of care recommends additional visits/medical evaluations during pregnancy, women participating in this study should comply with their regular antenatal care visit schedules, per local recommendations.

Study procedures are not intended to replace procedures performed by local healthcare providers as part of standard care.

Outline of Study Procedures (Section 8.3)

Table 4, List of Study Procedures.

No columns were added with this amendment. Only rows where changes were made have been presented. Only footnotes where changes were made have been presented.

Gestational age	**≥ 24 0/7 - 27 6/7**	**24 0/7 – 27 6/7**	**28 0/7 - 31 6/7**	**32 0/7 - 35 6/7**	**36 0/7 - delivery**			
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	**Screening**	**Visit 1**	**Visit 2** [2]	**Visit 3** [2]	**Visit 4** [2]	**Visit 5**	**Visit 6** [3, 4]	**Additional antenatal/medical evaluations** ~~(external to study visits/procedures)~~[4] [5]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Eligibility Review and Confirmation								
Informed consent [1]	●							
~~Inform study paediatrician and/or staff of subject's participation~~ ***Ensure that site study physicians (both obstetrician(s) and pediatrician(s)) are informed***		O				O		
Medical History / Examinations								
Distribute Maternal Subject Card		***O***						
Distribute maternal ~~health ***memory aid***~~ ***diary card***		O	O	O	O	O	***O***	
Review and collect maternal diary card			***O***	***O***	***O***	***O***	***O***	
Transcribe applicable diary card data to the eCRF			●	●	●	●	●	

Gestational age	**≥ 24 0/7 - 27 6/7**	**24 0/7 – 27 6/7**	**28 0/7 - 31 6/7**	**32 0/7 - 35 6/7**	**36 0/7 - delivery**			
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	**Screening**	**Visit 1**	**Visit 2** [2]	**Visit 3** [2]	**Visit 4** [2]	**Visit 5**	**Visit 6** [3, 4]	**Additional antenatal/medical evaluations** ~~(external to study visits/procedures)~~[4] [5]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Travel history to, or living in, ~~Zika virus endemic~~ ***countries/regions*** with Zika virus ***transmission***	O	●						
Record results of General and Obstetric examination [10]	●	●	●	●	●		●	● [13]
Check and record prescription medications, vaccinations, folate and/or iron (independently or included in a multivitamin) [12]	●	●	●	●	●	●	●	●

Gestational age	**≥ 24 0/7 - 27 6/7**	**24 0/7 – 27 6/7**	**28 0/7 - 31 6/7**	**32 0/7 - 35 6/7**	**36 0/7 - delivery**			
Epoch	**Epoch 001**	**Epoch 002**						
Type of contact	**Screening**	**Visit 1**	**Visit 2** [2]	**Visit 3** [2]	**Visit 4** [2]	**Visit 5**	**Visit 6** [3, 4]	**Additional antenatal/medical evaluations** ~~(external to study visits/procedures)~~[4] [5]
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Biological Specimens / Laboratory Test Results								
Record results of local hematology/ biochemical analysis (~~***up to*** 10 ***Visit 1~5.5 ml; Visit 3~2 ml – hemoglobin only)*** [6]		●		●				●[13]
Record results of urine dipstick to check for presence of proteins, glucose, RBC, WBC [7]		●	●	●	●			●[13]
Record results of any clinically significant abnormal laboratory tests (including positive urine culture) if performed by local healthcare provider and available [5]		O	O	O	O	O	O	●
Outcomes and Events of Interest								
Record pregnancy-related events of interest and other clinically significant events or diagnoses that could impact the pregnancy		●	●	●	●	●	●	●

[1] ***Refer to Section 6.2.1, fifth bullet.***

[8] ~~At Visit 3, only hemoglobin testing.~~

[13] Beginning the month before the estimated date of conception and while on study. (Routine ~~concomitant~~ medications administered during labor and delivery need not be collected.)
[14] Record ~~If~~ clinically significant ***abnormal results***

Table 5, List of Study Procedures

One column was added to account for the 6 month visit. Because a column was added, the amended table has been presented in its entirety. All footnotes (since only 1 was unchanged) have also been provided.

Epoch	***Epoch 002***		***Epoch 003***		***Epoch 002 and Epoch 003***	
Age	**0-10 days**	**42 Days**	***6 Months***	**12 months**	**0-12 months**	
Type of contact	**Visit 1-NB**	**Visit 2-NB [b]**	***Visit 3-NB [b]***	***Visit 4-NB [b]***	**Contact for active/ passive surveillance**	**Visit to assess potential LRTI [a]**
Timepoints	**Birth**	**Day 42**		**Y1**		
Check inclusion/exclusion criteria	●					
Obtain ***post-delivery*** informed consent ~~of~~ ***from*** parent(s)/LAR(s) ***if required per local regulations***	● [a]					
Record infant's subject number	●					
Record Apgar assessment	●					
Record demographic data	●					
Record lifestyle characteristics		●				
Distribute Infant's Subject Card	O					
Distribute ***infant*** ~~health and RTI memory aid~~***diary card [d]***	O	O	***O***			O
Review infant diary card		***O***	***O***	***O***		***O***
Collect infant diary card [e f]		***O***	***O***	***O***		***O***
Transcribe applicable infant diary card data to eCRF		●	●	●		●
Weight, length, head circumference, results of targeted medical history, and results of physical examination	●	●	●	●		
Record prescription medications / vaccinations	●	●	●	●	●	●
Record neonatal events of interest	●	●	●	●		
Clinical evaluation of potential LRTI						●
Nasal swab [b]						● [c]
Record all hospitalizations and clinically significant events	●	●	●	●	●	●
Record SAEs related to study ***participation***	●	●	●	●	●	●
Study conclusion				●		
Investigator sign-off on eCRF before analysis		●	● [g]	●		

[a] If local regulations require that confirmation of consent for the infant's participation be obtained at birth.

[b] ***Visits 2-, 3-, and 4-NB*** ~~Visit 2-NB (Day 42), Visit 3-NB (Year 1)~~ ***and LRTI assessment visits may take place in the subject's home (if the standard of care allows for home visits), at the investigator's clinical facility or at another facility per the investigator's judgment.***

[c] If more than one assessment visit is conducted to evaluate a potential LRTI episode, additional nasal swabs may be collected at the discretion of the Investigator.

[d] Distribute at V1-NB: Distribute additional diary cards at subsequent visits as needed.

[e] ***Collect diary cards that are fully filled out and / or document (L)RTI episodes that have ended (as defined in Section 8.6.5.1). Provide new diary cards as needed.***

[f] ***Collect all diary cards for potential RTIs that are considered resolved. Collect the diary card for the current potential LRTI once the episode has ended (as defined in Section 8.6.5.1).***

[g] ***After at least 50% of infants have completed Visit 3-NB, an interim analysis on data that is as clean as possible will be performed.***

Table 6: Intervals between study visits/contacts/observations

Interval	Optimal interval***	Allowed interval**
Birth → Visit 3-NB	***180 days***	***166 -194 days***
Birth → Visit ~~3~~ 4-NB	***365 days***	***351 –~~407~~- 379 days***

Eligibility Review and Confirmation (Section 8.5.1)

- Obtain informed consent as ~~The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. Refer to Section 7.1 for the requirements on how to obtain informed consent, ***as*** appropriate. The father of the unborn child should also sign the mother's ICF, if required by the local regulations/guidelines~~***described in Sections 6.2.1 and 7.1***.
- ~~Inform~~ ***For eligible pregnant women who complete visit 1 (are enrolled): ensure that site study*** ~~paediatrician~~ ***physicians (both obstetrician(s) and pediatrician(s)) are informed***. ***In particular,*** the study p***e***diatrician and/or staff ~~of the pregnant woman's participationA copy of the informed consent~~ ***should be*** ~~forwarded to the study paediatrician and/or staff~~ ***notified*** as soon as possible after a pregnant woman's enrolment to ensure the study p***e***diatrician is informed ~~in a timely manner~~ of the approximate date of delivery and potential enrolment of the neonate.

History and Examinations for pregnant women/mothers **(Section 8.5.2)**

- ~~Distribute ***the Maternal Health Memory Aid. It is intended to serve as a reference during study visits/contacts, to help the subject provide the investigator/ study staff with protocol-specified data (and contact information for other healthcare providers, so medical records may be requested if required). (Refer to the SPM for details).***~~
- Distribute ***the Maternal Subject Card*** (Section 9.3).
- ***Distribute the Maternal Diary Card*** to the subject ***(Section 8.5.4)***.
- Record demographic data, which may include (but is not limited to) information such as race, month and year of birth, ***and*** ethnicity~~***and geographic location***~~.
- Record information about whether the subject has travelled to / is living in ~~Zika virus endemic~~***countries / regions with*** Zika virus ***transmission***.

Maternal Diary Card **(Section 8.5.3)**

A maternal diary card will be provided to each subject at visit 1, then collected and replenished throughout the study as needed. It will document any prescription medications, folate and/or iron (independently or included in a multivitamin) taken, any vaccinations received during pregnancy and after delivery, and any additional visits the subject may make to a healthcare provider not affiliated with the study.

The diary card will be reviewed with the subject during study visits. If review indicates that the subject visited a healthcare provider not affiliated with the study, study staff should (if permitted by local regulation) contact that healthcare provider to obtain the medical record(s) for the visit.

Refer to the SPM for additional details.

Biological Specimens / Laboratory Data for pregnant women/mothers (Section 8.5.4)

- If performed by local healthcare provider and ***results are*** available, the investigator/site staff will also…….

Labor and Delivery (Section 8.5.4)

- ~~Medications~~ ***Any*** medications administered during labor and delivery ***as per standard of care*** if not ***considered*** routine

~~Concomitant medications~~ Medications**,** vaccinations, and supplements ~~for~~ ***administered to*** pregnant women/mothers ***as per standard of care*** **(Section 8.5.6)**

~~See Section 8.5.6 for medications administered during labor and delivery~~

Outcomes and Events of Interest in pregnant women/mothers (Section 8.5.7)

- If there is no live birth, all study visits and procedures related to the maternal subject should ***still*** be followed up to study end.
- Maternal events of interest (including, but not limited to, those described in Section 11.1.1) occurring up to Visit 6 (Post-delivery ~~Month 1.5~~***Day 42***) should be recorded in the eCRF

Additional Antenatal / medical evaluations external to study visits / procedures (Section 8.6.8)

For any additional antenatal / medical evaluations at which a pregnancy related event of interest is identified, record information that supports the diagnosis of the event, ***if available.***

Eligibility Review and Confirmation for Neonates **(Section 8.6.1)**

- Check all applicable inclusion and exclusion criteria ***as described in Sections 6.2.2 and 6.3.2.*** ~~A neonate who does not meet the eligibility criteria should be considered ineligible.~~
- ~~Obtain informed consent from parent(s) / LAR(s) at Visit 1-NB, as per local requirements.~~

History and Examinations for Neonates / Infants **(Section 8.6.2)**

- Record lifestyle characteristics. Data may include (but are not limited to) passive smoking and ~~***day-care attendance***~~ ***contact with young children under 6 years of age***.
- Distribute ***the Infant*** ~~Health and RTI Memory Aid~~ ***Subject Card*** to the parent(s)/LAR(s)/designate(s). ~~The memory aid is intended to serve as a reference during study visits/contacts, to help~~ (Section 9.3).
- ***Distribute the Infant Diary Card*** to the parent(s)/LAR(s)/designate(s) ~~provide the investigator/ study staff with protocol-specified data (and contact information for other healthcare providers, so medical records may be requested if required).~~ (***Section 8.6.3***).

