CLINICAL STUDY PROTOCOL

Primary Study Intervention	Not applicable
Other Study Intervention	Not applicable
Study Identifier	219510 (RSV MAT-015)
Eudra CT number	2022-003124-41
Approval Date	21 Jun 2023
Title	A ***Phase 3b,*** non-randomized, open label, multi-country, cohort study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies (RSV MAT-001, RSV MAT-004, RSV MAT-010, RSV MAT-011, RSV MAT-009, RSV MAT-012 and RSV MAT-039) during any pregnancy conceived post vaccination/control.
Brief Title	A follow-up study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies during any pregnancy conceived post vaccination/control.
Sponsor	GlaxoSmithKline Biologicals S.A. Rue De L'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Joon Hyung Kim Clinical and Epidemiology Project Lead, RSV Maternal Portfolio

Medical monitor name and contact information will be provided separately

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- 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 or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK 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 study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

Study identifier	219510 (RSV MAT-015)
Eudra CT number	2022-003124-41
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Title	A ***Phase 3b,*** non-randomized, open label, multi-country, cohort study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies (RSV MAT-001, RSV MAT-004, RSV MAT-010, RSV MAT-011, RSV MAT-009, RSV MAT-012 and RSV MAT-039) during any pregnancy conceived post vaccination/control.
Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____
Leiter der klinischen Prüfung name, function and title	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	21 Jun 2023
Amendment 1	17 January 2023
Original Protocol	16 September 2022

Amendment *2 (21 Jun 2023)*

This amendment is considered substantial **based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union** because it significantly impacts the scientific value of the study.

Overall rationale for the current Amendment: This amendment is being done to include details pertaining to the exclusion criteria for women of nonchildbearing potential, the timeframe for the primary and secondary objectives and the Phase of the study (Phase 3b). It also includes updated information indicating that all the prior studies listed are collectively called as 'prior RSV MAT studies' for both cohorts, to allow participants from any of the prior RSV MAT studies who are pregnant at enrollment to be enrolled in the prospective cohort. It further clarifies the method and source of data collection in the retrospective and prospective cohorts.

Additional updates were made in the objectives and endpoints section, schedule of activities, study design section, participant discontinuation/withdrawal from the study section, safety section, statistical considerations, and appendix.

The list of abbreviations and references were updated, additional information from the current protocol template were included, and some minor edits were made for clarity wherever applicable. Some minor typographical and grammatical corrections were also made in this amendment.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Title	Phase 3b added in the title.	Amended as per the request from the regulatory authorities (PEI).
List of abbreviations and definitions of terms	Updated the list of abbreviations.	Abbreviations were added with regards to the update in the protocol. Other abbreviations that were not spelled out in the previous protocol amendment were also updated as per the request from the regulatory authorities (PEI/AEMPS).

Section # and title	Description of change	Brief rationale
Table 2: Schedule of activities for prospective cohort – Adult/Adolescent participant Section 5.2: Exclusion criteria Section 7.2: Participant discontinuation/withdrawal from the study	Updated information regarding the women of nonchildbearing potential (WONCBP) to explain that WONCBP participants will be excluded if they do not plan to use any additional measures to conceive a pregnancy.	To add clarity that participants who plan to conceive during the study will be allowed to participate in the study.
Table 5: Objectives and endpoints	Added the timeframe in the primary and secondary objectives.	To define the timeframe for the analyses of data within 2 years.
	Added tertiary (exploratory) objectives.	CCI [redacted]
Section 9.3: Statistical analyses	Added a timeframe in the endpoints and statistical analysis methods for primary and secondary endpoint analyses.	To align with the updates in the objectives and endpoints section.
	Added new section for exploratory analyses.	
Section 1.2: Schema Section 4.1: Overall design Section 5.1.1: Retrospective cohort Section 5.1.2: Prospective cohort Section 10.1.4: Recruitment strategy	Removed all the prior study names and mentioned as 'prior RSV MAT studies' for both cohorts, to allow participants from any of the prior RSV MAT studies who are pregnant at enrollment to be enrolled in the prospective cohort.	To allow follow-up through day 42 post-delivery for any current study pregnancy ongoing at enrollment in the prospective cohort.
Section 8.4.5.2: Retrospective data source and data collection	Updated the information to explain how retrospective data collection is done.	As per the suggestion from regulatory authorities (PEI) this section has been updated to explain the method and source of retrospective data collection i.e., for pregnancies completed (through Day 42 post-delivery) prior to study enrollment.
Section 8.4.5.3: Prospective data source and data collection	Updated the information to explain how prospective data collection is done.	As per the suggestion from regulatory authorities (PEI) this section has been updated to explain the method and source of prospective data collection i.e., for participants with ongoing pregnancy at enrollment or conceived after enrollment.
Section 8.4.8.2: Reporting of congenital anomalies in relation to pregnancy outcomes and SAEs and/or AESIs	Added information to report all minor congenital anomalies that are neither reportable per MACDP nor medically attended, in the Adverse Event eCRF for infant participants.	To ensure reporting of minor congenital anomalies that are not reportable per MACDP or medically attended, such as Mongolian spots.
Section 10.6: Appendix 6: Definitions of maternal, fetal, and neonatal events of interest as per GAIA Section 11: References	Added GAIA references.	Amended as per the request from the regulatory authorities (PEI).
Section 10.6: Appendix 6: Definition of maternal, fetal and neonatal events of interest as per GAIA	Some maternal and neonatal events of interest have been specified as 'Not a study specific AESI'.	To clarify that some maternal and neonatal events of interest are not a study specific AESI.

Section # and title	Description of change	Brief rationale
Table 1: Study activities for retrospective cohort Table 2: Schedule of Activities for prospective cohort – Adult/Adolescent participant Table 3: Schedule of activities for prospective cohort – Infant participant	Explanation added for the collection of demographic and lifestyle data for mothers and infants. For mothers, demography data will be collected at enrollment and lifestyle data during or at the end of each pregnancy. For infants, demography data will be collected at birth and lifestyle data at Day 42 post-delivery.	Details and timing of data collection updated with necessary clarification.
	Information added to clarify the time-period for the collection of SAE.	Updated in alignment with Section 8.4.1.
Table 2: Schedule of Activities for prospective cohort – Adult/Adolescent participant Table 3: Schedule of activities for prospective cohort – Infant participant	Added details for the recording of MAEs, SAEs, and AEs leading to study withdrawal.	To clarify that AEs (AESI), MAEs and SAEs leading to withdrawal will be recorded.
Table 1: Study activities for retrospective cohort	Explanation added for the collection of medical and vaccination history.	To clarify that the information will be collected at each pregnancy.
Table 2: Schedule of Activities for prospective cohort – Adult/Adolescent participant Section 4.1: Overall design Section 4.4: End-of-study definition	Information added to define the end of study period for participants who are pregnant at study enrollment.	To clarify that if participants are pregnant at study enrollment, the study period ends at Day 42 post-delivery in the prospective cohort.
Section 7.2: Participant discontinuation/withdrawal from the study	Additional criteria included that will lead to participant discontinuation/withdrawal from the study.	To clarify that criteria which may lead to participant discontinuation/withdrawal from the study (such as occurrence of AEs (AESIs), MAEs, and SAEs (for the prospective cohort) and participant migration from the study area) will be recorded.
Section 8.1.1: Collection of demographic data and lifestyle characteristics	Added text from the current protocol template to explain why the collection of sex, race and ethnicity data is being done in the study.	To provide the rationale that sex, race, and ethnicity data will be collected to evaluate and monitor the diversity of participants in the study.
Section 8.3.1: Safety monitoring and committee	Added text to explain the role of safety review team.	Updated in alignment with the current protocol template.
	Replaced the term CRDL with CSL.	The functional designation of the clinical scientist in the organization has been changed to CSL.
Section 8.4.1: Time period and frequency for collecting MAE, SAE, and other safety information	Information added to clarify the time-period for the collection of SAE.	Updated in alignment with the current protocol template.
Section 8.4.10: COVID-19 infection Section 11: References	Updated the reference related to WHO case definition for COVID-19.	To align with the current updated reference (July 2022) which explains the WHO case definition for COVID-19.

Section # and title	Description of change	Brief rationale
Section 9.1: Statistical hypotheses Section 9.3: Statistical analyses	Removed the 'Per Protocol Set" for both maternal and infant participants and "Maternal Set" for maternal participants. Updated the information that primary and secondary analyses will be performed on the Full Analysis Set.	Amended as per the request from the regulatory authorities (PEI) to avoid any confusion. As this is a safety follow-up study, the Full Analysis Set (FAS) will contain all the maternal or post-delivery/birth data and it will be used for the analyses.
Section 10.1.3: Informed consent process	Added information to explain the process of obtaining assent from minor participants, obtaining consent if minor participants become legally emancipated during the study, and obtaining consent if participants are incapacitated.	To clarify the process of obtaining consent for adolescent and incapacitated participants prior to enrolling in the study, and the process of obtaining reconsent if the adolescent participants reach the legal age of consent according to the local law and regulations during the study.
Section 10.1.7: Data quality assurance	Added information about quality tolerance limit.	To explain that quality tolerance limit will be monitored during the study to identify systemic issues that may impact participant's right, safety and/or reliability of study results.
Section 10.1.9: Study and site start and closure	Added text to explain about the start of the study and first act of recruitment.	To explain that the start of study is defined as first subject first visit (FSFV)/first contact and the first act of recruitment is defined as first ICF signature date.
Section 10.2.2: Definition of SAE	Included abnormal pregnancy outcomes in the definition of SAE.	To categorize or collect abnormal pregnancy outcomes as SAEs.
Section 10.2.3.2: Assessment of intensity	Included 'SAE' for the assessment of intensity.	To clarify that assessment of intensity will be done for SAE.
Section 10.2.3.6: Updating of SAE, SAE due to study participation, MAEs and AESI information after removal of writer access to the participant's eCRF	Replaced 'electronic report' with 'paper report' for collecting information related to adverse events.	To clarify that additional adverse events will be recorded on the appropriate paper report after the write access to the participant's eCRF is removed.
Section 10.2.4: Reporting of SAEs, SAEs due to study participation, MAEs, and AESIs	Added text for the reporting of poststudy adverse events related to any GSK non-IMP if the site becomes aware of such adverse events.	Updated in alignment with the current protocol template.
Section 10.3.1.2: Women of nonchildbearing potential (WONCBP)	Deleted the text related to the cut-off for FSH levels.	To avoid misunderstanding, as no specific cut-off is defined for FSH levels for this study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AC	***Abdominal circumference***
ACOG	***American College of Obstetricians and Gynecologists***
AE	Adverse Event
AEMPS	***The Spanish Agency of Medicines and Medical Devices***
AESI	Adverse Event of Special Interest
AFI	***Amniotic fluid index***
AFLP	***Acute fatty liver of pregnancy***
BPD	***Biparietal diameter***
CDC	***Centers for Disease Control and Prevention***
CFR	***Code of Federal Regulations***
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRDL	***Clinical Research and Development Lead***
CRF/eCRF	***Case report form/electronic case report form***
CRL	***Crown-rump length***
CSL	***Clinical Science Lead***
CSR	***Clinical Study Report***
EDD	***Estimated Delivery Date***
ELBW	***Extremely low birth weight***
ET	***Embryo transfer***
FAS	***Full Analysis Set***
FH	***Fundal height***
FHR	***Fetal heart rate***
FL	***Femur length***
FSFV	First subject first visit
FSH	Follicle stimulating hormone
FTT	***Failure to thrive***
GA	***Gestational age***
GAIA	***Global Alignment of Immunization safety Assessment in pregnancy***
GCP	Good Clinical Practice