Infant Diary Cards (Section 8.6.3)

[Note that numbering for all subsections that follow this *new* section was incremented, and the adjustments are reflected in updated cross references].

Infant diary cards will be provided at the infant Visit 1 NB. They should be completed by the Parent(s)/LAR(s)/designate(s) of the infant subject.

The infant diary cards will be used to document:

- ***RTI symptoms experienced by the infant, including start and end dates for those symptoms, and***
- ***Additional visits to a pediatric healthcare provider not affiliated with the study, as well as prescription medications (including those taken to treat an RTI) and vaccinations administered to the infant. (If the infant subject was taken to a healthcare provider not affiliated with the study, the study staff should (if permitted by local regulation) contact that healthcare provider to obtain the medical record(s) for the visit.)***

Documentation of RTI episodes (Section 8.6.3.1):

One diary card should be completed for each RTI episode whether or not an Assessment Visit (Section 8.6.6) takes place. An RTI episode has "ended" if it satisfies the criteria in Section 8.6.5.1.

At each study visit (including any assessment visits), RTI episode(s) may have ended or may be ongoing.

For any RTI episode(s) that has/have ended by the time of a study visit:

- ***Study staff should collect the Diary card(s), and replenish the parent(s)/LAR(s)/designate(s) supply of blank cards as needed.***

For any RTI episode that is ongoing at the time of a study visit (including any assessment visit):

- ***Study staff should review the diary card, make a photocopy of it, and return it to the parent(s)/LAR(s)/designate(s) so information can continue to be collected until the episode has ended.***

- ***Once the episode has ended, study staff must collect the completed diary card by a site visit, home visit., or postal mail, whichever is most effective based on local practice. The site should make every effort to collect completed diary cards as soon after the end of an episode as possible. If diary card collection occurs during a visit to the study site or to the subject's home, a brief clinical evaluation may be performed to confirm that the episode has ended.***

Refer to the SPM for additional details.

Surveillance for Neonatal events of interest (Section 8.6.4)

~~In addition, the investigator or study staff will perform (if not performed by local healthcare provider) a minimum of 2 clinical examinations: one at birth (or up to 72 hours after birth), and another at approximately 42 days of age.~~

Surveillance for episodes of potential Lower Respiratory Tract Infection (Section 8.6.5)

Definitions (Section 8.6.5.1)

- ~~snot~~ ***nasal discharge*** running freely out of the infant's nose (runny nose), or
- An RTI episode starts on the day when (per parental report, as ***written in the Diary Card and/or provided verbally during an assessment visit***) the first RTI symptom started.
- An RTI episode ends on the day when (per parental report, ***as written in*** ~~the last RTI symptom~~ ***Diary Card and/or provided verbally during an assessment visit) either cough or difficulty in breathing has*** resolved***, whichever resolves later***.
- There must be at least 7 symptom-free days between 2 consecutive RTI episodes***; the only exception is runny nose, which is a symptom that can persist during that minimum 7-day period that would distinguish one episode from a new episode***.

Active surveillance (Section 8.6.5.3)

Three attempts should be made to contact the infant's parents/ LAR(s) (or their designates) within the week of a scheduled contact ~~before it is abandoned~~. ***If these attempts are unsuccessful, that active contact*** is ***considered a missed contact. The next active contact will be made according to schedule.***

Decision to conduct a visit to assess a potential LRTI (Section 8.6.6)

An assessment visit will be conducted as soon as possible, ideally within 3 calendar days after learning of the potential LRTI case. ***Note that the visit may be conducted, and a nasal swab collected, even if beyond the ideal 3-day window as long as symptoms are ongoing.***

Nasal Swab (Section 8.6.7.3)

A nasal swab will be collected using sponsor-provided supplies and sent to the sponsor ***(or sponsor-designated)*** laboratory for detection of RSV-A/B using quantitative RT-qPCR.

If more than one assessment visit is conducted to evaluate a potential LRTI episode, additional nasal swabs may be collected ***(using sponsor-provided supplies and sent to the sponsor laboratory)*** at the discretion of the Investigator.

Note: ***Only the results generated by the sponsor (or sponsor-designated) laboratory (analyzing nasal swabs collected using sponsor-provided supplies) will be used when applying the case definitions for data analysis in Table 3.*** If other nasal swabs are collected and tested locally as per routine standard of care, results will be ***required to be*** entered into the eCRF~~. However, only the sponsor laboratory results~~ ***however this will*** ~~be used when applying the~~***not form part of the sponsor's application of case definitions for data analysis*** ~~in Table 3.~~.

Therefore where mandated by the protocol every effort should please be made to obtain samples for analysis by the sponsor (or sponsor-designated) laboratory.

Missed assessment visit (Section 8.6.7.4)

~~Note that~~ ***If*** the ***criteria for an assessment*** visit ~~may be conducted, and a nasal swab collected, as long as~~***have been met, but the visit cannot take place while*** symptoms are ongoing***, it is a missed assessment visit.***

If it is truly not possible to perform an assessment visit (for example, if the child develops a potential LRTI while the family is travelling, and all symptoms have resolved by the time the family returns), then the LRTI assessment visit page of the eCRF should be filled in as completely as possible using available medical ***history and medical*** records.

Follow-up after an assessment visit to evaluate a potential LRTI (Section 8.6.8)

~~Additional~~ ***After an RTI episode that resulted in one or more assessment visits has ended (Section 8.6.5.1), site staff will ensure that the diary card for that episode is returned to the site via site visit, home visit, or postal mail (depending on the most effective local best practice for prompt retrieval of the completed infant diary card following the end of an RTI episode).***

Important details ~~can be found~~ ***are provided*** in the SPM.

Biological sample handling and analysis (Section 8.10)

- ….. to allow GSK or a contracted partner use ***of*** the samples for future research …..

Table 7 Biological Samples

Sample Type†	Quantity	Unit	Timepoint	Group
Samples preferentially collected by local health care provider per local practice[1]				
Maternal Blood for hematology/ biochemistry [1]	Up to ~~10~~***5.5***	ml	Visit 1 (Day 1)	All Pregnant women (mothers)
Maternal Blood for hemoglobin	Up to ~~10~~ ***2***	ml	Visit 3 (Day 56)[2]	

[2] ~~Hemoglobin only~~

Table 8 Humoral immunity (Antibody determination

System	Component	Method****	Kit / Manufacturer	Unit	Cut-off	Laboratory***
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALISATION	In house	ED60	To be defined	GSK Biologicals***** or GSK designated lab********

Ab = antibody; **ED60** = serum dilution inducing 60% inhibition in plaque forming units.

~~* Assay cut-off and unit might be subject to change during the course of the study (e.g. in case of requalification, revalidation or standardization). In this case, this will be documented in the study report.~~

*** Refer to APPENDIX B for the laboratory addresses.

***** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.

******** Testing may possibly be outsourced to a laboratory designated by GSK. In this case, the method and unit may be different than the one indicated in this table.

Table 9 Molecular Biology

For Multiplex real time PCR of nasal swabs, Allplex™ Respiratory Panel ***(Seegene)*** or equivalent** * has been added as the kit manufacturer

Haematology, biochemistry and urinalysis (Section 8.10.3.3)

The investigator~~s~~ will perform ~~a~~ urine dipstick test***s*** to detect ~~for~~ the presence of proteins, glucose, RBC***s*** and/or WBC***s***. ***These tests do not replace those performed by local healthcare practitioners, per local practice, for clinical management of study subjects*.**

Table 10 Hematology, biochemistry, urine tests: ***neutrophils, lymphocytes, monocytes, basophils, and eosinophils*** have been added as components**.**

Additional tests (Section 8.10.3.4)

Additional exploratory testing on the disease under ***study and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns*** may be

…...

Table 11 Immunological read-outs

Blood sampling timepoint Type of contact and time point	Group	No. subjects	Component	Component priority rank
Maternal Blood				
Visit 5 (Delivery)	All pregnant women (mothers)	~400 ~~maximum~~ by country	Respiratory Syncytial Virus A Ab (RSV-A neutralising antibody)	1
Cord Blood				
Visit 5 (Delivery)	All pregnant women (mothers) (provides infant antibody levels)	~400 ~~maximum~~ by country	Respiratory Syncytial Virus A Ab (RSV-A neutralising antibody)	1

~~**RSV-A/B** = Respiratory syncytial virus subtype A/B.~~

Table 13 Hematology/blood chemistry

Blood sampling timepoint Type of contact (timepoint)	Group	No. subjects	Component
Visit 1 (Day 1)	All pregnant women (mothers)	~400 ~~maximum~~ by country*	Hematology (Leukocytes, Hemoglobin, Platelets) Biochemistry (ALT, AST, Creatinine, blood urea nitrogen)
Visit 3 (Day 56)	All pregnant women (mothers)	~400 ~~maximum~~ by country*	Hematology (Hemoglobin)

Subject Cards (Section 9.3)

Study subjects/parents/LARs must be provided with the address and telephone number of the main contact for information about the clinical study. The investigator (or designate) must therefore provide subjects/parents/LARs with a "subject card."

For this study, a subject card will be provided to each pregnant woman who enrolls. A second subject card will be provided for each infant who is enrolled.

In an emergency situation these cards serve to inform the responsible attending physician(s) that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

In a non-emergency situation, if subjects visit a local healthcare provider not affiliated with the study, these cards serve to inform the responsible local healthcare provider that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator. Further, subject will have information on the card to contact the study site at any time.

Subjects/parents/LARs must be instructed to keep the subject cards in their possession at all times during the study.

GSK Contact information, GSK Reporting Timeframes, and Regulatory reporting requirements (Section 9.4)

GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies ***(as applicable, per country)*** about the event.

Primary endpoints (Section 11.1.1), Primary Objectives Analysis (Section 11.6) and Synopsis

- ***Pregnancy*** ~~Occurrence of pregnancy~~ related events of interest from Visit 1 through Visit 6. ***(Although pregnancy related events of interest occur within the first 42 days after delivery they may only be detected later, and are to be reported throughout the study.) They***~~These~~
- Neonatal ~~Occurrence of neonatal~~ events of interest from birth through 28 days of age.. ***Neonatal AEs of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study. They***. ~~These~~ include…

Secondary endpoints (Section 11.1.2), Secondary Objectives Analysis (Section 11.7) and Synopsis

- ***Pregnancy***~~Occurrence of pregnancy~~ related events of interest from Visit 1 through Visit 6 (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible)
- ***Neonatal***~~Occurrence of neonatal~~ events of interest from birth through 28 days of age (as defined in primary endpoints) for each GAIA level of diagnostic certainty (where applicable and feasible)
- ~~Maternal~~ RSV-A neutralizing antibody ~~titer~~***titers in maternal blood*** at delivery
- ~~Titers of~~ RSV-A neutralizing ~~antibodies~~***antibody titers*** in cord blood ***at delivery.***
- ***Episode(s)***~~Occurrence~~ of RSV-LRTI from birth up to 1 year of age***.***
- ***Episode(s)*** of~~Occurrence~~ RSV hospitalization from birth up to 1 year of age.

Tertiary endpoints (Section 11.1.3), Tertiary Objectives Analysis (Section 11.8) and Synopsis

- ***Co-infections***~~Occurrence~~ of RSV-LRTI ~~associated~~ with other respiratory viruses ***in infants***, confirmed by PCR of nasal swabs in infants from birth up to 1 year of age:
- ***Potential***~~Occurrence of potential~~ risk factors for ~~maternal, fetal~~ ***pregnancy related*** and neonatal events of interest.
- Any further exploratory ~~immunology to detect disease-related~~ ***characterization of immune*** responses~~, such as but not limited~~ to RSV ~~B neutralizing antibody titers~~.***and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood).***

Derived and transformed data (Section 11.4)

Duration of the study for each subject will be computed as the difference between the date of last contact (i.e., active or passive surveillance contact or the date of the censoring) and the date ~~of enrollment (date~~ when ICF was first signed by ***the subject*** / subject's parent[s]/LAR[s]).

Analysis of primary objectives (Section 11.6)

- To ~~detect and describe~~ ***determine the frequencies of pregnancy outcomes.***

  The number and percentage (with exact 95% CI) of women presenting the following ~~events of interest~~ ***outcomes***: live birth, fetal death/still birth, and elective/therapeutic termination will be reported for each event by presence or absence of congenital anomalies.

- To ~~detect and describe~~ ***determine the frequencies of*** pregnancy related events of interest.

- To ~~detect and describe~~ ***determine the frequencies of*** neonatal ~~related~~ events of interest***.***

Analysis of secondary objectives (Section 11.7)

- To ~~detect and describe~~ ***determine frequencies of*** pregnancy related events of interest according ~~(where these are specified)~~ to GAIA levels of diagnostic certainty ***(where these are specified)*** (APPENDIX D)

- To describe ***the distribution of RSV-A antibody titers in maternal blood*** ~~**collected**~~ ***at delivery.***

- To ~~**detect and describe**~~ ***determine frequencies of*** neonatal events of interest according ~~**(where these are specified)**~~ ***to GAIA levels of diagnostic certainty (where these are specified).*** (APPENDIX D)

- To describe ***the distribution of*** RSV-A antibody titers in cord blood ***at delivery.***

- To ~~**describe occurrences of**~~ ***determine the incidence of all, of severe, and of very severe*** RSV-lower respiratory tract infections ***(***LRTI***s).***

  – ….. from visit 1-NB to visit ~~3~~ ***4***-NB……..

  – Incidence rates of LRTI infections will be calculated, with exact 95% CI~~, taking into account all LRTI events reported in the study during the first year of life. The period at risk would be the whole follow-up time of the subjects during the study.~~

- To ~~describe occurrences~~ ***determine the incidence*** of RSV hospitalization***.***

  – … from visit 1-NB to visit ~~3~~ ***4***-NB…

  – Incidence rates of RSV hospitalizations will be calculated, with exact 95% CI~~, taking into account all RSV hospitalisations reported in the study during the first year of life. The period at risk would be the whole follow-up time of the subjects during the study~~.

Analysis of tertiary objectives (Section 11.8)

- To ~~explore the association of~~ ***describe co-infections of RSV-LRTI with*** other respiratory viruses ~~with the occurrence of RSV-LRTI~~ in infants**.**
  - … from visit 1-NB to visit ~~3~~***4***-NB…….
- To ~~evaluate~~ ***estimate*** the association ~~between~~ ***of*** RSV-LRTI in ***neonates/***infants and the level of RSV neutralizing antibodies in cord blood.
- To ~~describe~~ ***determine*** risk factors for ~~maternal, fetal and neonatal~~ pregnancy-related ***and neonatal*** events of interest.
  - … (such as multiple logistic regression for binary outcomes and multiple Poisson/negative binomial ***and/or other appropriate*** models for count outcomes) ….
- If deemed necessary, to further characterize the immune responses to ~~the disease under study in mothers/infants, or to explore~~ ***RSV and other*** ~~parameters~~ ***infections in pregnant women/mothers*** ~~or their~~ ***and infants (based on maternal serum and cord blood).***

Statistical considerations for interim analyses (Section 11.11.1)

~~All analyses are descriptive. Therefore, the conduct of interim analyses has no impact on interpretation of study results.~~

Interim analysis for RSV LRTIs

An interim analysis will be performed on RSV surveillance data as part of the secondary objective of determining incidence of RSV LRTI. This interim analysis will be performed to obtain preliminary information on the performance of the case definitions used for RSV LRTI, severe LRTI, and very severe LRTI (Table 3). The interim analysis will occur after the database freeze at the time point when at least 50% of infants will have completed 6 months of follow up during the surveillance period following birth. Data cleaning plans will be scheduled as needed to supply data for interim analyses in a timely manner. This interim analysis will be performed on data that is as clean as possible. Preliminary results will be made available in a timely manner for use in the potential adjustment of the RSV LRTI case definitions to be used in pivotal clinical trials scheduled to begin shortly thereafter. The results pertaining to this analysis will be purely descriptive, with no adjustment of type I error, and will be reported in an interim statistical report.

References (Section 14)

Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women. Advisory Committee on Immunization Practices (ACIP) - 2012. MMWR. 2013a ; 62 (7) :131 -135.

Centers for Disease Control and Prevention (CDC). Influenza Vaccination Coerage Among Pregnant Women — United States, 2012–13 Influenza Season. MMWR. 2013b; 62 (38): 787–792.

Appendix A Laboratory Assays

Neutralization assay

~~First, virus~~ ***Virus*** neutralization is performed by incubating a fixed amount of RSV-A ~~long~~ strain (***Long***, ATCC No. VR-26***) or RSV-B strain (18537, ATCC No. VR-1580)*** with serial dilutions of the test serum. ~~Then, the~~ ***The*** serum-virus mixture is ***then*** transferred onto a monolayer of Vero cells (African Green Monkey, kidney, Cercopitheus aethiops, ATCC CCL-81) and incubated for three days to allow infection of ***the*** Vero cells by non-neutralized ~~viruses~~ ***virus*** and the formation of plaques in the cell monolayer. Following ~~the~~ ***a*** fixation ~~period~~ ***step***, RSV-infected cells are detected using a primary antibody directed against RSV (anti-RSV IgG) and a secondary antibody conjugated ~~with fluorescein isothiocyanate~~***to horse-radish peroxidase (HRP),*** allowing the visualization of plaques ~~by~~ immunofluorescence ***after coloration with TrueBlueTM peroxidase substrate***.

- Quantitative ***RT***-PCR able to discriminate RSV-A and RSV-B subtypes:
- Qualitative multiplex ***RT***-PCR for detection of a panel of viruses.

A qualitative ***RT***-PCR multiplex assay is used …:

Table 18 Outsourced laboratories

Laboratory	Address
DDL Diagnostic Laboratory B.V.	~~Fonteijnenburghlaan 7~~ ~~Voorburg~~ ~~Netherland~~ ***Headquarters*** ***Visseringlaan, 25*** ***2288 ER Rijswijk - NL***

GlaxoSmithKline Biologicals Vaccines R & D Protocol Amendment 3	
eTrack study number and Abbreviated Title	207636 (EPI-RSV-008 BOD)
Amendment number:	Amendment 3
Amendment date:	18-FEB-2019
Co-ordinating author:	PPD, Lead Science Writer

The protocol has been amended to reflect the following changes and provide the following clarifications / corrections.

- The overall sample size has been reduced from 4,000 to 2,300, as the original number of subjects will no longer be required to move the RSV Maternal immunization program to the next stage of development.
- The terms respiratory tract infection and lower respiratory tract infection have been replaced with the terms respiratory tract illness and lower respiratory tract illness to improve consistency with World Health Organization terminology.
- The phrase “pregnant women (mothers)” has been replaced with the term “maternal subjects.”
- The List of Abbreviations and Glossary of terms have been updated.
- Language describing mitigation of the risks associated with venipuncture has been clarified.
- The reference to nasal obstruction in Footnote 1 of Table 3 has been removed.
- Eligible maternal subjects may now be up to 45 years of age and must now have a pre-pregnancy body mass index within the range specified in the inclusion criteria.
- “Geographic ancestry (race)” replaces the word “race.”
- A footnote has been added to Table 4 to indicate that if results of an oral glucose challenge / tolerance test are not available, then fasting blood glucose or haemoglobin A1C test results may be used as described in Table 26.
- Language has been added to clarify that “parental concern” as described in Sections 8.6.4 through 8.6.8 occurs in the context of a respiratory tract illness.
- Instructions for infant diary completion and for collection of RTI/LRTI symptom start and stop dates have been re-written in an effort to improve clarity.
- A definition for respiratory tract illness/lower respiratory tract illness symptom “worsening” has been added.
- Objectives, endpoints and the text of Appendix D have been adjusted to improve consistency with GAIA criteria.
- References to country and/or region-specific analyses have been removed from Section 11.10.
- Assessment of blood oxygen saturation (by pulse oximetry) in maternal subjects has been added.

• Text has been added to clarify that levels of RSV-A neutralising antibody in maternal and cord blood at delivery will be assessed during the interim analysis. • Text that addresses study / site closure has been added. • Laboratory addresses in Appendix B have been updated. Additional editorial changes have been made to ensure consistency with the modifications noted above, and typographical errors have been corrected
Text that has been moved or added is presented in ***bold italics*** and deleted text in ~~strikethrough~~ in the following sections.

Global changes:

- ~~"Pregnant women (mothers)"~~ has been replaced with ***maternal subjects***
- Age 18 – ~~40~~ has been replaced with 18-***45***
- ~~<28$^{0/7}$~~ has been replaced with ≤***27^{6}***$^{/7}$ weeks gestational age (GA)
- Number of subjects enrolled has changed from ~~4000~~ to ***2300*** ("~~up to 400~~" to "***200-300***" per country)
- "Respiratory tract ~~infections"~~ has been replaced with respiratory tract ***illnesses***
- "~~Race~~" has been replaced with ***"geographic ancestry (race)"***

List of contributing authors:

- PPD ***, Lead*** PPD Epidemiologist
- ~~PPD , Clinical Research and Development Lead~~
- PPD ***, Expert Epidemiology Biostatistician***, PPD , Lead Epi Statistician
- PPD **,** PPD , Study Delivery Leads
- PPD , Clinical Trial Supply manager
- PPD ***, Clinical Read-Out Team Leader***
- PPD ***, Safety Physician***
- PPD , Oversight Data Manager
- PPD Study Data Manager (Tata Consultancy Services for GSK Biologicals)
- PPD , Regulatory Affairs Representative

Authors who contributed to previous versions of the protocol

- PPD , Study Delivery Leads
- PPD ***, Safety Physician***

Synopsis and Secondary Objectives

Neonatal ***events*** ~~AEs~~ of interest occur within the first 28 days after birth, but may only be detected later and are to be reported throughout the study

Synopsis and Introduction

4th pargraph: Secondarily, the study will establish surveillance mechanisms for RSV ***associated illnesses*** ~~infections~~

7th paragraph: Pregnant women $24^{0/7}$ up to ***and*** ~~but not~~ including 27^{6}~~$28^{0/7}$~~ weeks of gestation

Section 1.5, Introduction:

RSV infects 50-70% of infants in their first year of life, and practically all children have experienced RSV infection ***and / or illness***

Synopsis Table 2 and Table 2

Study groups and epochs foreseen in the study

Study Groups	Number of **subjects** enrolled	Age (Min/Max)	Epochs		
			Epoch 001	**Epoch 002**	**Epoch 003**
Maternal subjects ~~Pregnant women (mothers)~~	Up to ~ ***2300*** ~~400 (per country)~~	18 years – ***45*** ~~40~~ years	x	x	
Infants	Up to ~ ***2300*** ~~400 per country)~~	NA		x	x

Approximately 200 to 300 subjects per country. To achieve the enrollment targets noted above, the number of pregnant women SCREENED in each country may exceed ***the country-specific enrolment target.*** ~~400~~

Synopsis and Section 11.1, Primary Endpoints

- Pregnancy outcomes. ***Of note, fetal death/stillbirth has multiple subcategories. For example, fetal death/stillbirth with no congenital anomalies is an outcome with two subcategories that include: 1) antepartum stillbirth; 2) intrapartum stillbirth. For each outcome, the investigator should select the applicable sub-category.***
  - Fetal death/stillbirth ~~(~~loss at or after 22 weeks of gestation~~)~~ with no congenital anomalies:
    - ***Antepartum stillbirth***
    - ***Intrapartum stillbirth***
  - Fetal death/stillbirth ~~(~~loss at or after 22 weeks of gestation) with congenital anomalies:
    - ***Antepartum stillbirth***
    - ***Intrapartum stillbirth***
  - Pregnancy related events of interest from Visit 1 through Visit 6…… They ***are listed below. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features***

(including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.