GDM	***Gestational diabetes mellitus***
GSK	GlaxoSmithKline
HC	***Head Circumference***
HCP	***Health Care Provider***
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal replacement therapy
IADPSG	***International Association of Diabetes and Pregnancy Study Groups***
IAF	***Informed Assent Form***
IB	***Investigator's Brochure***
ICF	***Informed Consent Form***
ICH	International Council for Harmonization
ICMJE	***International Committee of Medical Journal Editors***
ICP	***Intrahepatic Cholestasis of Pregnancy***
ICSR	***Individual case safety report***
IgM	***Immunoglobulin M***
IHD	Individual Human Data
IRB/*IEC*	Institutional Review Board/***Independent Ethics Committee***
IRM	Individual Rights Management
IUI	***Intrauterine Insemination***
IVF	***In vitro fertilization***
LAR	***Legally acceptable representative***
LBW	***Low birth weight***
LMP	***Last menstrual period***
LRTI	Lower respiratory tract illnesses
LSLV	***Last Subject Last Visit***
MACDP	***Metropolitan Atlanta Congenital Defects Program***
MAE	***Medically attended adverse event***
MAP	***Mean arterial pressure***
MedDRA	***Medical Dictionary for Regulatory Activities***
MUAC	***Mid Upper Arm Circumference***
NDDG	***National Diabetes Data Group***
NICE	***The National Institute of Health and Care Excellence***

Non-IMP	***Non-investigational medicinal product***
OGTT	***Oral glucose tolerance test***
PEI	***Paul-Ehrlich Institute***
qSOFA	***Quick SOFA***
QTL	***Quality tolerance limit***
RSV	Respiratory Syncytial Virus
SAE	Serious adverse event
SD	***Standard Deviation***
SoA	Schedule of activities
SOFA	***Sequential [Sepsis-related] Organ Failure Assessment***
SRT	***Safety Review Team***
U/S	***Ultrasound examination***
URI	***Upper respiratory infection***
US	***United States***
VLBW	***Very low birth weight***
WHO	***World Health Organization***
WOCBP	Woman of Childbearing Potential
WONCBP	***Woman of nonchildbearing potential***
YOA	Years of age

Term	Definition
Child in care	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
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.***
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.

Term	Definition
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Provisional Lost to Follow-Up:	A sustained inability of the site to make any contact with the participant (or parent(s)/LAR(s)) over the period of three contact attempts and/or after a final attempt has been made by mail (in accordance with local regulations/preferred site practices), but the participant is still within the study follow-up period. A provisional lost to follow-up participant who subsequently contacts the site and wants to resume follow-up may resume study activities, provided that the participant has not reached the end of the study follow-up period.
Remote visit	This term refers to the visit conducted in the place other than the study site.
Self-contained study	Study with objectives not linked to the data of another study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Term	Definition
Study completion date	The date on which the last participant in a clinical study to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Telemedicine	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A ***Phase 3b,*** non-randomized, open label, multi-country, cohort study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies (RSV MAT-001, RSV MAT-004, RSV MAT-010, RSV MAT-011, RSV MAT-009, RSV MAT-012 and RSV MAT-039) during any pregnancy conceived post vaccination/control.

Brief Title:

A follow-up study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies during any pregnancy conceived post vaccination/control.

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

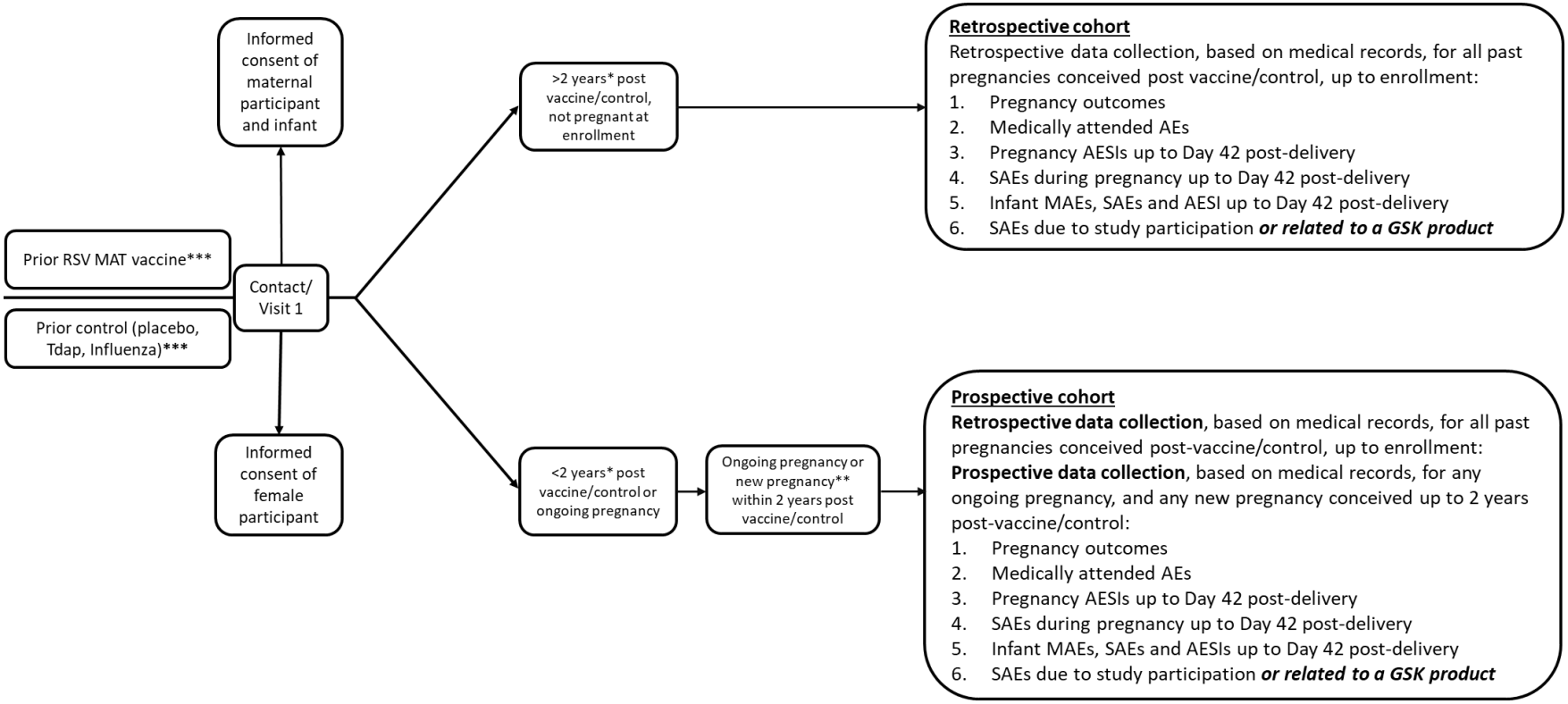
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 8.3.1.

1.2. Schema

Figure 1 Overall Study design overview



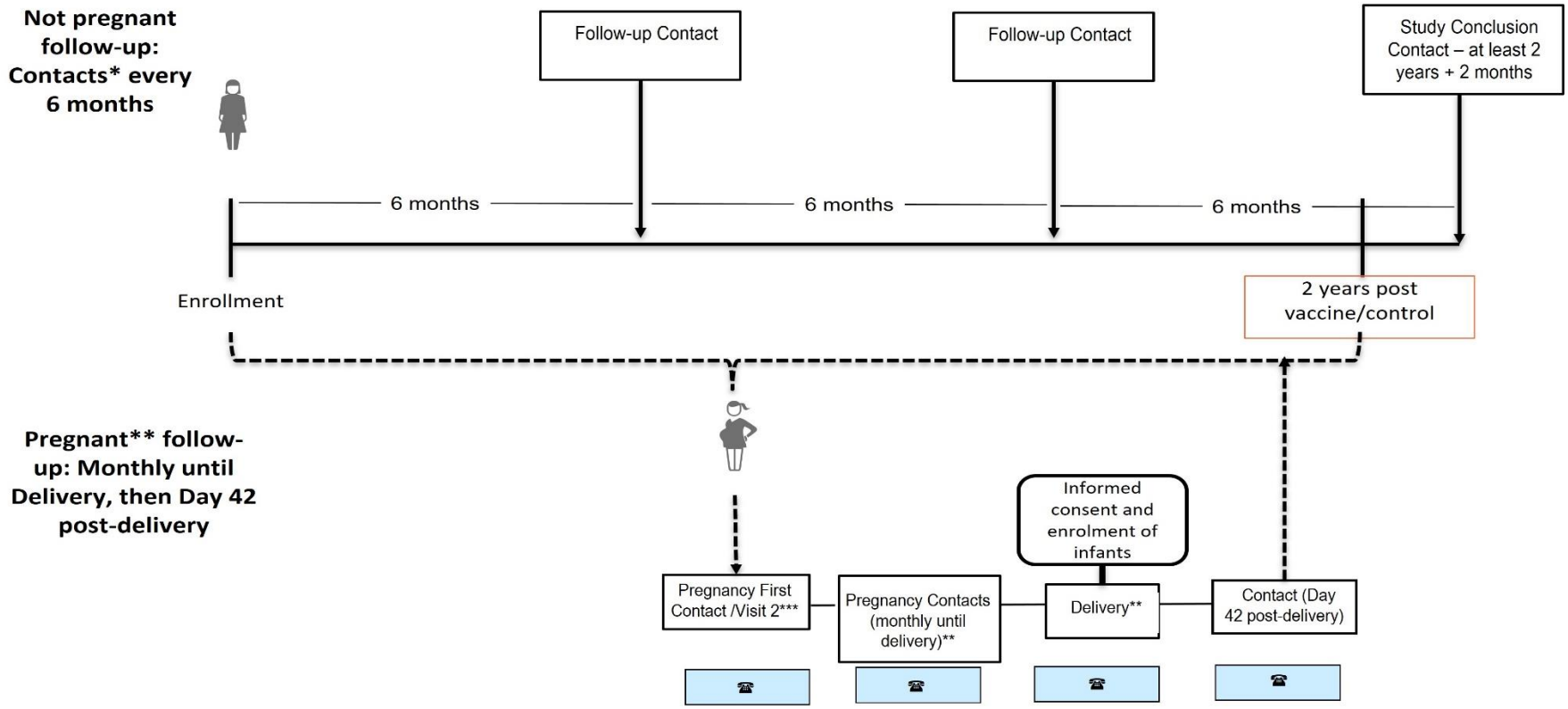
AESI: Adverse Events of Special Interest; **SAE**: Serious Adverse Event; **MAEs**: Medically attended Adverse Events

*2 years+2 months post vaccine/control to give time for the participant to be aware of a pregnancy if it is conceived very close to 2 years post-vaccination. The retrospective cohort will also include participants who have not reached 2 years+2 months post vaccine/control prior to/at enrollment but are a Woman of Nonchildbearing Potential (WONCBP) as defined in Section 10.3.1.2 at study enrollment, or recipient of bilateral tubal ligation prior to study enrollment.

**For participants enrolled in prior studies of pregnant women (i.e., MAT-004, MAT-009, MAT-012), this study will include pregnancies conceived after the prior study pregnancy in which RSVPreF3 vaccination (or control) was administered.

*** ***For participants enrolled in prior RSV MAT studies i.e., RSV MAT-001, RSV MAT-004, RSV MAT-009, RSV MAT-010, RSV MAT-011, RSV MAT-012 and RSV MAT-039.***

Figure 2 Study design overview- Prospective cohort



*Contacts every 6 months up to 2 years (+2 months) post-vaccine/control (received as part of prior RSV MAT study participation), unless a pregnancy conceived post-vaccine/control is reported.

** Once a pregnancy is reported, the participant is followed monthly during pregnancy until delivery, then again at Day 42 post-delivery. Pregnancy follow-up will include all pregnancies ongoing at enrollment or newly conceived during follow-up within 2 years post vaccine/control. If Day 42 post-delivery is <2 years+2 months, the woman returns to contacts every 6 months until 2 years (+2 months) post-vaccine/control.

***In addition to the planned study contacts, additional unplanned visits or medical procedures can be done as per the investigator's discretion.

1.3. Schedule of activities (SoA)

Table 1 Study activities for retrospective cohort

Type of contact	Visit 1/Contact 1	Notes
Timepoint	**Day 1[c]**	
Participant Contact [a]	●	
Informed consent	●	Maternal and infant informed consent
Inclusion and exclusion criteria	●	
Demography and lifestyle characteristics	●	Mothers: ***Demography at enrollment, and lifestyle*** during or at the end of each pregnancy Infants: ***Demography at*** birth, and ***lifestyle at*** Day 42 post-delivery
Medical and vaccination history	●	Collect information prior to start of study pregnancies ***(for each pregnancy)***
Contact information for all HCPs seen by mother or infant from start of current study pregnancies through day 42 post-delivery	○	
Safety assessments during current study pregnancies (from medical record review)		
Record concomitant medications/vaccinations	●	One month prior to conception to Day 42 post-delivery
Record medically attended AEs [b] until Day 42 post-delivery	●	Mothers: conception to Day 42 post-delivery Infants: birth to Day 42 post-delivery
Record pregnancy outcomes, pregnancy AESIs until Day 42 post-delivery and infant AESIs until Day 42 post-delivery	●	
Infant SAEs from birth until Day 42 post-delivery	●	
Infant MAEs from birth until Day 42 post-delivery	●	
SAEs during pregnancy until Day 42 post-delivery	●	
Record SAEs related to study participation ***or related to a GSK product*** [d]	●	
Final Activities		
Study conclusion	●	

● 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] Contact may be via telephone, SMS, email, video-telephone/telemedicine or other means, depending on local best practice. If the study site is the participant's primary healthcare facility, contact with study personnel may also be made in the context of a visit for routine or event-driven care

[b] events reported in the context of routine follow-up or unrelated to the event causing an event-driven visit will not be counted as 'medically attended' (e.g., a minor URI noted in the context of a routine prenatal visit would not be a 'medically attended event')

[c] All information needed for retrospective cohort participants can likely be collected on a single day, but it is possible that study personnel may need to re-contact participants to complete/clarify data collection.

[d] Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

Table 2 Schedule of Activities for prospective cohort – Adult/Adolescent participant

Type of contact	Visit 1/Contact 1 [a]	Follow-up contact [a]	Unscheduled contact [a]	Initial Pregnancy Contact [a, b]	Pregnancy contacts	Delivery [b]	Day 42 Contact [b]	Notes
Timepoints	**Day 1**	**Bi-annual, to 2 years+2 months post vaccine/control**			**Monthly until delivery****		**Day 42 post-delivery**	
Informed consent/Informed Assent	●							
Inclusion and exclusion criteria	●							
Demography and lifestyle characteristics	●					●		***Demography at enrollment, and lifestyle during or at the end of each pregnancy***
Medical and vaccination history prior to pregnancy	●			●				Collect information prior to start of study pregnancies
Spontaneous pregnancy reporting by participants	●	●	●	●	●	●	●	
Contact information for all HCPs seen from start of current study pregnancies through day 42 post-delivery	○	○	○	○	○	○	○	
Safety assessments during current study pregnancies (from medical record review)								
Record medications/vaccinations	●			●	●	●	●	One month prior to conception to Day 42 post-delivery
Record medically attended AEs until Day 42 post-delivery	●			●	●	●	●	Conception to Day 42 post-delivery
Record pregnancy outcomes, pregnancy related AESIs until Day 42 post-delivery	●		●	●	●	●	●	
SAEs during pregnancy until Day 42 post-delivery	●			●	●	●	●	

Type of contact	Visit 1/Contact 1 [a]	Follow-up contact [a]	Unscheduled contact [a]	Initial Pregnancy Contact [a, b]	Pregnancy contacts	Delivery [b]	Day 42 Contact [b]	Notes
Timepoints	**Day 1**	**Bi-annual, to 2 years+2 months post vaccine/control**			**Monthly until delivery****		**Day 42 post-delivery**	
Record SAEs related to study participation ***or related to a GSK product*** [d]	●	●	●	●	●	●	●	
MAEs, SAEs and AEs (AESIs) leading to study withdrawal	●	●	●	●	●	●	●	
Final Activities								
Study conclusion		●[c]					●[c]	

● 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] Any study contact may be via telephone, SMS, email, video-telephone/telemedicine or other means, depending on local best practice. If the study site is the participant's primary healthcare facility, contact with study personnel may also be made in the context of a visit for routine or event-driven care.

[b] May be combined with another contact where pregnancy is first reported [e.g., combined with Visit 1/Contact 1 (for past/ongoing pregnancies at enrollment), follow-up contact, unscheduled contact.]

[c] For participants who are not pregnant at 2 years post vaccine/control, the study conclusion will be completion of the last bi-annual contact, at least 2 months after 2 years post-vaccine/control. If the participant is pregnant at 2 years post vaccine/control ***or at study enrollment***, study conclusion will be completion of Day 42 post-delivery***. WONCBP at study enrollment, or recipient of bilateral tube ligation prior to study enrollment will be excluded from the study if she has not conceived a pregnancy post-vaccine/control and does not plan to use any additional measures to attempt to conceive a pregnancy (e.g., sterilization reversal or in vitro fertilization (IVF)).***

[d] Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

Table 3 Schedule of Activities for prospective cohort – Infant participant

Type of contact [a]	Delivery [b]	Day 42 Contact [b]	Notes
Timepoints	**Day 1**	**Day 42**	
Informed consent	●		Infant informed consent is anticipated at delivery, but may be done at any time up to the delivery contact if allowed at the site (or at Visit 1/Contact 1 for an infant born from a past pregnancy)
Inclusion and exclusion criteria	●		
Demography and lifestyle characteristics	●	●	***Demography at birth, and lifestyle at Day 42 post-delivery***
Contact information for all HCPs seen by infant from birth through Day 42	○	○	
Safety assessments (from medical record review)			
Record medications/vaccinations	●	●	
Record medically attended AEs until Day 42	●	●	
Infant AESIs from birth until Day 42	●	●	
Infant SAEs from birth until Day 42	●	●	
Record SAEs related to study participation ***or related to a GSK product*** [c]	●	●	
MAEs, SAEs and AEs (AESIs) leading to study withdrawal	●	●	
Final Activities			
Study conclusion		●	

● 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] Any study contact may be via telephone, SMS, email, video-telephone/telemedicine or other means, depending on local best practice. If the study site is the participant's primary healthcare facility, contact with study personnel may also be made in the context of a visit for routine or event-driven care.

[b] May be combined in one contact where delivery and day 42 have already occurred at the time of maternal enrollment.

[c] Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

Table 4 Intervals between study contacts for prospective cohort

Contact(s)	Planned contact interval	Allowed interval range
Visit 1/Contact 1→Bi-annual contacts Bi-annual contact→ next Bi-annual contact	180 days*	135-225 days[1]
Prior study vaccination→ last Bi-annual contact/Study Conclusion	2 years+2 months (790 days)**	790 days-835 days[2]
Monthly contacts until delivery	Every 30 days	15-45 days[3]
Delivery contact***	Delivery+3 days	Delivery – Day 42 post-delivery
Day 42 contact	Day 43 post-delivery	Day 43-Day 58[4]

* This contact interval does not apply while the participant is pregnant.

** The study conclusion visit interval is planned at least 2 months after 2 years post-vaccine/control, to give time for the participant to be aware of a pregnancy if it is conceived very close to the end of 2 years post-vaccine/control; Once a participant reaches 2 years+2 months the study conclusion can occur at any time (the last Bi-annual contact does not need to be 180 days from the prior contact. For participants who are not pregnant at 2 years post vaccine/control, the study conclusion will be completion of the last bi-annual contact, at least 2 months after 2 years post-vaccine/control. If the participant is pregnant at 2 years post vaccine, study conclusion will be completion of Day 42 post-delivery.

[1]Maximum Allowed interval range is +/- 3 months.

[2]Maximum interval range 880 days.

[3]Maximum interval range can be +59 days.

[4]Maximum interval range can be Day 133*** The delivery contact will be based on expected delivery date.

2. INTRODUCTION

2.1. Study rationale

The study is designed to describe the safety during pregnancies conceived after the prior study vaccination (or control) and to collect all the medically related information in subsequent pregnancies in women who previously were administered RSVPreF3 maternal vaccine or control from any RSV MAT study.

2.2. Background

GSK was developing an investigational Respiratory Syncytial Virus (RSV) vaccine for administration to pregnant women, with the aim of preventing medically assessed, RSV-associated lower respiratory tract illnesses (LRTIs) in their infants by transfer of maternal antibodies. The primary endpoint for efficacy in the development program was their infants' protection from RSV for first 6 months of life. The vaccine candidate is an engineered version of the RSV fusion (F) surface glycoprotein, stabilized in the pre-fusion conformation (RSVPreF3).