- Antenatal bleeding:
  - ***Morbidly adherent placenta***
  - ***Placental abruption***
  - ***Cesarean Scar Pregnancy***
  - ***Uterine rupture***
- Dysfunctional labor
  - ***first stage of labor***
  - ***second stage of labor***
- ***Gestational Liver Disease:***
  - ***Intrahepatic Cholestasis of Pregnancy (ICP)***
  - ***Acute Fatty Liver of Pregnancy***
- ***Maternal Sepsis***

Neonatal events of interest from birth through 28 days of age. Neonatal ***events*** ~~AEs~~ of interest……

- Congenital microcephaly,
  - ***Postnatally diagnosed***
  - ***Prenatally diagnosed***
- Congenital anomalies
  - ***Major external structural defects***
  - ***Internal structural defects***
  - ***Functional defects***
- Neonatal death,
  - ***Neonatal death in a preterm live birth (gestational age>=28 to < 37 weeks)***
  - ***Neonatal death in a term live birth***
- Neonatal infections,
  - ***Blood stream infections***
  - ***Meningitis***
  - ***Respiratory infection***
- ***Failure to thrive,***

Any other neonatal event considered by the investigator to be of concern (specify, ***e.g. neurodevelopment delay***).

Section 11.1.1 (Primary Endpoints – pregnancy outcomes and pregnancy related events of interest; text does not appear in Synopsis):

Section 11.1.1.2: ***For events of interest that include subcategories, the frequency of the main event of interest and of each event subcategory will be included in the analysis. The overall frequency will include mothers who present at least one of the subcategory events.***

Section 11.1.1.3: ***For events of interest that include subcategories, the frequency of the main event of interest and of each event subcategory will be included in the analysis. The overall frequency will include infants who present at least one of the subcategory events.***

Synopsis and Secondary Endpoints

Of note, some events of interest fall under a single category but have multiple subcategories. For each event, the investigator should identify the event and select the applicable sub-category and the GAIA level of diagnostic certainty.

List of Abbreviations

BMI	***Body mass index***
LRTI	Lower Respiratory Tract ***Illness*** ~~Infection~~
RTI	Respiratory Tract ***Illness*** ~~Infection~~

Glossary of Terms

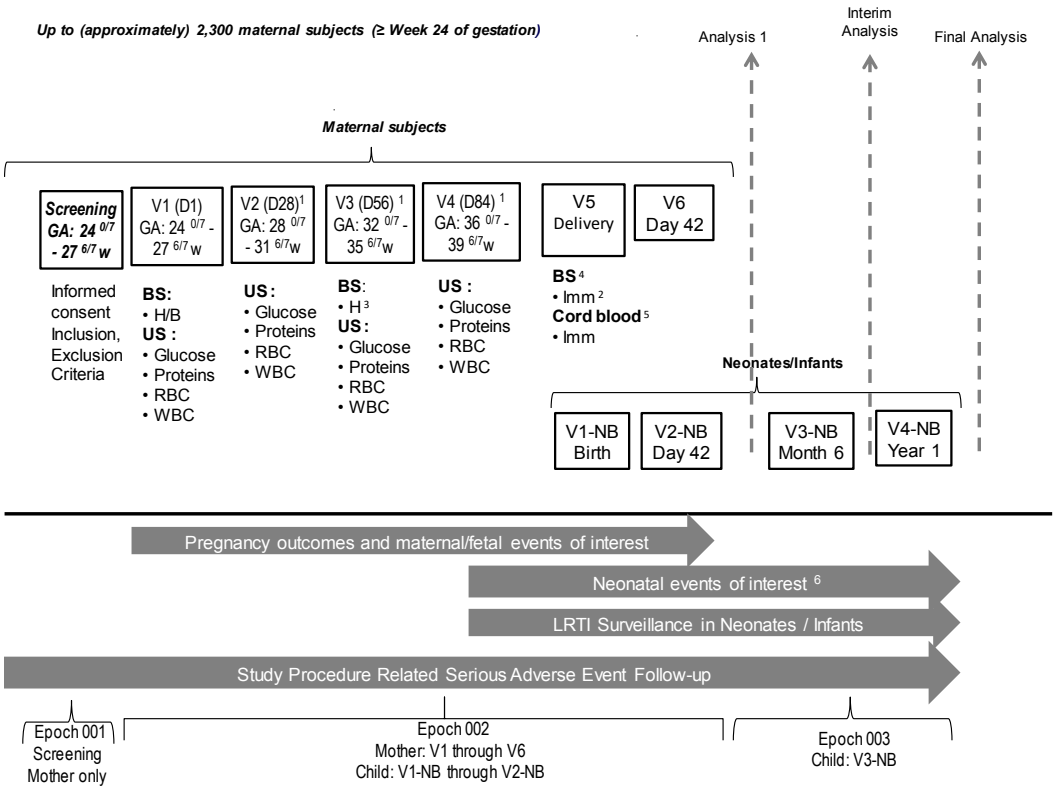
Body Mass Index	***A key index for relating weight to height. Calculated as follows: Weight (kg) / (Height (m))^2***
Parental concern	The parent(s) / Legally Acceptable Representative(s) or their designates are concerned about the infant's respiratory tract illness, or general health ***in the context of the respiratory tract illness,*** and intend to seek medical care

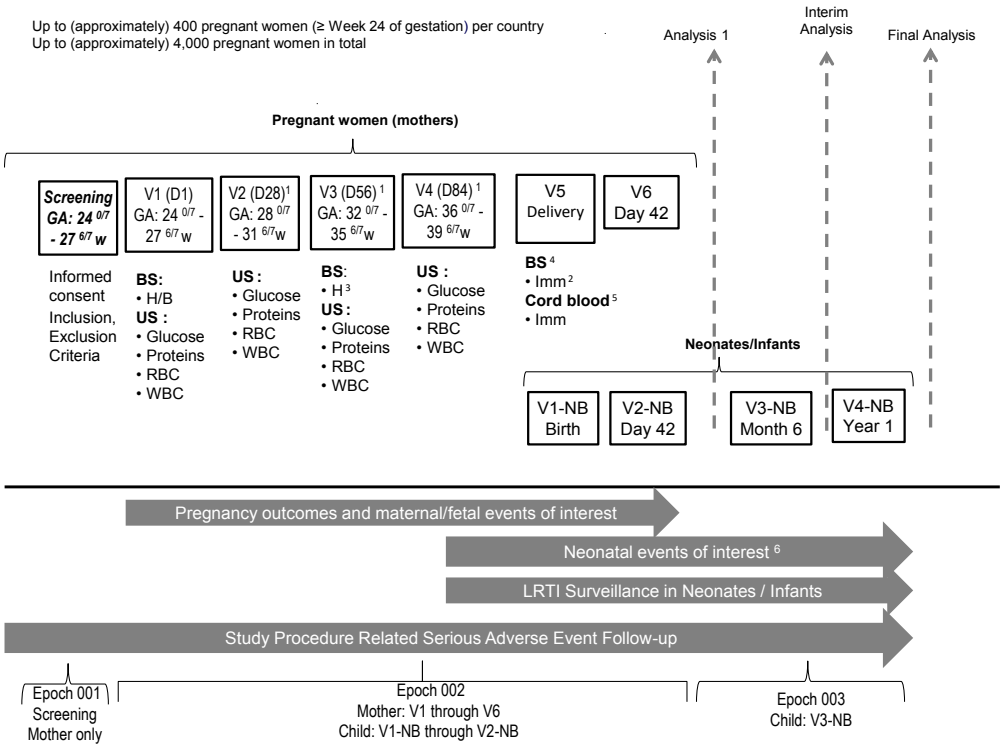
Section 2.1, Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood sample collection- While giving blood the subject may feel faint, or locally experience mild pain, bruising, irritation or redness.	Spontaneous data	Sample collection will only be performed by appropriately trained study personnel. ***All*** Subjects will ***remain under observation, post venipuncture, through completion of the applicable study visit*** ~~be observed for at least 30 minutes after blood sample collection.~~ Subjects will be notified of this risk in the informed consent form.

Section 4, Study Design Overview

Figure 1 has been replaced. The current Figure, followed by the Figure as presented in Amendment 2, follow.





- Primary Completion Date (PCD): 42 days post-delivery/birth (i.e. Visit 6 for ***maternal subjects*** ~~the mothers~~ and Visit 2-NB for ***infant subjects*** ~~the infants~~) or last visit of Epoch 002.
- Duration of the study: Approximately 4.5 to 6 months for ***maternal subjects*** ~~participating pregnant women~~; approximately 1 year for ***infant subjects*** ~~participating infants.~~
- Epoch 002: Primary starting at Visit 1 and ending 42 days post-delivery/birth (Visit 6 for ***maternal subjects*** and Visit 2-NB for ***infant subjects***).*

Section 5.4, Case Definitions, Table 3:

Footnote 1: Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnoea) ~~associated with nasal obstruction~~.

Footnote 5: RSV sampling and testing is ***described in Sections 8.6.7, 8.6.8 and 8.6.9.*** ~~based on judgment of medical practitioner or driven by algorithm.~~

Section 6.2.1, Inclusion criteria for maternal subjects

* The level of diagnostic certainty of the gestational age should be established by using the GAIA gestational age assessment ***form*** ~~tool~~ (provided in APPENDIX C).

- ***Women with pre-pregnancy body mass index (BMI) ≥18.5 and ≤ 39.9 kg/m².***

6.3, Exclusion criteria for enrollment in maternal subjects:

The following criteria should be checked at the ***screening visit and at Visit 1.*** ~~time of study entry.~~

- primary ***genital*** herpes simplex infection

Section 8, Detailed Study Procedures

Table 4

Review and collect obstetric history from current pregnancy, including: gestational age, expected date of delivery and method of EDD estimation ***including pre-pregnancy weight***	O	●						
Travel history to, or living in, countries/regions with Zika virus transmission ***(during the current pregnancy)***	O	●	***O***	***O***	***O***	***O***		●

Footnote 7: If results of an oral glucose challenge / tolerance test are not available to confirm that the subject does not have Gestational Diabetes at screening, then fasting blood glucose or hemoglobin A1C test results (if performed by local healthcare provider and available) may be used as described in Table 27.

Footnote 10: ***In the Philippines, where*** ~~If~~ ***HIV*** ~~test results are~~ ***testing is not*** ~~available at time~~ ***part of the standard of care for pregnant women, the screening*** ~~the~~ ***HIV test can be performed locally as a study procedure*** ~~under certain conditions~~. Refer to SPM for further details. If results are positive, subject will be referred per local standard of care.

Footnote 11: Height***, weight during the month before the subject became pregnant, and pre-pregnancy BMI*** at screening. Weight, ***temperature, systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest, blood oxygen saturation by pulse oximetry*** ~~vital signs~~, fetal heart tones, fetal movement, and fundal height at Screening and Visits 1 – 4. ***Temperature, systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest, and blood oxygen saturation by pulse oximetry*** ~~Vital signs~~ at Visit 6.

Table 5 footnotes

[a] If local regulations require that ***written consent /*** confirmation of consent for the infant's participation be obtained at birth.

[c] If more than one assessment visit is conducted to evaluate a potential LRTI~~episode~~, additional nasal swabs may be collected at the discretion of the Investigator.

[e] Collect diary cards that are fully filled out and / or document (L)RTI ~~episodes~~ ***symptoms*** that have ended ~~(as defined in Section 8.6.5.1).~~ Provide new diary cards as needed.

[f] Collect all diary cards for potential RTIs that are considered resolved. Collect the diary card for the current potential LRTI once the ~~episode~~ ***LRTI symptoms have*** ~~has~~ ended ~~(as defined in Section 8.6.5.1~~).

[g] ***When approximately 50% of infants have completed up to Visit 3-NB, an interim analysis will be conducted to assess the accumulated RSV LRTI cases and the distribution of maternal and cord blood serum RSV A Ab.***

Section 8.5.2, History for *Maternal subjects* ~~and Examinations for pregnant women/mothers~~

Record demographic data, which may include (but ***are*** ~~is~~ not limited to) information such as ***geographic ancestry (***race***)***, month and year of birth, ***and*** ethnicity.

Record information about whether ***(during the current pregnancy)*** the subject has travelled to / is living in countries / regions with Zika virus

Record the subject's pre-pregnancy weight (i.e., weight during the months before the subject became pregnant) at screening. This information can be obtained either via medical record review or subject interview and should be recorded in the subject's eCRF.

Confirm that the subject's pre-pregnancy BMI is within the range specified in Section 6.2.1. This information can be obtained from the medical record, or, if unavailable, may be calculated based on the subject's height and reported pre-pregnancy weight.

Obtain the subject's medical ***and obstetric*** history by interview and/or ……

- ~~Obtain the subject's obstetric history by interview and/or review of her medical records.~~

Section 8.5.3: ***Examinations of maternal subjects***

Record height at screening ~~and weight at screening and Visits 1-4.~~

- Screening and Visits 1 - 4 should include assessment of ***weight***, fetal heart tones, fetal movement, and fundal height;
- Screening, Visits 1 to 4, and Visit 6 should include assessment of ***temperature***, ~~vital signs~~ systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest) and ***blood oxygen saturation by pulse oximetry.***

Section 8.5.8, Outcomes and Events of Interest

- Record delivery and pregnancy outcomes. ***Of note, fetal death/stillbirth has multiple subcategories. For example, fetal death/stillbirth with no*** ~~Record Delivery and Pregnancy Outcomes~~ ***congenital anomalies is an outcome with two subcategories that include: 1) antepartum stillbirth; 2) intrapartum stillbirth. For each outcome, the investigator should select the applicable sub-category.***
- Maternal events of interest (including, but not limited to, those described in Section 11.1.1) occurring up to Visit 6 (Post-delivery ***Day 42***) should be recorded in the eCRF along with additional details pertinent to the diagnosis, GAIA assessment and level of diagnostic certainty (APPENDIX D), when applicable. ***Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.***
- Information about maternal ***hospitalizations***, ~~hospitalization and~~ clinically significant events, ***and*** diagnoses that could impact the pregnancy will be recorded.

Section 8.6, Description of Study Procedures for Neonates/Infants

Note that the investigator or study staff will perform (if not performed by local healthcare provider) a minimum of 2 clinical examinations: one at birth (or up to 10 days after birth), and another at approximately 42 days of age.

Section 8.6.2, History and Examinations for Neonates/Infants

- Record demographic data including month and year of birth, gender, ***geographic ancestry (***race***)*** and ethnicity.

Section 8.6.3, Infant Diary Cards

~~8.6.3.1 Documentation of RTI episodes:~~

~~*One diary card should be completed for each RTI episode whether or not an Assessment Visit (Section 8.6.6) takes place. An RTI episode has "ended" if it satisfies the criteria in Section 8.6.5.1.*~~

At each study visit (including any assessment visits), RTI ***symptoms*** ~~***episode(s)***~~ may have ended or may be ongoing.

If blocked nose, cough and symptoms of difficulty in breathing (including wheezing) ~~For any RTI episode(s) that has/~~have ended by the time of a study visit:

- Study staff should collect the Diary card(s), and replenish the parent(s)/LAR(s)/designate(s) supply of blank cards as needed.

~~For any RTI episode that *is*~~ ***If blocked nose, cough or symptoms of difficulty in breathing (including wheezing) are*** ongoing at the time of a study visit (including any assessment visit):

- Study staff should review the diary card, make a photocopy of it, and return it to the parent(s)/LAR(s)/designate(s) so information can continue to be collected until ~~the episode has~~ ***the symptoms have*** ended.
- ***As soon as possible after*** ~~Once~~ ~~the episode~~ ***these symptoms have***~~has~~ ended, study staff must collect the completed diary card by a site visit, home visit, or postal mail, whichever is most effective based on local practice. The site should make every effort to collect completed diary cards as soon after the ~~end of an episode~~ ***symptoms have ended*** as possible. If diary card collection occurs during a visit to the study site or to the subject's home, a brief clinical evaluation may be performed to confirm that the ~~episode~~ ***symptoms have*** ~~has~~ ended.

8.6.4, Surveillance for ~~episodes of~~ potential Lower Respiratory Tract ***Illness*** ~~Infection~~ (LRTI)

- ***A*** ~~An episode of~~ potential lower respiratory tract ***illness*** ~~infection~~ (LRTI) is one in which the infant has one or more of the RTI symptoms listed above AND at least one of the following:

- Wheezing (a whistling sound when the infant breathes out) ***(another sign of difficulty in breathing***);
- Parental concern (the parent(s)/LAR(s) or their designate(s) are concerned about the infant's respiratory tract illness, or general health ***in the context of the respiratory tract illness***, and intend to seek medical care).

Worsening means any clinically observed/diagnosed symptoms and signs that are reported during the same respiratory tract illness and reflect a deterioration in the child's respiratory tract functions.

- ~~An RTI episode starts on the day when (per parental report, as *written in the Diary Card* and ***stop dates will be collected in***or provided verbally during an assessment visit) the ***diary card for*** first RTI symptom started~~
- ~~An RTI episode ends on the day when (per parental report, as written in the Diary Card and/or provided verbally during an assessment visit) either cough, runny nose, blocked nose, wheezing and difficulty in breathing has resolved, whichever resolves later~~.
- ***Start and stop dates will be collected in the diary card for cough, runny nose, blocked nose, wheezing and difficulty in breathing.***
- ***Start dates for all symptoms will also be recorded in the eCRF.***
- ***Only stop dates for cough and difficulty in breathing will be recorded in the eCRF so that GSK may later define the end of each LRTI episode (Section 5.4)***
- ~~There must be at least 7 symptom-free days between 2 consecutive RTI episodes; the only exception is runny nose, which is a symptom that can persist during that minimum 7-day period that would distinguish one episode~~

Figure 5 footnote

Worsening is defined in Section 8.6.5.1

8.6.5.3 Active Surveillance

- there is parental concern ***as defined in Section 8.6.5.1***

8.6.5.4 Passive Surveillance

- the infant's symptoms worsen ***as defined in Section 8.6.5.1***

8.6.6 Decision to conduct a Visit to assess……

If there is NO suspicion of difficulty in breathing, nor wheezing, nor parental concern ***in the context of the RTI***:

If there IS difficulty in breathing, or wheezing (both based on parental assessment), or there is parental concern ***in the context of the RTI***:

8.6.7.3 Nasal swabs

…..If more than one assessment visit is conducted to evaluate a potential LRTI~~episode~~

8.6.8 Follow up after an assessment……

After an assessment visit (Section 8.6.7) the child will be followed with at least weekly active surveillance contacts, until the RTI/LRTI ~~episode~~ has resolved. During these active contacts, worsening of symptoms ***(clinically observed/diagnosed symptoms and signs that are reported during the same respiratory tract illness and reflect a deterioration in the child's respiratory tract functions; for example, onset of additional symptoms or an increase in the intensity of a previously reported symptom)*** will be assessed. Parent(s) / LAR(s) / designate(s) will be reminded to call/contact/visit the site if symptoms worsen.

After symptoms ~~*an RTI episode*~~ that resulted in one or more assessment visits ***have*** ~~has~~ ended (Section 8.6.5.1), site staff will ensure that the diary card for ***those symptoms*** ~~that episode~~ is returned to the site via site visit, home visit, or postal mail (depending on the most effective local best practice for prompt retrieval of the completed infant diary card following the end of ***the symptoms*** ~~an RTI episode~~***).***

Table 7, Biological samples

Sample Type†	Quantity	Unit	Timepoint	Group
Samples preferentially collected by local health care provider per local practice[1]				
Maternal Blood for ~~Hematocrit~~ ***Hemoglobin***	Up to 2	ml	Visit 3 (Day 56)	

Table 8, Humoral Immunity, footnote

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. ***Marburg, Germany***

Table 9, Molecular Biology, footnote

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. ***Marburg, Germany***

Section 11.2 Determination of Sample size

Assuming a drop-out rate of about 10% during the course of follow-up, there will be up to approximately ***180 to 270*** ~~360~~ evaluable subjects by country.

Considering a sample size of up to approximately ***180 to 270*** ~~360~~ evaluable subjects by country, Table 16 illustrates the precision (exact 95% confidence interval [CI]) one can get on the percentage of subjects with maternal, fetal and neonatal events of interest.

Precision (exact 95% CI) has also been computed for a sample size of 270, ***180*** and 100 evaluable subjects for estimate by study site.

Table 16: Precision (exact 95% confidence interval) on the percentage of subjects with maternal, fetal and neonatal events of interest for sample size of ~~360~~ 270, *180* and 100 subjects

	~~360 subjects~~			270 subjects			*180 subjects*			100 subjects		
%	~~N~~	~~Lower limit~~	~~Upper limit~~	N	Lower limit	Upper limit	N	Lower limit	Upper limit	N	Lower limit	Upper limit
35	~~126~~	~~30.1~~	~~40.2~~	94.5	29.3	41.0	***63***	***28.1***	***42.4***	35	25.7	45.2
30	~~108~~	~~25.3~~	~~35.0~~	81	24.6	35.8	***54***	***23.4***	***37.3***	30	21.2	40.0
25	~~90~~	~~20.6~~	~~29.8~~	67.5	19.9	30.6	***45***	***18.9***	***32***	25	16.9	34.7
20	~~72~~	~~16.0~~	~~24.5~~	54	15.4	25.3	***36***	***14.4***	***26.6***	20	12.7	29.2
15	~~54~~	~~11.5~~	~~19.1~~	40.5	11.0	19.8	***27***	***10.1***	***21.1***	15	8.6	23.5
10	~~36~~	~~7.1~~	~~13.6~~	27	6.7	14.2	***18***	***6***	***15.3***	10	4.9	17.6
5	~~18~~	~~3.0~~	~~7.8~~	13.5	2.7	8.3	***9***	***2.3***	***9.3***	5	1.6	11.3
3	~~10.8~~	~~1.5~~	~~5.3~~	8.1	1.3	5.8	***5.4***	***1***	***6.8***	3	0.6	8.5
1	~~3.6~~	~~0.2~~	~~2.7~~	2.7	0.2	3.0	***1.8***	***0.1***	***3.9***	1	0	5.4
0	~~0~~	~~0~~	~~1~~	0	0	1.4	***0***	***0***	***2***	0	0	3.6

Section 11.6, Analysis of primary objectives

The primary objectives analyses will be performed on the PPS cohorts overall ~~by country,~~ ***and possibly by*** region or other relevant grouping.