Several Phase I to Phase III studies were conducted in pregnant and non-pregnant women; ***throughout this document these studies are collectively referenced as the 'prior RSV MAT studies'***. Briefly, these were:

- RSV MAT-001: ***RSVPreF3 in*** non-pregnant women, first time in human, safety and immunogenicity
- RSV MAT-004: ***RSVPreF3*** first time in pregnant women, safety and dose confirmation
- RSV MAT-010: RSVPreF3 co-administration with influenza vaccination, lot-to-lot consistency
- RSV MAT-011: RSVPreF3 co-administration with Tdap (*Boostrix*) vaccination, second dose of RSVPreF3
- RSV MAT-009: Efficacy in infants of RSVPreF3-vaccinated pregnant women
- RSV MAT-012: RSVPreF3 in high-risk (high-risk adult ***women*** + healthy adolescents 15-17 years) pregnancies
- RSV MAT-039: RSVPreF3 in healthy non-pregnant girls ages 9-17 years and non-pregnant adult women ages 18-49 years

In all studies, the study participants received one dose of RSV MAT vaccine (or control) except in RSV MAT-011 study, where some participants received a second dose. For participants in MAT-011 study who received a second dose, any pregnancy conceived after first dose will be considered in this study; MAT-011 participants enrolled in the prospective cohort will be followed for pregnancies conceived up to 2 years post last dose. In studies with non-pregnant women, the study participants were followed up to 6 months post-vaccination. In studies including pregnant women, safety of the candidate

vaccine was evaluated in maternal participants for up to 6 months after delivery. Safety in infants was evaluated for up to 12 months after birth. Safety evaluation included assessment of medically attended AEs, serious adverse events, pregnancy outcomes, and pregnancy-related and infant adverse events of special interest (AESIs).

Following review of the data collected from the RSV MAT-009 study in pregnant women, a safety signal was identified. An imbalance in the proportion of preterm births was observed in infants born to vaccinated mothers who received RSV maternal vaccine versus those who received placebo. The safety signal was investigated and based on the above observations, GSK decided to stop enrollment and vaccination for all actively enrolling RSV MAT studies as of 28 February 2022. From this date, no new pregnant or non-pregnant women were enrolled or vaccinated in the studies. Children born to participating pregnant women ***who were vaccinated were*** continued to be followed-up in these studies. Safety monitoring of all enrolled participants continued during the rest of the study period.

As the ***identified*** safety signal is pregnancy-related and related to neonatal events, GSK decided to continue to evaluate safety of RSVPreF3 in pregnancies conceived after the prior study vaccination. This current study will enroll women who were enrolled in the RSV MAT-001, RSV MAT-004, RSV MAT-010, RSV MAT-011, RSV MAT-009, RSV MAT-012 or RSV MAT-039 studies and record information about their pregnancies conceived post-study vaccination (if they occur prior to/during the current study period). To clarify, for those enrolled in prior studies of pregnant women (i.e., RSV MAT-004, RSV MAT-009, RSV MAT-012), this study will follow-up the subsequent pregnancies conceived after the *prior* study pregnancy in which RSVPreF3 vaccination (or control) was administered.

2.3. Benefit/risk assessment

No intervention will be administered in this study.

Detailed information about the known benefits and risks and expected AEs of RSV Maternal Vaccine (RSVPreF3) can be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the incidence of pregnancy outcomes, pregnancy related adverse events of special interest (AESIs) and infant AESIs during the first pregnancy conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.	Incidence of pregnancy outcomes, pregnancy related AESIs and infant AESIs during the first pregnancy conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
Secondary	
To describe the incidence of pregnancy outcomes, pregnancy related adverse events of special interest (AESIs) and infant AESIs during any pregnancy conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.	Incidence of pregnancy outcomes, pregnancy related AESIs and infant AESIs during any pregnancy conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
To describe the incidence of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by risk status and by selected risk factors for or causes of those events/outcomes during pregnancies conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to day 42 post-delivery.	Incidence of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by risk status and by selected risk factors for or causes of those events/outcomes during any pregnancy conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
	Incidence of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by risk status and by selected risk factors for or causes of those events/outcomes during the first pregnancy conceived ***within 2 years*** post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
Tertiary (Exploratory)	
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall design

See Section 1.2 for the study schematic diagram.

This study will be a combination of retrospective and prospective cohort design with two groups. RSVPreF3 vaccine group will include participants who received RSVPreF3 vaccine in RSV MAT studies and control group will include participants who received any control (placebo, Tdap or influenza vaccine) during ***prior*** RSV MAT studies.

- **Retrospective cohort**
  - Current study participants who are more than 2 years after vaccination/control and are not currently pregnant at the time of study enrollment will be included in this study cohort.
    - Participants previously enrolled in ***prior*** RSV MAT studies will be included in this cohort.
    - For participants enrolled in prior studies of pregnant women (i.e., MAT-004, MAT-009, MAT-012), data collection for this cohort will not include the prior study pregnancy.
  - Medical data related to any pregnancy conceived post RSVPreF3 vaccine or any control (placebo, Tdap or influenza vaccine) through study enrollment (even if the pregnancy was conceived after 2 years post-vaccine/control) will be collected retrospectively from the date of start of current study pregnancy up to Day 42 (approximately 6 weeks) post-delivery.
  - Infants will be enrolled with the maternal participants at Visit 1 and all relevant medical data until Day 42 post-delivery will be retrieved.
- **Prospective cohort:**
  - Current study participants who are within 2 years+2 months after vaccination/control or with ongoing pregnancies (pregnancies prior to Day 42 post-delivery) at the time of study enrollment will be included in this study cohort.
  - Study participants enrolled in ***prior*** RSV MAT studies will be included in this study cohort.
    - For participants enrolled in prior studies of pregnant women (i.e., MAT-004, MAT-009, MAT-012), data collection for this cohort will not include the prior study pregnancy.
  - All participants will be followed up for 2 years+2 months post RSVPreF3 or control vaccination to record any pregnancy conceived within 2 years post vaccine/control. If the participant is pregnant at 2 years post-vaccine/control, study follow-up will continue until day 42 post-delivery.

Note: Pregnancies reported during prospective follow-up at approximately 2 years+2 months that were conceived after 2 years post-vaccine/control will not be included in the study.

- Medical data related to any pregnancy conceived post RSV MAT (RSVPreF3) vaccine and any control (placebo, Tdap or influenza vaccine) will be collected from the date of start of current study pregnancy up to day 42 (approximately 6 weeks) post-delivery.
- Infants will be enrolled at Delivery and all relevant medical data until Day 42 post-delivery will be collected.

- **Type of study and design:** A safety follow-up cohort study.
- **Study period:** ***The*** study period starts from the date of start of any pregnancy conceived after RSV MAT vaccination (RSVPreF3) or control vaccination in RSV MAT studies or from the date of current study enrollment, whichever date is earlier. The study period ends at current study enrollment for retrospective cohort participants. The study period ends at 2 years+2 months post vaccine/control for prospective cohort participants who are not pregnant at 2 years post vaccine/control. The study period ends at Day 42 post-delivery for prospective cohort participants who are pregnant at 2 years post vaccine/control ***or at study enrollment.***
- **Number of participants:** All adolescent or adult study participants (approximately 8240) from the above-mentioned RSV MAT studies will be considered for enrollment based on the eligibility criteria. Approximately 650 enrolled study participants are estimated to have at least one pregnancy of interest for this study (see Section 9.5 for detailed calculations). Even approximately 300 participants with pregnancy information included in the study would still provide reasonable precision to detect and estimate most of the events of interest in the study.

4.2. Scientific rationale for study design

See Section 2.1 and Section 2.2.

4.2.1. Participant input into design

Not applicable

4.3. Justification for dose

Not applicable

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last contact (study conclusion). This last contact can be either 1) at current study enrollment for retrospective cohort participants, 2) at 2 years+2 months post vaccine/control for prospective cohort participants who are not pregnant at 2 years post vaccine/control, or 3) at Day 42 post-delivery for prospective

cohort participants who are pregnant at 2 years post vaccine/control ***or who are pregnant at enrollment***. The study may be terminated earlier if other research demonstrates no impact of vaccination on pregnancies conceived post-vaccination.

4.5. Study limitations

- The study participants who decide to enroll in this study are already aware whether they received RSVPreF3 or control. Study participants from prior RSV MAT pregnancy studies who experienced an adverse pregnancy outcome or a pregnancy/infant event from a prior pregnancy, may choose to participate in the current study at different rates than those who did not. This may lead to selection bias. As we have information on prior vaccination/control and prior adverse events/outcomes, we can evaluate whether this occurs and consider statistical analysis approaches to adjust for this.
- Comparison between incidence of events or outcomes in this study and events or outcomes in previous RSV MAT studies likely cannot be made directly because of the following possible limitations: 1) the expected sample size for this study is too small for the study to be adequately powered for comparisons, 2) this study has different inclusion and exclusion criteria, 3) this study has different timepoint of pregnancy at enrollment (as early as possible), and 4) different risk factors for participants in this study, such as a relatively short inter-pregnancy interval for pregnancies included in this study.
- This study includes two cohorts, one for which ***all*** data will be collected retrospectively and the other cohort for which data will be collected prospectively ***(with some retrospective data collection)***. This approach was taken so that the number of enrolled participants can be maximized. However, this may result in underestimation of the true incidence of AESIs in a pooled cohort (retrospective and prospective), as the retrospective cohort is more subject to recall bias.
- This study is conducted with a proportion of the same participants enrolled in previous RSV MAT studies which uncovered a safety signal, as described in Section 2.2. As there is still no plausible mode of action or known imbalance in risk factors across RSVPreF3 vs. control groups identified that explains the safety signal, the possibility remains there is unknown confounding (an unmeasured risk factor or exposure) leading to the safety signal. If there is unknown confounding, that may lead to a similar safety finding in this study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population will include up to 8240 participants ***(those who had conceived before study enrollment, those with ongoing pregnancy or who at enrollment may not have conceived but are followed for conception within 2 years post vaccine/control)*** from RSV MAT studies to collect pregnancy outcome, pregnancy related AESIs and infant AESIs for any pregnancy conceived post-vaccination ***(refer Section 9.5)***.

All study participants who have received either RSVPreF3 vaccine or control (placebo, Tdap only, influenza vaccine only) will be included in this study.

Study participants with any pregnancy conceived after vaccination with Day 42 post-delivery at or before study start (i.e., any pregnancy conceived after vaccination is a past pregnancy) will be included in the retrospective cohort and retrospective data will be collected from medical records.

Study participants with any pregnancy conceived after vaccination ongoing at study start (pregnancy prior to Day 42 post-delivery) or newly reported during current study follow-up will be included in the prospective cohort and relevant data will be collected from medical records, as identified through structured follow-up contacts.