The number and percentage (with exact 95% CI) of women presenting the following outcomes: live birth, fetal death/***stillbirth*** (***antepartum or intrapartum***), and elective/therapeutic termination will be reported for each event by presence or absence of congenital anomalies.

- ***To determine the frequencies of pregnancy related events of interest as specified in Section 11.1.1.2.***

The number and percentage (with exact 95% CI) of pregnant women presenting with the ~~following~~ events of interest ***specified in Section 11.1.1.2.*** The number and percentage (with exact 95% CI) of pregnant women presenting with the ~~following~~ events of interest ***specified in Section 11.1.1.2*** will be tabulated for each event within appropriate time windows to be specified in the statistical analysis plan (SAP).

~~The events are:~~

- ~~Hypertensive disorders of pregnancy:~~
  - ~~gestational hypertension, and~~
  - ~~Pre-eclampsia, and~~
  - ~~Pre-eclampsia with severe features (including eclampsia)~~
- ~~Antenatal bleeding~~
- ~~Fetal growth restriction~~
- ~~Non reassuring fetal status~~

- ~~Pathways to preterm birth:~~
  - ~~premature preterm rupture of membranes,~~
  - ~~preterm labor, and~~
  - ~~provider-initiated preterm birth~~
- ~~Postpartum h*e*morrhage~~
- ~~Chorioamnionitis~~
- ~~Oligohydramnios~~
- ~~Polyhydramnios~~
- ~~Maternal death~~
- To determine the frequencies of neonatal events of interest ***as specified in Section 11.1.1.3.***

The number and percentage (with exact 95% CI) of neonates presenting the ~~following~~ events of interest ***specified in Section 11.1.1.3……***

- ~~All of the following events of interest.~~
  - ~~Small for gestational age~~
  - ~~Low birth weight including very low birth weight~~
  - ~~Large for gestational age~~
  - ~~Macrosomia~~
  - ~~Preterm birth~~
  - ~~Neonatal encephalopathy~~
  - ~~Respiratory distress in the neonate~~
  - ~~Neonatal infections~~
  - ~~Congenital microcephaly~~
  - ~~Congenital anomalies~~

Section 11.7 Analysis of Secondary objectives

The secondary objectives analyses will be performed on the PPS cohorts (maternal or infant as applicable) overall ~~by country~~ ***and possibly*** by region or other relevant grouping.

Section 11.8 Analysis of Tertiary objectives

The following tertiary objectives analyses will be performed on infants within the PPS cohort overall ***and possibly*** by ~~country~~ region or other relevant grouping.

- ***To describe co-infections of RSV-LRTI with other respiratory viruses in infants.***

Considering all infants followed from visit 1-NB to visit ***4***-NB, the percentage of subjects with the occurrence of RSV-LRTI and having other respiratory viral co- infection ~~or colonized with another viral etiology~~ identified

Section 11.11, Conduct of analyses

Analyses will be performed in a stepwise manner after ***all subjects in all*** ~~each country / group of countries /~~ countries ~~in a region~~ have completed all study visits in Epoch 002 and again after completion of all study visits in Epoch 003.

… For these analyses a statistical report ***but no CSR*** will be prepared.~~for each country/ group of countries / countries in a region. No CSRs will be prepared~~.

Final analyses will be performed when all data up to study end are available (Epoch 002 and Epoch 003). ~~One or more~~ ***An*** integrated ***CSR*** ~~clinical study reports (bycounty / group of countries / countries in a region)~~……..

Section 11.11.1 Statistical considerations for interim analysis

This interim analysis will be performed to obtain preliminary information on the performance of the case definitions used for RSV LRTI, severe LRTI, and very severe LRTI (Table 3) ***and to assess levels of RSV-A neutralising antibody in maternal and cord blood at delivery.*** The interim analysis will occur after the database freeze at the time point when ***approximately*** 50% of infants will have completed ***up to*** 6 months of follow up during the surveillance period following birth ***(up to Visit 3-NB). No CSR will be prepared.***

Section 12.1, Electronic case report form instructions

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

Section 12.3, Study and site closure has been added.

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- ***Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines***
- ***Inadequate recruitment of subjects by the investigator***
- ***Discontinuation of further study treatment development***

Appendix B, Clinical Laboratories, table 17

GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany	***Emil-von-Behring-Str. 76 35041 Marburg Germany***

Appendix B, Clinical Laboratories, Table 18

~~NÉOMED-LABS Inc.~~	~~525, Cartier Ouest Laval, Québec Canada H7V 3S8~~

Appendix D, Definitions of maternal, fetal and neonatal events of interest as per GAIA

The order of the tables has been adjusted for consistency with the order in which endpoints are presented in the body of the protocol. Stillbirth (now Table 19) is presented as a pregnancy outcome rather than as a neonatal event of interest.

Table 29 has been updated to include the following events:

Gestational liver disease (Intrahepatic Cholestasis of Pregnancy or ICP)[1]	***Intrahepatic cholestasis also called obstetric cholestasis should be suspected when pruritis develops during pregnancy in the absence of a rash. Lab evidence of cholestasis includes elevated bile acids (Glyco and Taurochenodeoxycholic Acid)(> 10 umol/L). Up to 60% of patients will have elevated transaminases and 20% of patients will have increased direct bilirubin levels. Jaundice may or may not be present. ICP typically is transient and resolves after delivery. Women that had ICP in previous pregnancy have higher risk to developing ICP in the following pregnancies or other hepatobiliary disorders in later life. ICP is associated with adverse fetal outcome like meconium-stained liquor, fetal asphyxia, spontaneous preterm delivery and intrauterine death.***
Gestational liver disease (Acute Fatty Liver of Pregnancy)[2]	***Acute fatty liver of pregnancy (AFLP) is a rare, potentially fatal complication that occurs in the third trimester or early postpartum period. AFLP is characterized by microvesicular fatty infiltration of hepatocytes without any inflammation or necrosis. Most frequent signs and symptoms are the following: Jaundice Abdominal Pain (usually right upper quadrat, midepigastric or radiating to back) Central nervous system (altered sensorium, confusion, disorientation, psychosis, restlessness, seizures or even coma) Disseminated intravascular coagulation Nausea and vomiting Gastrointestinal bleeding Acute renal failure Oliguria Tachycardia***

	Late onset pyrexia ***Hypoglycemia*** ***ALT<500 U/L*** ***Hyperbilirubinemia, elevated ammonia, leukocytosis, hypofibrinogenemia*** ***Ultrasound examination and computed tomography may demonstrate fatty infiltration of the liver but are not sufficient for diagnosis***
Maternal Sepsis[3]	***Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, child-birth, post-abortion, or post-partum period.*** ***Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.*** ***The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.*** ***A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.***
	Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a] Score System | 0 | 1 | 2 | 3 | 4 Respiration Pao_2/Fio_2, mm Hg (kPa) | ≥400 (53.3) | <400 (53.3) | <300 (40) | <200 (26.7) with respiratory support | <100 (13.3) with respiratory support Coagulation Platelets, $\times 10^3/\mu L$ | ≥150 | <150 | <100 | <50 | <20 Liver Bilirubin, mg/dL (µmol/L) | <1.2 (20) | 1.2-1.9 (20-32) | 2.0-5.9 (33-101) | 6.0-11.9 (102-204) | >12.0 (204) Cardiovascular | MAP ≥70 mm Hg | MAP <70 mm Hg | Dopamine <5 or dobutamine (any dose)[b] | Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b] | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b] Central nervous system Glasgow Coma Scale score[c] | 15 | 13-14 | 10-12 | 6-9 | <6 Renal Creatinine, mg/dL (µmol/L) | <1.2 (110) | 1.2-1.9 (110-170) | 2.0-3.4 (171-299) | 3.5-4.9 (300-440) | >5.0 (440) Urine output, mL/d | | | | <500 | <200 Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen. [a] Adapted from Vincent et al.[27] [b] Catecholamine doses are given as µg/kg/min for at least 1 hour. [c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
	MAP = mean arterial pressure; qSOFA = quick SOFA; SOFA = Sequential [Sepsis-related] Organ Failure Assessment

References: ***1 Geenes V et al . Intrahepatic cholestasis of pregnancy***
2 Can J Gastroenterol Vol 20 26 No 1 January 2006
3 Bonet et al. Reproductive Health (2017) 14:67

Table 39, Failure to Thrive, has been added.

Failure to Thrive (FTT) can be broadly defined as a faltering of growth from a previously established pattern of growth. It is universally established that a diagnosis of failure to thrive should be based on anthropometric data. However no consensus exits as to which measurements achieve the highest specificity and sensitivity. Weight is generally regarded is the indicator of choice, particularly a change in growth velocity, and as such has been selected as the standard for this case definition with a weight for

age deceleration as the primary indicator of failure to thrive. The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Level	*Description*
1	*Infant age[1] determined by a documented birth date* *AND* *Weights obtained using an electronic scale* *AND* *At least 2 weights, measured at least 4 weeks apart* *AND* *Weight for age deceleration[2] through at least 2 centile spaces on growth chart[3]*
2a	*Infant age determined by a documented birth date* *AND* *Weights obtained using a beam balance scale* *AND* *At least 2 weights, measured at least 4 weeks apart* *AND* *Weight for age deceleration through at least 2 centile spaces on growth chart* *OR* *Infants with an undocumented birth date, where age is determined based on Mothers recall to nearest month* *AND* *Weights obtained using electronic scale* *AND* *At least 2 weights, measured at least 4 weeks apart* *AND* *Weight for age deceleration through at least 2 centile spaces on growth chart*
2b	*Infant age determined by a documented birth date* *AND* *Weights obtained using a spring balance scale* *AND* *At least 2 weights, measured at least 4 weeks apart* *AND* *Weight for age deceleration through at least 2 centile spaces on growth chart* *OR* *Weight measured using electronic scale or beam balance scale* *AND* *Length taken using Infantometer* *AND* *Weight for length less than or equal to the 3rd centile on the appropriate growth chart*
3a	*Infants with an undocumented birth date, where age is determined based on Mothers recall to nearest month* *AND* *Weight obtain using either beam balance or spring balance scale* *AND* *At least 2 weights, measured as least 4 weeks apart* *AND* *Weight for age deceleration through at least 2 centile spaces on*

Level	*Description*
	growth chart
3b	***Infants with no weight available*** ***AND*** ***Physical examination consistent with FTT[4]*** ***AND*** ***MUAC[5] indicative of severe wasting***

[1]This case definition is limited to infants up to 12 months of age.

[2] Weight should be documented on the appropriate growth chart at the time of assessment. A fall through 2 centile spaces may be demonstrated at any point in the first 12 months of life, using any two weights as long as they are taken at least 4 weeks apart. Details of use of the weight balances allowable under this case definition and use of the Infantometer for length assessment are presented in the reference given below.

[3] For infants born at 37 weeks gestation or above, the WHO growth charts should be applied. When using weight for age use the growth chart most accurate for the infants age. The birth to 6 months age range should be used where data is available for this range only, the birth to 2 years chart should be used where data is available beyond 6 months of life. When using weight for length, use the chart for birth to 2 years. For infants born less than 37 completed weeks gestation, the Intergrowth charts for postnatal growth standards in preterm infant should be used. All infants should be plotted on their respective growth chart using their corrected age. Links to relevant growth charts are presented in the reference given below.

[4] Physical examination with signs of Failure to Thrive (must include at least 2 findings, with at least one major finding) Major findings: Reduced subcutaneous fat stores; poor muscle mass; loose skin folds; prominent ribs; thin limbsOther less specific signs include: sparse hair; rashes; pallor; miserable; lethargy/fatigue.

[5] Mid Upper Arm Circumference (MUAC): For infants 0–6 months, a MUAC of 6 110 mm is indicative of severe wasting.For infants 6–12 months, a MUAC of 6 115 mm is indicative of severe wasting. Instructions on performing MUAC are presented in the reference given below.

Reference: Ross E, Munoz F, Edem B et al. Failure to thrive: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35:6483-6491.

Table 40, macrosomia definition has been corrected

Macrosomia	BW >4000 g (8 ***lb,*** 13 ***oz*** ~~lb~~).

GlaxoSmithKline Biologicals
Vaccines R & D
Protocol Amendment 4

eTrack study number and Abbreviated Title	207636 (EPI-RSV-008 BOD)
Amendment number:	Amendment 4
Amendment date:	29-MAY-2020
Co-ordinating author:	PPD, Lead Science Writer

Rationale/background for changes:

This amendment outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The primary purpose of the amendment is to protect the subject's welfare, and as far as possible ensure the potential benefit to the subject and promote data integrity. Several additional modifications and clarifications have also been made.

Changes are outlined below.

- Globally:
  - Intervals between study visits/contacts/observations: the window for the first infant subject visit has been extended from 0-10 to 0-21 days to provide site personnel with additional time to obtain and document post-delivery/birth informed consent (where this is required).
  - References to Gestational Age Range at maternal Visits 2, 3 and 4 have been removed as their inclusion was only intended as a guide and was not intended to further restrict allowed intervals between study visits.
- Synopsis, Section 3.3, Tertiary Objectives, and Section 11.1.3, Tertiary Endpoints, have been updated to indicate that the incidence of LRTIs/ Severe LRTIs (using alternative case definitions) will also be evaluated.
- Synopsis and Section 11.1.3, Tertiary Endpoints, has been updated to clarify that further exploratory characterization of immune responses to RSV and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood) includes, for example, levels of RSV-B neutralizing antibodies.
- The List of Abbreviations has been updated to include a reference to COVID-19.
- Section 2.3, Overall Benefit: Risk Conclusion has been updated.
- Section 4, Figure 1: A note has been added to indicate that COVID-19 cases identified within the surveillance framework of the study will be captured to the eCRF.
- Section 5.4, Table 4, Alternative LRTI/Severe LRTI Case Definitions, has been added. All subsequent Table numbers therefore increase by one.
- Section 8.2.1, Study procedures during special circumstances, has been added.

- Section 8.3, Tables 5 and 6, List of study procedures for maternal subjects, and List of study procedures for neonates/infants, have been clarified to indicate that COVID-19 cases are considered clinically significant events and will be recorded as such in the eCRF.
- Sections 8.5.8, 8.6.2, 8.6.7 have been modified to reference the collection of COVID-19 case information.
- Section 8.6.5.2 has been modified to clarify that RTI surveillance in infants cannot begin before additional consent for the infant's participation (where required) has been supplied.
- Section 8.7, Reporting COVID-19 cases, has been added.
- Section 11.3 has been modified to introduce definitions for the Enrolled set, and to clarify definitions for the Exposed and Per Protocol sets for analysis.
- Sections 11.6, 11.7 and 11.8 have been modified for consistency with the changes in Section 11.3.
- Section 11.11.1, Statistical considerations for interim analysis, has been modified to indicate that an interim analysis for RSV LRTIs may be performed if deemed necessary.
- Section 14 has been updated to include a reference to the WHO Guidance for surveillance of COVID-19.
- Additional editorial clarifications have been made and typographic errors have been corrected.

Text that has been moved or added is presented in ***bold italics*** and deleted text in ~~strikethrough~~ in the following sections.

Contributing Authors:

- PPD, Expert ~~***Epidemiology***~~ Biostatistician, PPD PPD Lead ~~Epidemiology Statistician~~***Biostatistician***
- ~~PPD***, Clinical Trial Supply manager***~~
- PPD***, Clinical Laboratory Sciences Study Manager, Business & Decision Life Sciences Contractor for GSK Biologicals***
- PPD, Oversight Data Manager
- ~~PPD Study Data Manager (Tata Consultancy Services for GSK Biologicals)~~

Synopsis and Section 3.3, Tertiary objectives:

- ***To determine the incidence of LRTIs/ Severe LRTIs (using alternative case definitions)***

Synopsis and Section 11.1.3, Tertiary endpoints:

- ***Episodes of LRTIs/Severe LRTIs up to one year of age - using alternative case definitions***

Any further exploratory characterization of immune responses to RSV and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood). (***For example, levels of RSV-B neutralizing antibodies).***

List of Abbreviations:

COVID-19	***Corona Virus Disease 2019***

Section 2.3, Overall Benefit:Risk Conclusion:

This is an epidemiologic study that describes the prevalence of pregnancy outcomes and maternal/neonatal events of interest. The study does not include the administration of any investigational vaccine. It is not expected that the participation of pregnant women and their babies in the study would create any further risk to study participants. The study includes the establishment of a surveillance system for lower respiratory tract infections (LRTI) which may facilitate detection of respiratory tract infections, including COVID-19 cases, that might be diagnosed in children enrolled in the study.

Section 4, Figure 1, Study Design:

References to GA in the original figure have been removed and a footnote specifically referencing COVID-19 has been added. The previous figure and the current figure are presented in full below.

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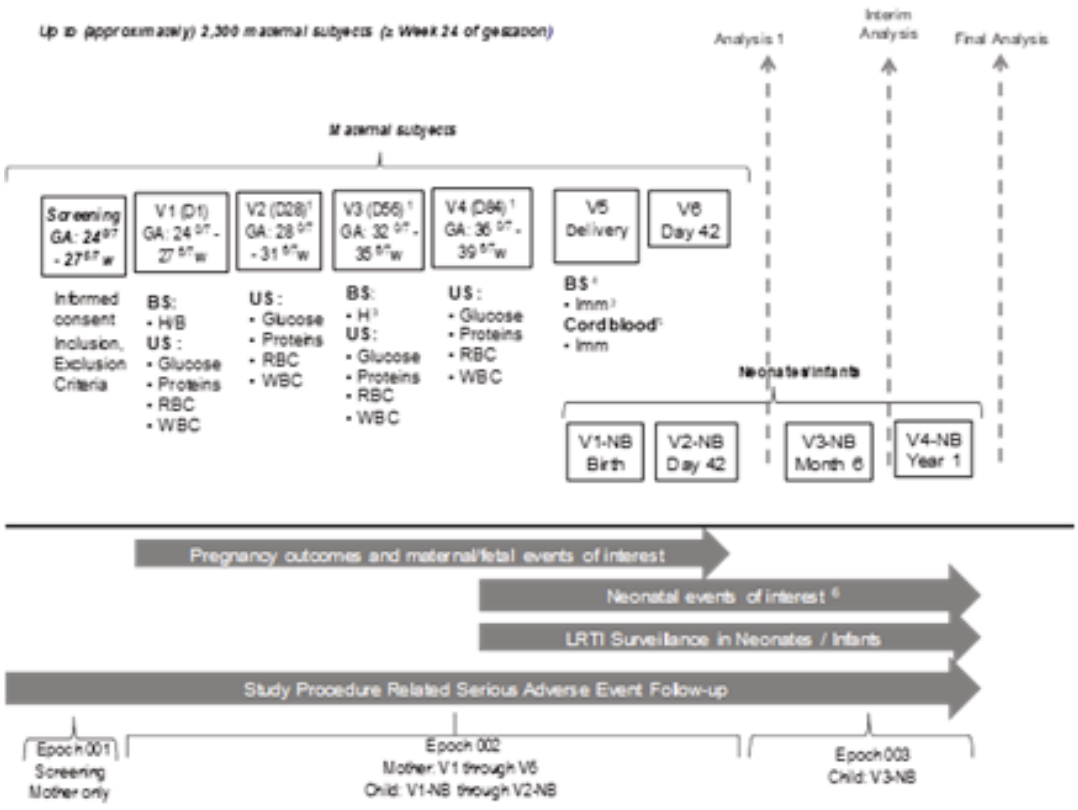
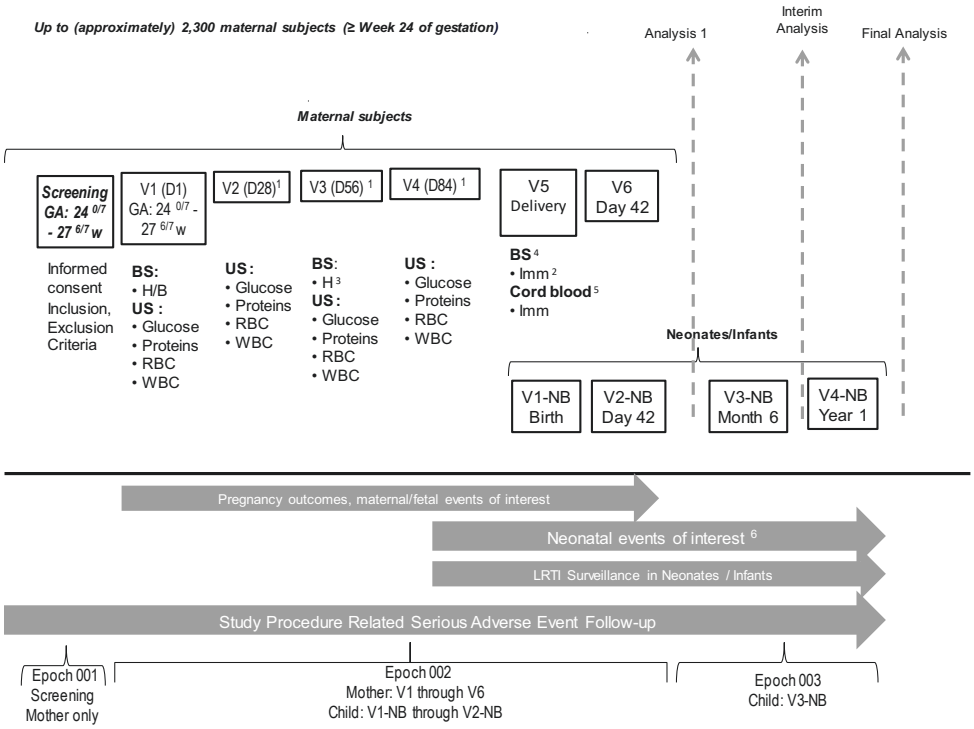
Previous:



Current:



NOTE: Covid-19 cases identified within the surveillance framework of the study in maternal and infant subjects will also be recorded.