5.1. Inclusion criteria

5.1.1. Retrospective cohort

Adult/Adolescent Participant:

- Adult/Adolescent study participant, from ***any of the prior RSV MAT*** studies who have either received RSV MAT vaccine or control (placebo, Tdap or influenza vaccine).
- Study participant:
  - Who has reached 2 years+2 months post vaccine/control prior to/at enrollment or
  - who has not reached 2 years+2 months post vaccine/control prior to/at enrollment but is a Woman of Nonchildbearing Potential (WONCBP) as defined in Section 10.3.1.2 at study enrollment, or recipient of bilateral tubal ligation prior to study enrollment.
- Study participant with any pregnancy conceived post-vaccination/control, that has reached Day 42 post-delivery prior to/at enrollment.
- Provide signed and dated informed consent form.
- Be willing to comply with all study requirements and be available for the duration of the study.

Infant Participant:

- Participant live born as the result of a pregnancy followed in an adult/adolescent participant in this study.
- Signed and dated informed consent form obtained from the participant's parent(s)/LAR(s) prior to performance of any study-specific procedure.

5.1.2. Prospective cohort

Adult/Adolescent Participant:

- Adult/adolescent study participant from ***any of the prior RSV MAT*** studies who have either received RSV MAT vaccine or control (placebo, Tdap or influenza vaccine).
- Study participant:
  - Who has not reached 2 years+2 months post vaccine/control prior to/at enrollment or
  - Who has reached at least 2 years+2 months post vaccine/control but has an ongoing pregnancy (prior to Day 42 post-delivery) at enrollment. Participants who have reached 2 years post-vaccine/control before enrollment but are pregnant at enrollment will be enrolled and followed until Day 42 post-delivery for the pregnancy ongoing at enrollment.
- Female participants of childbearing potential.
- Provide signed and dated informed consent form.
- Be willing to comply with all study procedures and be available for the duration of the study.

Infant Participant:

- Participant live born as the result of a pregnancy followed in an adolescent/adult participant in this study.
- Participant's parent(s)/LAR(s), in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Signed and dated informed consent form obtained from the participant's parent(s)/LAR(s) prior to performance of any study-specific procedure.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Adult/adolescent participant otherwise eligible for the prospective cohort:

- Woman of Nonchildbearing Potential (WONCBP) as defined in Section 10.3.1.2 at study enrollment, or recipient of bilateral tubal ligation prior to study enrollment, if she has not conceived a pregnancy post-vaccine/control ***and does not plan to use any additional measures to attempt to conceive a pregnancy (e.g., sterilization reversal or IVF).***

Infant participant:

- Child in care.

5.3. Lifestyle considerations

No lifestyle restrictions are required for this study.

5.4. Screen failures

No screen failures are expected.

5.5. Criteria for temporarily delaying enrollment

Not applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Not applicable.

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for compliance reasons. ***Investigators may also withdraw participants from the prospective cohort who become a WONCBP as defined in Section 10.3.1.2 or receive bilateral tubal ligation during the prospective follow-up, if they do not plan to use any additional measures to attempt to conceive a pregnancy (e.g., sterilization reversal, or IVF).***

Investigators will attempt to contact participants who do not respond to or complete scheduled follow-up contacts.

All data collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:

- ***Adverse event requiring expedited reporting (AESI and SAE) (prospective cohort only)***
- ***Non-serious adverse event (MAE) (prospective cohort only)***

- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Site terminated by Sponsor
- Study terminated by Sponsor
- Withdrawal by participant
- ***Migrated/moved from the study area***
- Other (specify).

Participants who are withdrawn from the study because of MAEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to a MAE/SAE until the event is resolved (see Section 10.2.3.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to complete follow-up contacts (or scheduled visits) and is unable to be contacted by the study site.

A participant will be considered 'provisional lost to follow-up' if the participant is considered lost to follow-up but has not reached the end of the study follow-up period. Unless there is a compelling reason, participants with a provisional lost to follow-up status should not receive further study-related contact from the study sites. A provisional lost to follow-up participant who subsequently contacts the site and wants to resume follow-up may resume study activities, provided that the participant has not reached the end of the study follow-up period.

The following actions must be taken if a participant fails to complete a follow-up contact (or fails to return to the clinic for a required study visit):

1. The site must attempt to contact the participant and reschedule the missed visit or follow-up contact as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule or follow-up contact and ascertain whether the participant wishes to and/or should continue in the study.
2. Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
3. The site will then mark the participant as provisional lost to follow-up. This designation can be removed if the participant recontacts the site to resume study follow-up before the end of their study follow-up period.

4. Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
5. Final lost to follow-up status should be determined at the end of the study when a ***participant*** has reached the end of the study follow-up period (e.g., 2 years post-vaccine/control + 2 months) without returning for or responding to one or more of his/her final study visits or study contacts. The date of last participant contact will be considered to be the date of study withdrawal for lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

6. Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 1.3). Protocol waivers or exemptions are not allowed.
7. Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
8. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
9. In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data and lifestyle characteristics

Record demographic data such as date of birth, ***sex (for infant participants),*** race, and ethnicity in the participant's eCRF. Record lifestyle characteristics data such as smoking and substance use in the participant's eCRF will be collected towards the end of pregnancy.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the participants, and to determine if the participants are truly representative of the impacted population.

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history prior to the current study pregnancy follow-up by interviewing the participant/parent(s)/LAR(s) and/or review of the participant's medical records. Record any vaccinations received from one month prior to the current pregnancy. Record any pre-existing conditions, signs and/or symptoms present prior to the current pregnancy in the eCRF.

8.2. Immunogenicity assessments

Not applicable.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Safety monitoring and committee

Safety evaluations will include those performed by investigators, as well as those by a SRT composed of GSK RSV team members.

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

If the SRT's decision(s) after a safety evaluation require(s) them to take some action (e.g., to suspend, modify, or continue the conduct of the study for all groups or for selected groups), the SRT Chair (or his/her representative) will notify the study ***CSL***. The study ***CSL*** will be accountable for notifying investigators in writing of the SRT's decision(s).

An external case adjudication committee will provide an independent, objective, blinded review and judgement on cases of preterm births. The scope of review by this committee will be limited to only review of gestational age at birth (to determine status of preterm birth cases) and preterm birth cases but may be expanded at the discretion of the GSK clinical study team. The details of structure and scope of this committee will be included in external case adjudication committee charter.

8.4. MAEs, serious adverse events (SAEs) and SAEs due to study participation, AESIs, and other safety reporting

For definitions relating to safety information see Section 10.2.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of a MAE, SAEs, AESI (see Section 10.2) , SAE due to study participation and other safety information and remain responsible for following up all MAEs, SAEs, AESIs, SAEs considered related to the study participation that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

SAEs due to study participation, defined as SAEs which in the opinion of the investigator are related to the study participation (e.g., accident during any of the study contact and/or ***study*** visit) will be recorded throughout the study period.

The method of recording, evaluating, and assessing causality of SAEs and SAEs due to study participation and the procedures for completing and transmitting SAE due to study participation reports are provided in Section 10.2 and/or Section 8.4.6.

8.4.1. Time period and frequency for collecting MAE, SAE, and other safety information

All SAEs due to study participation will be collected from the signing of the ICF and/or IAF until Day 42 post-delivery or study conclusion at the time points specified in the SoA (Section 1.3).

SAEs assessed as related to study participation (e.g., protocol-mandated procedures) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

MAEs and SAEs for maternal participants will be collected during pregnancy until Day 42 post-delivery at the time points specified in the SoA (Section 1.3).

Table 6 Collection and reporting of safety information

Event	Visit 1 D1	Bi-annual contacts for 2 years until pregnancy	*Initial Pregnancy Contact*	Monthly contacts until Delivery	Delivery	Contact Day 42 post-delivery	Study Conclusion
SAEs related to study participation** ***or related to a GSK product***							
Pregnancy outcome							
MAEs							
SAEs							
Pregnancy related AESIs							
Infant AESIs							
Infant MAEs							
Infant SAEs							

* i.e., consent obtained; D: Day, M: Month
** Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures) ***or related to a GSK product*** will be recorded from the time a participant consents to participate in the study.
The shaded regions in the table indicate time period of data collection

All SAEs, AESIs and SAEs related to study participation will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available and/or awareness.

A poststudy SAE is defined as any event that occurs outside of the SAE reporting period defined in Section 8.4.1 and Table 6.

Investigators are not obligated to actively seek information on SAEs after conclusion of the study participation. ***However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to study participation, the investigator must promptly notify the sponsor.***

8.4.2. Method of detecting SAEs and SAEs due to study participation

Care will be taken not to introduce bias when detecting SAEs and SAEs due to study participation. Open-ended and nonleading verbal questioning of the participant/participants' parent(s)/LAR(s) is the preferred method to inquire about SAEs and SAEs due to study participation occurrences.

8.4.3. Follow-up of SAEs and SAEs due to study participation

After the initial SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and SAEs due to study participation will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.3.5.

8.4.4. Adverse events of special interest

All pregnancy related AESIs will be collected during pregnancy until Day 42 post-delivery at the time points specified in the SoA (Section 1.3).

Infant AESIs will be collected from birth until Day 42 post-delivery at the time points specified in the SoA (Section 1.3).

8.4.5. Data Source and Data Collection for AESIs

8.4.5.1. List of AESIs

Pregnancy-related AESIs	**Infant** AESIs

• Hypertensive disorders of pregnancy:
  ○ gestational hypertension,
  ○ pre-eclampsia,
  ○ pre-eclampsia with severe features including eclampsia;
• Fetal growth restriction;
• Pathways to preterm birth:
  ○ premature preterm rupture of membranes,
  ○ preterm labor,
  ○ insufficient cervix
  ○ provider-initiated preterm birth;
• Gestational diabetes mellitus; and
• Chorioamnionitis.
	• Small for gestational age,
	• Low birth weight including very low and extremely low birth weight (<2500 g, <1500 g, <1000 g),
	• Congenital anomalies:
	  ○ major external structural defects,
	  ○ internal structural defects,
	  ○ functional defects,
	• Neonatal death
	  ○ in a non-viable live birth [<22 weeks gestation]
	  ○ in an extremely pre-term birth [22.GA<28 weeks],

Pregnancy-related AESIs	**Infant** AESIs
	○ in a preterm live birth [28.GA<37 weeks], ○ in a term live birth, • Preterm birth

8.4.5.2. Retrospective data source *and data collection*

For ***pregnancies completed (through Day 42 post-delivery) prior to enrollment***, medical data related to pregnancy outcome, pregnancy related AESIs and infant AESIs of any pregnancy conceived post-RSVPreF3 or control vaccination, based on medical records, will be retrospectively collected. ***Data collection will be done through a single structured participant contact to retrospectively collect information about any healthcare received by the mother and infant during pregnancy up to Day 42 post-delivery. This will identify the medical records for review, so that information about any outcome, medically attended event, SAE, or event of special interest is obtained directly from medical records.***

All relevant data collected in the medical records will be recorded in an electronic case report form (eCRF).

8.4.5.3. Prospective data source and data collection

For participants in the prospective cohort, prospective data collection related to pregnancy outcome, pregnancy related AESIs and infant AESIs of any pregnancy conceived post-vaccination ***and ongoing at enrollment or conceived after enrollment*** will be done through ***multiple*** structured ***participant*** follow-up contacts to collect information about any healthcare received ***by the mother and infant during pregnancy up to Day 42 post-delivery. This will identify the medical records for review, so that*** information about any outcome, ***medically attended event, SAE*** or event of special interest ***is obtained directly*** from medical records.

- Follow-up contact every six months if not pregnant, up to 2 years (+2 months) post-vaccination/control.
- A follow-up Contact or Visit at the start of the pregnancy.
- Spontaneous reporting of pregnancy by study participants.
- Monthly contacts during any pregnancies conceived within 2 years post-vaccination/control, until Day 42 post-delivery.
- Follow-up Contact at Delivery.
- Follow-up Contact at Day 42 (~6 weeks) post-delivery.

All relevant data collected in the medical records will be recorded in an electronic case report form (eCRF).

8.4.6. Regulatory reporting requirements for SAEs, SAEs due to study participation and AESIs

- Prompt notification by the investigator to the sponsor of an SAE, SAE due to study participation and AESI is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs, SAEs due to study participation and AESI, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.2.3.3.
- An investigator who receives an investigator safety report describing an SAE due to study participation or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 7 Timeframes for submitting SAE due to study participation and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Electronic Adverse Events Report	24 hours*	[paper/electronic] Adverse Events Report
SAEs due to study participation	24 hours*‡	Electronic Adverse Events Report	24 hours*	[paper/electronic] Adverse Events Report
AESIs	24 hours*‡	Electronic Adverse Events Report	24 hours*	[paper/electronic] Adverse Events Report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper Adverse Events Report will be dated and signed by the investigator (or designee). For each SAE due to study participation, the investigator(s) must document in the medical notes that they have reviewed the SAE due to study participation and have provided an assessment of causality

8.4.7. Contact information for reporting SAEs, SAEs due to study participation and AESIs

Table 8 Contact information for reporting SAEs, SAEs due to study participation and AESIs

Study contact for questions regarding *SAEs,* SAEs due to study participation and AESIs Contact GSK's local and/or medical contacts
Contacts for reporting SAEs due to study participation Available 24/24 hours and 7/7 days ogm28723@gsk.com

8.4.8. Additional reporting guidance for pregnancies reported during study period

8.4.8.1. Labor and Delivery

- An *uncomplicated* vaginal delivery or planned cesarean section *expected* to occur in a hospital setting should NOT be reported as an AE, MAE or SAE.
- A medical *complication* that requires a cesarean section or an emergency induction may be reported as an SAE/AESI (as applicable), using the corresponding Expedited AE report form.

8.4.8.2. Reporting of congenital anomalies in relation to pregnancy outcomes and SAEs and/or AESIs

Table 9 summarizes the requirements for AESI/SAE reporting of adverse pregnancy outcomes when congenital anomalies are/are not present.

Table 9 Reporting pregnancy outcomes with or without congenital anomalies as AESIs and/or SAEs

	Live birth		Fetal death /stillbirth		Elective / Therapeutic Termination	
Congenital anomalies*	**AESI**	**SAE**	**AESI**	**SAE**	**AESI**	**SAE**
None	-	-	-	X	-	X
Major[1]	X	if reportable per MACDP[3]	-	X	-	X
Minor[2]	-	if reportable per MACDP[3]	-	X	-	X

* In the event of infant's participation in the study, congenital anomalies are to be reported in the infant's eCRF. However, when there is no live birth, or no signed informed consent for the infant or the congenital anomaly is being reported for a subsequent pregnancy, it will be encoded in the maternal participant's eCRF.
[1]Structural or functional defects that require surgical and/or medical treatment and that have serious adverse effects on health or development (functional) or have significant cosmetic impact.
[2]Anatomic variants or defects that do not have serious medical, functional or cosmetic consequences for the child.
[3] Metropolitan Atlanta Congenital Defects Program (MACDP) 6-Digit Code Defect List

Additional guidance when congenital anomalies are present are as follows:

The term "congenital anomaly" is broad. GSK uses the case definitions provided in the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program guidelines, with specific reference to the MACDP 6-Digit Code Defect List [MACDP, 2021] to ensure that the collection and recording of these data is complete and consistent across studies and projects.

To report a pregnancy outcome of live birth with congenital anomaly as an SAE per these guidelines, an infant must have a birth defect that is *included in MACDP surveillance data* per the MACDP 6-Digit Code Defect List. (Congenital anomalies that are not included in MACDP surveillance data may be reported as medically attended or serious adverse events, if appropriate).

The characterization of major and minor congenital anomalies will follow CDC definitions [CDC, 2019]. Major congenital anomalies are structural or functional defects that require surgical and/or medical treatment and that have serious adverse effects on health or development (functional) or have significant cosmetic impact. They are always reported as AESIs, even if they are not reportable as SAEs.

Minor congenital anomalies are anatomic variants or defects that do not have serious medical, functional or cosmetic consequences for the child. Minor congenital anomalies are not to be reported as AESIs, even if they are reportable as SAEs.

If minor congenital anomalies are ***not*** reportable ***as per MACDP***, they should be recorded on the infant ***AE eCRF***. ***Whether the event was medically attended or not should also be recorded in the infant AE eCRF. If they are not medically attended, they should be reported in the infant AE eCRF as medically attended event category "none".***

For example:

- Cleft palate is a major congenital anomaly and should be reported as an AESI. Per the MACDP 6 Digit Code Defect list, cleft palate is always included in MACDP surveillance data and should therefore also be reported as an SAE.
- If congenital aortic valve insufficiency or regurgitation meets the criteria for a major congenital anomaly, it is an AESI. Per the MACDP 6-digit code list, congenital aortic valve insufficiency or regurgitation is only included in MACDP surveillance data and should only be reported as an SAE if designated as moderate or severe, or (if the degree is not specified) if another heart defect is present. Other cases could be reported as medically attended or serious adverse events if the infant meets any other protocol criterion for a medically attended or serious AE because of the condition.
- Mongolian spots, in the absence of any associated findings represent a minor congenital anomaly. Per the MACDP 6-digit code list, they are never included in MACDP surveillance data. They are neither an AESI nor an SAE. They do not typically satisfy the criteria for a medically attended AE and so, in general, would only be recorded ***on*** the ***infant AE*** eCRF.

8.4.9. Treatment of adverse events

- Any medication administered for the treatment of an SAE/AESI should be recorded ***on*** the Expedited Adverse Event Report of the participant's eCRF screen.

8.4.10. Covid-19 Infection

Maternal and infant COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard medically attended AE or SAE criteria, as outlined in Section 10.2. Additionally, all reported COVID-19 infections during a study pregnancy will be captured and reported on a COVID-19 screen of the eCRF.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition [***WHO, 2022***] using one of the following terms:

- Suspected COVID-19 infection
- Probable COVID-19 infection
- Confirmed COVID-19 infection.

8.5. Pharmacokinetics

PK is not evaluated in this study.

8.6. Pharmacodynamics

PD is not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Not applicable for this study.

8.10. Health economics or medical resource utilization and health economics

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical hypotheses

This study is descriptive without statistical hypotheses. The primary and secondary objectives, as outlined in Section 3, are planned to be addressed using descriptive statistics.

9.2. Analysis sets

Table 10 Maternal Participants

Analysis Set	Definition / Criteria
Screened	All participants who were screened for eligibility.
Enrolled	All maternal subjects who completed the informed consent process and signed the informed consent form and were determined eligible for study participation. Note screening failures (who never passed screening even if rescreened) are excluded from the Enrolled analysis set as they did not enter the study.
Full Analysis Set (FAS)	***All maternal subjects who had pregnancy defined by this study (defined in Section 5.1).***

Table 11 Infant Participants

Analysis Set	Definition / Criteria
Enrolled Infant	Infants live born to the maternal set, whose parents/LARs completed the informed consent process and signed the informed consent form.
Full Analysis Set (FAS)	All infant subjects in the infant set who have post-delivery/birth data.

9.3. Statistical analyses

9.3.1. General considerations

All statistical analyses are descriptive. Besides the primary analyses, sub-group analyses may be conducted.

All primary and secondary analyses will be performed on the ***Full Analysis Set***.

9.3.2. Primary endpoints analysis

	Primary Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs within the **first** pregnancy ***conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery***.	The number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs within the first pregnancy conceived ***within 2 years*** post-vaccine/control will be tabulated with its exact 95% CI by study arms. By participant listings of pregnancy related outcomes and AESIs will be prepared
Infant participants	Number and percentage of infant participant reporting infant AESIs from the **first** pregnancy ***conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery***.	The Number and percentage of infant participant reporting infant AESIs from the first study pregnancy conceived ***within 2 years*** post-vaccine/control will be tabulated with its exact 95% CI by study arms. By participant listings of infant AESIs will be prepared.

Pregnancy outcomes include (not limited to) spontaneous abortion, stillbirth, and preterm birth. The pregnancy related adverse events of special interest (AESIs) and infant AESIs are listed in Section 8.4.5.1.

9.3.3. Secondary endpoints analyses

9.3.3.1. Pregnancy outcomes and AESIs from any study pregnancy

	Secondary Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs during **any** study pregnancy ***conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery***.	The number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs during any pregnancy ***conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery,*** will be tabulated with its exact 95% CI by study arms on subject level. By participant listings of pregnancy related outcomes and AESIs will be prepared.
Infant participants	Number and percentage of infant participant reporting infant AESIs from **any** study ***pregnancy conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery***.	The Number and percentage of infant participant reporting infant AESIs from any pregnancy ***conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery,*** will be tabulated with its exact 95% CI by study arms on subject level. By participant listings of infant AESIs will be prepared.

9.3.3.2. Selected pregnancy outcomes and AESIs by selected risk factors

The number and percentage of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by study arms, stratified by selected risk factors, will be tabulated with exact 95% CIs for both first and any study pregnancy ***conceived within 2 years post-vaccination in participants enrolled in prior RSV MAT studies up to Day 42 post-delivery***. Their relative risk estimates with 95% CIs and observed p-values will be reported for all comparisons accordingly.

Regarding preterm birth outcome, the comparisons will be conducted by study arms and by the combination of study arms and preterm birth history (Yes/No) in prior MAT study. The risk factors to be explored may include maternal smoking/household smoke exposure, maternal substance abuse, infections during pregnancy, COVID infection during pregnancy, prior preterm delivery, multiple gestation pregnancy, and short inter-pregnancy interval (less than 18 months between pregnancies), pregnancy complications such as preeclampsia and fetal distress.

9.3.4. Exploratory endpoints analyses

Exploratory analyses of pregnancy outcomes, pregnancy related adverse events of special interest (AESIs), infant AESIs, and any other analysis (as applicable) will be described in the statistical analysis plan and may be summarized in one or more annexes to the clinical study report.

9.3.5. Other safety analyses

For medically attended AEs until Day 42 post-delivery (Mothers: conception to Day 42 post-delivery; Infants: birth to Day 42), the number and percentage of maternal or infant participants with each medically attended AE with exact 95% CIs will be tabulated by study arms and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-participant listings will be prepared.