Section 5.4, Table 4, Alternative LRTI / Severe LRTI Case Definitions*:*

	RSV confirmed	*Documented physical examination (PE) findings indicating lower respiratory tract involvement (at least one symptom)*	*Objective measures of clinical severity (at least one symptom)*
LRTI	*Confirmed RSV infection*	*Rhonchi*[1] *Rales*[1] *Crackles* *Wheeze*	*Increased respiratory rate (bpm)* *≥ 60 for < 2 mo* *≥ 50 for 2-6 mo*
			Hypoxemia: *SpO2 <95% at ≤1800 meters* *SpO2 <92% at > 1800 meters*
			New onset apnea
			Nasal flaring
			Retractions[2]
			Grunting
Severe LRTI	*Confirmed RSV infection*	*Rhonchi*[1] *Rales*[1] *Crackles* *Wheeze*	*Hypoxemia* *SpO2 <93% at ≤1800 meters* *SpO2 <90% at > 1800 meters*
			Acute hypoxic or ventilatory failure[3]
			Dehydration due to respiratory distress requiring IV hydration[4]
			Failure to respond or unconscious

[1]Term not listed in the eCRF page in this study.

[2] Intercostal recession or chest wall indrawing are considered synonymous with and will be used as alternatives to the term "retractions," which is not listed in the eCRF page for this study.

[3] Acute hypoxic or ventilatory failure is not listed in the eCRF page for this study. Instead, the presence of either respiratory support excluding mechanical ventilation OR requirement for mechanical ventilation or both will be used.

[4] Dehydration due to respiratory distress requiring IV hydration is not listed in the eCRF page for this study. Skin turgor > 2 seconds or administration of IV fluid therapy will be used instead.

Section 6.1, Number of subjects / centers:

The study will be conducted at multiple ~~centres~~ cent*e*rs…..

Section 6.2.2, Inclusion criteria for enrollment; infants:

- If local law requires it: Written or witnessed/thumb printed informed consent for study participation of the infant obtained from parent(s)/LAR(s) within ~~10~~ ***21*** days of birth.

Section 8.2.1, Study procedures during special circumstances:

During special circumstances (e.g., the 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 subjects if deemed feasible by the investigator.

- ***If it is not possible to conduct a protocol-specified, scheduled or event-driven (e.g., LRTI assessment) visit as described in Section 8.3, the visit may be replaced with a contact conducted by telephone, videotelephony or telemedicine. SMS and email are not allowed.***
- ***Biological samples may be collected at a different location* other than the study site, or at-the subject's home. Biological samples should not be collected if they cannot be obtained within the visit interval (Section 8.4), processed in a timely manner or appropriately stored until the intended use.***
- ***Nasal swabs should only be collected using centrally provided supplies.***
- ***Cord Blood for assessment of immune response may be collected locally but must be retrieved, processed and stored in accordance with the Investigator Laboratory Manual.***
- ***Additional blood samples for assessment of immune response should only be collected using centrally provided supplies.***
- ***Diary cards may be transmitted from and to the site by electronic mail, and / or conventional mail.***

Impact on the per protocol sets for analysis will be determined on a case by case basis.

Any impact of the above mentioned measures on the study results will be described in the clinical study report.

**** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.***

Section 8.3, Outline of Study Procedures, Table 5, list of study procedures for maternal subjects:

Gestational age	24 0/7 – 27 6/7	24 0/7 – 27 6/7	~~28 0/7 – 31 6/7~~	~~32 0/7 – 35 6/7~~	~~36 0/7 – delivery~~			
Timepoints		**Day 1**	**Day 28**	**Day 56**	**Day 84**	**At Delivery**	**Post-Delivery Day 42**	
Record pregnancy-related events of interest. Record other clinically significant events or diagnoses[15]		●	●	●	●	●	●	●

[1] Refer to Section 6.2.1, ~~fifth~~ ***sixth*** bullet.

[10] ***~~In the Philippines~~ Where*** HIV testing is not part of the standard of care for pregnant women, the screening HIV test can be performed locally as a study procedure. Refer to SPM for further details. If results are positive, subject will be referred per local standard of care.

[15]Includes events or diagnoses that could impact the pregnancy including COVID-19 cases

Section 8.3, Outline of study procedures, Table 6, list of study procedures for neonates/Infants:

Age	0-~~10~~ *21* days	42 Days	6 Months	12 months	0-12 months	
Timepoints	**Birth**	**Day 42**	***M6***	**Y1**		
Record all hospitalizations and clinically significant events [h]	●	●	●	●	●	●
Investigator sign-off on eCRF before analysis		●		●		

LAR = legally acceptable representative; **LRTI** = lower respiratory tract illness; **NB** = newborn; **RTI** = respiratory tract illness; **SAE** = serious adverse event; ***M=month***; **Y** = year.

[g]When approximately 50% of infants have completed up to Visit 3-NB, an interim analysis ~~will~~ ***may*** be conducted to assess the accumulated RSV LRTI cases and the distribution of maternal and cord blood serum RSV ~~A~~ Ab. .

[h] Includes COVID-19 cases

Section 8.4, Intervals between study visits, Table 7:

Interval	Optimal interval	Allowed interval**
Birth → Visit 1-NB	0 days	0 – ~~10~~ ***21*** days

Section 8.5.8, Outcomes and Events of Interest in maternal subjects:

- Any events of interest in mother or fetus ~~detected by surveillance~~ will be referred to and managed by the routine health services as locally appropriate.
- Record all hospitalizations and/or clinically significant events, ***including COVID-19 cases.***

Section 8.6, Description of study procedures for Neonates / Infants:

Note that the investigator or study staff will perform (if not performed by local healthcare provider) a minimum of 2 clinical examinations: one at birth (or up to ~~10~~ ***21*** days after birth), and another at approximately 42 days of age.

Section 8.6.2, History and Examinations for Neonates / Infants:

Record all hospitalizations and/or clinically significant events, ***including COVID-19 cases.***

Section 8.6.5.2, Surveillance for potential Lower Respiratory Tract Illness (LRTI); Overview:

Surveillance for potential LRTIs begins at birth ***(or after additional consent, has been provided for the infant's participation in the study, if required,)*** and ends with the Year 1 study visit.

Section 8.6.7.1, Visit to assess a potential LRTI; Overview:

The appropriately qualified person will also evaluate whether the LRTI might be related to COVID19. The appropriately qualified person must follow the local standard of care regarding the reporting, and management of COVID-19 cases (suspected, probable or confirmed COVID-10 case), and complete both the COVID-19 form and LRTI form in the CRF. Refer to Section 8.7.

Section 8.6.7.2, Visit to assess a potential LRTI; Clinical Evaluation:

- ***Possible presence of COVID-19 infection (Section 8.7). As noted above, both the LRTI and COVID-19 eCRFs are to be completed (whether or not the investigator/study staff consider the LRTI to be due to COVID-19.***.

Section 8.7, Reporting Covid-19 Cases – Maternal and Infant subjects:

In addition to satisfying local reporting requirements for COVID-19 cases, maternal and infant COVID-19 cases identified within the existing framework of the study will be captured and reported on the COVID-19 eCRF for the study.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition [WHO, 2020] using one of the following terms:

- ***Suspected COVID-19 infection***
- ***Probable COVID-19 infection***
- ***Confirmed COVID-19 infection***

Section 8.11.3.1, Antibody determination, Table 9:

System	Component	Method	Kit / Manu-facturer	Unit	Cut-off	Laboratory*
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALISATION	In house	ED60 ***and/or IU/ML***	***ED60: 18; IU/ml: 56***	GSK Biologicals** or GSK designated lab***

Ab = antibody; **ED60** = serum dilution inducing 60% inhibition in plaque forming units; ***IU/mL: International Unit/milliliter***

Section 9.7, Follow-up of SAEs related to study participation:

The investigator will follow-up subjects with SAEs related to study participation until the event has resolved, subsided, ~~stabilised~~ ***stabilized***…..

Section 9.7.2, Follow-up after the subject is discharged from the study:

The investigator is obliged to assist. If a subject dies during participation in the study or during a ~~recognised~~ ***recognized*****…..**

Section 11.1.3, Tertiary endpoints:

- Any further exploratory characterization of immune responses to RSV and/or other respiratory tract infections or infections of relevance to pregnant women and their newborns (based on maternal serum and cord blood) (***For example, levels of RSV-B neutralizing antibodies.)***
- ***Episode(s) of RSV-LRTI/severe LRTI based on alternative case definitions, from birth up to 1 year of age.***

Section 11.3.1.1, Exposed Sets, Pregnant women (mothers):

The ES will include all pregnant women (mothers) ***who signed a valid*** informed consent ***form.***

Section 11.3.1.2, Exposed Sets, Neonates/Infants:

Not applicable.

Section 11.3.2.1, Enrolled Sets, Pregnant women (mothers):

The enrolled set will include all pregnant women (mothers) with a valid informed consent who completed Visit 1.

Section 11.3.2.2, Enrolled Sets, Neonates/infants:

The ~~ES~~Enrolled Set will include all~~ study eligible~~ neonates/infants~~ with~~

- ***born to pregnant women in the enrolled set, and***
- ***Who have*** a valid ICF signed by the mother/ parent(s) /LAR(s) (as appropriate per local regulations).

11.3.3, Per Protocol Sets (PPS), Pregnant women (mothers):

- The maternal PPS will include all pregnant women (mothers) ~~meeting~~ ***in the enrolled set who*** meet…..

11.3.3.2, Per Protocol Sets (PPS), Neonates/infants:

The infant PPS will include all ~~enrolled~~ neonates / infants ~~meeting~~

- *born to pregnant women in* ***the PPS and***
- ***who*** meet……..

Sections 11.6, Analysis of primary objectives and 11.7, Analysis of Secondary Objectives:

If there is a difference of 5% or more between the number of participants in the enrolled set and the PPS, primary objectives analyses on the enrolled set will also be performed.

Section 11.8, Analysis of tertiary objectives:

If there is a difference of 5% or more between the number of participants in the enrolled set and the PPS, primary objectives analyses on the enrolled set will also be performed.

- ***To determine the incidence of LRTIs/Severe LRTIs (using alternative case definitions)***
- If deemed necessary, to further characterize the immune responses to RSV and other infections in maternal subjects and infants (based on maternal serum and cord blood).
  - ***For example, for levels of neutralizing antibodies*** ~~such as but not limited~~ ***to RSV-B:***

Section 11.11.1, Statistical considerations for interim analysis:

If deemed necessary, an interim analysis ~~will~~ ***may*** be performed on RSV surveillance data as part of the secondary objective of determining incidence of RSV LRTI. This interim analysis ~~will~~ ***may*** be performed to obtain preliminary information on the performance of the case definitions used for RSV LRTI, severe LRTI, and very severe LRTI (Table 3) and to assess levels of RSV~~A~~ neutralising antibody in maternal and cord blood at delivery. The interim analysis ~~will~~***may*** occur after the database freeze at the time

point when approximately 50% of infants will have completed up to 6 months of follow up during the surveillance period following birth (up to Visit 3-NB). ***If an interim analysis is performed,*** data cleaning plans will be scheduled as needed to supply data for interim analyses in a timely manner. This interim analysis ~~will~~ ***may*** be performed on data that is as clean as possible. Preliminary results will be made available in a timely manner for use in the potential adjustment of the RSV LRTI case definitions to be used in pivotal clinical trials scheduled to begin shortly thereafter. The results pertaining to this analysis ***(if performed)*** will be purely descriptive, with no adjustment of type I error, and will be reported in an interim statistical report. No CSR will be prepared.

Section 14, References:

World Health Organization [WHO]. Global Surveillance for COVID-19 caused by human infection with COVID-19 virus: Interim Guidance. March 2020. Available at: https://apps.who.int/iris/rest/bitstreams/1272502/retrieve. Accessed 8 May 2020.