For SAEs due to study participation, the number and percentage of participants with each SAE with exact 95% CIs will be tabulated by study arms and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-participant listings will be prepared.

9.4. Interim analyses

Not applicable.

9.5. Sample size determination

All analyses will be descriptive and thus no hypothesis driven sample size calculation was conducted.

As noted in Section 4.1, all study participants (approximately 8240) from prior RSV MAT studies will be considered for enrollment in this study based on the eligibility criteria. Assuming the study will start on December 7th, 2022, the study potential subjects include: (1) those who had deliveries defined in Section 5.1.1 (to be enrolled to Retrospective cohort); (2) those with ongoing pregnancy, or who at enrollment have not conceived but subsequently conceive within two years since the vaccination/control in previous RSV MAT studies as defined in in Section 5.1.2 (to be enrolled to Prospective cohort). The actual sample size will mainly depend on: (1) the enrollment rate of those subjects who participated in the previous RSV MAT studies; (2) the incidence rate of pregnancy conceived post RSVPreF3 (or control) vaccination during study period.

To estimate the incidence rate of first pregnancy conceived post RSVPreF3 (or control) vaccination, we considered the likelihood of pregnancy among participants in prior studies of non-pregnant women and pregnant women separately (approximately 8240 total). Among non-pregnant women (approximately 2540), we estimate approximately 10% will have a pregnancy during the time period of this study [Curtin, 2013]. Assuming 60% enroll in this study, we estimate approximately 150 non-pregnant women in prior studies who enroll in this study will have a pregnancy. Among pregnant women (approximately 5700), we estimated approximately 50% would have another pregnancy. From data on inter-pregnancy intervals in US women, we estimated approximately 30% of those subsequent pregnancies will occur during the time period of this study [Thoma, 2016]. Assuming 60% enroll in this study, we estimate approximately 500 non-pregnant women in prior studies who enroll in this study will have a pregnancy. In total, we estimate approximately 650 enrolled study participants will have at least one pregnancy of interest for this study and contribute to the total number of pregnancies from which incidence rates for events will be calculated.

The lowest rate of the safety signal observed in a MAT-009 study group was approximately 5% (see Section 2.2). A sample size of 300 pregnancy participants will provide 100% probability to detect at least one event (e.g., preterm birth event), providing the true rate is 5%. Assuming only 100 of 300 pregnancy participants are from the previous RSVPreF3 group, it can provide 99.4% probability to detect at least one event on the condition of the true event rate at 5%. For a sample size of 300 pregnancy participants, it will still provide a probability of 78%, 95% or 99% to observe at least one participant with event of interest, even if the true event rate is as low as 0.5%, 1% or 1.5%, respectively. A sample size of 650 pregnancy participants will provide a probability of 96% or 100% to observe at least one participant with event of interest, even if the true event rate is as low as 0.5% or 1%, respectively. The table below presents more scenarios of sample size consideration regarding event rates.

Table 12 Sample size, event rate and probability

Sample size	Event Rate	Probability to observe at least one event
300	0.5%	78%
	1%	95%
	1.5%	99%
	3%	100%
	5%	100%
	7%	100%
500	0.5%	92%
	1%	99%
	1.5%	100%
	3%	100%
	5%	100%
	7%	100%
650	0.5%	96%
	1%	100%
	1.5%	100%
	3%	100%
	5%	100%
	7%	100%
1000	0.5%	99%
	1%	100%
	1.5%	100%
	3%	100%
	5%	100%
	7%	100%

In consideration of the precision of 95% Clopper-Pearson confidence interval (CI) for the event rate, if observed 5% participants experienced a pregnancy outcome AESI among 300 participants, the two-sided 95% CI would be within (2.8%, 8.1%). And among 650 participants, the two-sided 95% CI would be within (3.5%, 7%). The table below presents the precision one can get in more scenarios. Even approximately 300 participants with pregnancy information are included in the study would still provide reasonable precision to detect and estimate most of the events of interest in the study.

Table 13 95% CI on the percentage of participants with event(s) of interest

Sample size	Number of Event(s)	% of Event	95% CI	
			Lower Limit	Upper Limit
300	1	0.33	0.0	1.8
	3	1	0.2	2.9
	5	1.67	0.5	3.8
	9	3	1.4	5.6
	15	5	2.8	8.1
	21	7	4.4	10.5
	30	10	6.8	14.0
500	1	0.2	0.0	1.1
	5	1	0.3	2.3
	10	2	1.0	3.6
	15	3	1.7	4.9
	25	5	3.3	7.3
	35	7	4.9	9.6
	50	10	7.5	13.0
650	1	0.15	0.0	0.9
	7	1	0.4	2.1
	10	1.5	0.7	2.8
	20	3	1.8	4.6
	33	5	3.5	7.0
	46	7	5.2	9.2
	65	10	7.8	12.6
1000	5	0.5	0.2	1.2
	10	1	0.5	1.8
	15	1.5	0.8	2.5
	30	3	2.0	4.3
	50	5	3.7	6.5
	70	7	5.5	8.8
	100	10	8.2	12.0

Note: Precision estimation using PASS2019 19.0.1 (Clopper-Pearson Confidence Intervals for One Proportion).

Participants who withdraw from the study will not be replaced.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, ***IAF (if applicable)***, IB, and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants/participants' parent(s)/LAR(s) and answer all questions regarding the study.
- Potential participants/participants' parent(s)/LAR(s) must be informed that their participation is voluntary. They or their LAR will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant or their LAR.
- ***The investigator must obtain assent from the minor participant in addition to the consent provided by the participants' parent(s)/LAR(s) when a minor can assent to participate in a study. The investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.***
- ***In accordance with local laws and regulations, participants who become legally emancipated during the study, i.e., reach the legal age of consent, must be reconsented.***
- ***The participant must provide consent by signing an ICF, which summarizes the study, includes a consent statement and provides documentation that the participant agrees to continue participating in the study.***
- ***If the participant is incapacitated and cannot provide consent, the parent(s)/LAR(s) can provide consent by signing the ICF on their behalf.***

10.1.4. Recruitment strategy

This study will contact approximately 8240 female participants who were enrolled in one of the ***prior RSV MAT*** studies for participation into this follow-up study. Pre-screening and screening will be tracked on a routine basis and projected enrollment per country will be discussed with the central team on a regular basis.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant/participants' parent(s)/LAR(s) must be informed that their personal/their child's study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant/participants' parent(s)/LAR(s) ***that*** their/their child's data ***will*** be used as described in the informed consent
- The participant/participants' parent(s)/LAR(s) must be informed that their/their child's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report

will be made available upon request, after decision on marketing authorization by regulatory authorities.

- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- ***QTLs will be predefined in the QTL report to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.***
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF/or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, medical records must be available.
- Definition of what constitutes source data and its origin can be found in [e.g. source data acknowledgment or monitoring guidelines].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and site start and closure

***Start of Study and* First Act of Recruitment**

The start of study ***and the first act of recruitment are*** defined as first subject first visit (FSFV)/first contact ***and first ICF signature date*** at a country-level.

Study/Site Termination

GSK or 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. Study sites will be closed upon study completion. A study site is considered closed when all required 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: MAEs and SAEs due to study participation: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.2.1. Unsolicited AE

• **Definition of unsolicited AE**
• An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by participants/ participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/ participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of [participant/ participant's parent(s) /LAR(s)] concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.2.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is 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 that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • 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, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant.
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies*, ectopic pregnancy) ****Refer to Section 8.4.8.2 for additional information.***

10.2.3. Recording, assessment and follow-up of MAEs, SAE, SAE due to study participation and AESIs

10.2.3.1. SAE recording

- When an SAE and/or SAE due to study participation occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant SAE and/or SAE due to study participation information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the SAE and/or SAE due to study participation.

10.2.3.2. Assessment of intensity

The investigator will make an assessment of intensity for each MAE, AESI, ***SAE*** and SAE due to study participation reported during the study and assign it to one of the following categories:

- Mild:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.3.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

- The investigator must review and provide an assessment of causality for each MAE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.2.3.4. Assessment of outcomes for SAEs and SAEs due to study participation

The investigator will assess the outcome of all SAEs and/or SAEs due to study participation recorded during the study as:

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

10.2.3.5. Follow-up of SAEs, SAEs due to study participation, MAEs and AESIs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature of the SAE and SAE due to study participation as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

After the initial SAE, SAE due to study participation or AESIs, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, SAEs due to study participation and events of special interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Follow-up during the study

AESIs, SAEs, MAEs and SAEs due to study participation documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until end of the study.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.2.3.6. Updating of SAE, SAE due to study participation, MAEs and AESI information after removal of write access to the participant's eCRF

When additional SAE, SAE due to study participation, MAEs and AESI information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate ***paper*** report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.2.4. Reporting of SAEs, SAEs due to study participation, MAEs and AESIs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE, AESIs, MAEs and/or SAEs due to study participation to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE, AESIs, MAEs and/or SAEs due to study participation data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE, AESIs, MAEs and/or SAEs due to study participation from a study participant or receives updated data on a previously reported SAE, AESIs, MAEs and/or SAEs due to study participation after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the medical monitor/SAE coordinator by telephone.
- If the site during the course of the study ***or poststudy*** becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE, AESIs and/or SAEs due to study participation reporting can be found in section 8.4.7.

10.2.4.1. Medically attended visits

For each unsolicited symptom the participant experiences, the participant/participant's parent(s)/LAR(s) will be asked if he/she/the participant received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

10.3. Appendix 3: Definition of childbearing potential

10.3.1. Definitions

10.3.1.1. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.3.1.2. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

Premenarchal: Tanner stage 1 (prepubertal)

Permanently sterile due to one of the following procedures:

a. Documented hysterectomy
b. Documented bilateral salpingectomy
c. Documented bilateral oophorectomy

   For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note: the information above is a standard definition of ***WONCBP*** for interventional studies. No additional medical examination or medical procedures will be conducted to determine if someone is a WONCBP for the purposes of this study.

10.4. Appendix 4: Country-specific requirements.

France specific requirements are included in the additional appendix provided with this protocol.

10.5. Appendix 5: Gestational Age Assessment

10.5.1. GAIA GESTATIONAL AGE ASSESSMENT FORM

Based on Quinn, JA, Munoz FM, Gonik B et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016; 34: 6047 – 6056.

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 [1] or 1st trimester U/S
Level 2A	Certain LMP WITH 2nd trimester U/S [1] or Certain LMP WITH 1st trimester physical examination[2]
Level 2B	Uncertain LMP WITH 2nd trimester U/S [1]
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

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;
[1] If LMP and U/S do not correlate, default to U/S GA assessment
[2] For singleton pregnancies only. Unreliable if obesity, or uterine anomalies.

10.5.2. METHODS OF GESTATIONAL AGE ASSESSMENT AND ESTIMATION OF DUE DATE

Adapted from: 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 700, May 2017 (accessed on-line on 05/Mar/2020 at: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/05/methods-for-estimating-the-due-date).

Gestational age range	Method of measurement	Discrepancy between U/S dating and LMP (or IUI or ET dating) prompting re-dating of EDD considering U/S
1st trimester ≤$13^{6/7}$ weeks		
≤$8^{6/7}$ weeks $9^{0/7}$ to $13^{6/7}$ weeks	CRL	> 5 days > 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
3rd trimester		
$28^{0//7}$ weeks and beyond	BPD, HC, AC, FL	> 21 days

U/S: ultrasound examination; LMP: last menstrual period; IUI: intrauterine insemination; ET: embryo transfer; CRL: crown-rump length; BPD: biparietal diameter; HC: head circumference; AC: abdominal circumference; FL: femur length; , EDD: estimated date of delivery
* Based on LMP *(or, if applicable, IUI/ET date)*

10.6. Appendix 6: Definitions of maternal, fetal and neonatal events of interest as per GAIA

- Section 8.4.5.1 lists events of interest per GAIA that must be reported as AESIs.
- Other GAIA events of interest that meet the SAE definition should be reported with enough detail in the SAE narrative to permit level of diagnostic certainty assessment by GAIA criteria.
- Articles that discuss GAIA events of interest in detail can be found in the following issues of *Vaccine* [***Bauwens, 2016; Jones, 2016a; Jones, 2016b; Kochhar, 2017***]:
  - Bauwens J, Bonhoeffer J, Chen RT, editors. Harmonizing Immunisation Safety Assessment in Pregnancy. Vaccine. 2016. 34 (49): 5991 – 6110.
  - Kochhar S, Bauwens J, Bonhoeffer J, editors. Harmonizing Immunization Safety Assessment in Pregnancy – Part II. Vaccine. 2017. 35 (48): 6469-6582.

- ***Jones CE, Munoz FM, Spiegel HM, et. al. Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women. Vaccine. 2016a;34(49):5998-6006.***
- ***Jones CE, Munoz FM, Kochhar S, et. al. Guidance for the collection of case report form variables to assess safety in clinical trials of vaccines in pregnancy. Vaccine. 2016b;34(49):6007-14.***

- Definitions and Levels of Diagnostic Certainty are presented in the following Tables. References specific to each event of interest are given at the end of the relevant Table.

Pregnancy Outcomes	
Fetal Death / Stillbirth	Table 14
Maternal Events of Interest	
Maternal Death ***(Not a study specific AESI)***	Table 15
Hypertensive Disorders of Pregnancy	Table 16
Antenatal bleeding ***(Not a study specific AESI)***	Table 17
Postpartum hemorrhage ***(Not a study specific AESI)***	Table 18
Fetal Growth restriction	Table 19
Gestational Diabetes Mellitus	Table 20
Non-reassuring fetal status ***(Not a study specific AESI)***	Table 21
Pathways to Preterm Birth	Table 22
Chorioamnionitis	Table 23
Standard definitions for events of interest not defined as such in GAIA (Oligohydramnios, Polyhydramnios, Intrahepatic Cholestasis of Pregnancy (ICP), Acute Fatty Liver of Pregnancy, Maternal Sepsis) ***(Not a study specific AESI)***	Table 24
Neonatal Events of Interest	
Small for Gestational Age	Table 25
Low Birth Weight	Table 26
Neonatal encephalopathy ***(Not a study specific AESI)***	Table 27
Congenital Microcephaly ***(Not a study specific AESI)***	Table 28
Congenital Anomalies	Table 29
Neonatal Death	Table 30
Neonatal Infections ***(Not a study specific AESI)***	Table 31
Respiratory Distress in the Neonate ***(Not a study specific AESI)***	Table 32
Preterm Birth	Table 33
Failure to thrive ***(Not a study specific AESI)***	Table 34
Standard definitions for events of interest not defined as such in GAIA (large for gestational age, macrosomia) ***(Not a study specific AESI)***	Table 35

Table 14 Fetal death / Stillbirth

Fetal death occurring before birth after 20 to 28 weeks of gestation (variation due to country definitions).

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 1. Prenatal ultrasound examination documenting lack of fetal cardiac activity or movement before the onset of labor. OR 2. Auscultation for fetal heart tones (using electronic devices or non-electronic devices) documenting lack of fetal heartbeat. AND 3. Maternal report of lack of fetal movement for 24 h or more. OR 4. Maternal physical examination confirming lack of fetal movement. OR 5. Radiology findings consistent with intrauterine fetal death. AND 6. 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 7. 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 1. Maternal report of lack of fetal movement for 24 h or more. OR 2. Maternal physical examination confirming lack of fetal movement. OR 3. Auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND 4. 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 5. 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 1. Maternal report of lack of fetal movement for 24 h or more prior to delivery. OR 2. Report of auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND 3. 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 4. 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, 2016]***: DaSilva FT, Gonik B, McMillan M, et al. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2016; 34(49):6057-6068.

Table 15 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: 1. Ultrasound examination 2. Fetal heart tones 3. Positive serum or urine human chorionic gonadotropin pregnancy test 4. Delivery of a neonate or other products of conception (abortus, stillborn) AND 5. 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: 6. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications 7. Indirect: non obstetric complications 8. 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: 1. LMP date 2. 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: 3. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications 4. Indirect: non-obstetric complications 5. Death during pregnancy, childbirth and the puerperium: other or coincidental 6. Unspecified: unknown or undetermined
3	Absence of Level 1 or 2 criteria for establishing diagnosis of pregnancy and: 1. Unsure LMP 2. 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: 3. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications 4. Indirect: non-obstetric complications 5. Death during pregnancy, childbirth and the puerperium: other or coincidental 6. Unspecified: unknown or undetermined.

Reference ***[Patwardhan, 2016]***: 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 16 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: 1. Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110mmHg, which is confirmed after only minutes OR 2. Development of severe, persistent headache OR 3. Development of visual changes OR 4. Eclampsia* OR 5. New onset thrombocytopenia (platelets <100,000/L) OR 6. New onset unremitting epigastric pain OR 7. AST and ALT elevated to twice upper limit of normal OR 8. Evidence of liver capsular hematoma or liver rupture (diagnosed on clinical exam or with imaging) OR 9. 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 pre-existing seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status:

In Ev = Insufficient Evidence

Reference ***[Rouse, 2016]***: 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 17 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, 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 sub placental 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. Ultrasound evidence of placenta previa, AND hypervascularity at the site of the uteroplacental interface, diagnosed at laparotomy. OR 1. 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.

Antenatal Bleeding continued	
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, 2017]***: 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 18 Postpartum hemorrhage

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

ICD-10 definition: “hemorrhage after delivery of a fetus 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, 2016]***: Kerr R, Eckert LO, Winikoff B, et al. Postpartum hemorrhage: 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 19 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).
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 above, 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, 2017]***: 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 20 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 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 AND Diagnosis of gestational diabetes based on positive internationally recognized oral glucose tolerance test ("major criteria" [1,2]) using capillary blood sample/samples
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 internationally recognized 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, 2017]***: 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 21 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, 2016]***: 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 22 Pathways to preterm birth

Premature preterm rupture of membranes; Preterm labor; Insufficient cervix; 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)	
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): 1. Positive intra-amniotic dye-injection method 2. Positive result on amniotic fluid alpha-fetoprotein test kit 3. Amniotic fluid pH measurement (nitrazine paper test) 4. Amniotic fluid placental alpha macroglobulin-1 protein assay (PAMG-1) test (AmniSure test) 5. 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: – Cervical dilation 2 cm or greater at the internal os by digital examination – Cervical length of 1 cm or less by digital examination – 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: – Cervical dilation 2 cm or greater at the internal os by digital examination – Cervical length of 1 cm or less by digital examination – 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
Insufficient cervix	
Level	***Description***
All	Patient is determined to: • be ≥16 weeks and <24 weeks gestation per definitions of gestational age in Section 10.5 • have advanced cervical dilation (>2 cm) resulting in either treatment with a cerclage (cervical stitch) or preterm delivery • not be in preterm labor, having ≤4 contractions per hour documented clinically or on tocodynometer (with anything >4 contractions per hour falling into the category of preterm labor)
1	• Internal cervical os dilation (>2 cm) with ≤4 contractions/h, as determined by transvaginal ultrasound AND • digital examination
2	• Internal cervical os dilation (>2 cm) with ≤4 contractions/h, as determined by digital examination
3	• Patient reports fetal delivery without any painful contractions • History excludes other causes of mid-trimester delivery

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, 2016]***: 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 23 Chorioamnionitis

Chorioamnionitis encompasses a broad spectrum of disease during pregnancy that is characterized by inflammation and/or infection of intrauterine structures such as the placenta, the chorion and amnion.

This case definition focuses on the infectious manifestation of chorioamnionitis, intra-amniotic infection. Four definitions of chorioamnionitis have been developed based on systematic literature review, are summarized below, and must be considered when applying the case definitions.

It is important to rule out other obvious sources of acute systemic infection (i.e. pyelonephritis) prior to chorioamnionitis diagnosis.

Level	Description
All levels	**Clinical Definition A:** Maternal fever ≥ 38 degrees Celsius on one occasion *plus one or more of*: • Baseline fetal tachycardia (FHR > 160 bpm for 10 min or longer, excluding accelerations, decelerations and periods of marked variability or, where continuous monitoring is not available, an FHR exceeding 160 bpm during and after at least three consecutive contractions) • Maternal WBC ≥ 15,000 per mm3 in the absence of corticosteroids. • Definite purulent fluid from the cervical os. **Clinical Definition B** Maternal fever ≥ 38 degrees Celsius on one occasion *plus two of*: • Maternal tachycardia (HR > 100 bpm) • Baseline fetal tachycardia (FHR > 160 bpm for 10 min or longer, excluding accelerations, decelerations and periods of marked variability or, where continuous monitoring is not available, an FHR exceeding 160 bpm during and after at least three consecutive contractions • Purulent fluid from the cervical os. • Uterine tenderness • Maternal WBC ≥ 15,000 per mm3 in the absence of corticosteroids

Level	Description
	Histologic diagnosis: • Positive finding of invasion of maternal polymorphonuclear leukocytes into the placental plate, the chorion and/or amnion which meets criteria based on a widely accepted histopathologic staging and grading system [such as Blanc1 Redline2, or Salafia3 criteria]. **Culture criteria:** • Positive culture of amniotic fluid (via amniocentesis), and/or • Positive culture of placental membranes (between chorion/amnion) **GAIA gestational age** level 1–2 criteria denote higher gestational age certainty including a combination of certain last menstrual period (LMP), first or second trimester ultrasound or first trimester exam confirmation. Level 3 diagnostic certainty for gestational age has a lower accuracy compared to levels 1–2.
1a	Clinical Definition A AND Confirmation via histopathology or culture AND Gestational age ≥ 22–0/7 weeks by GAIA gestational age level 1–2 criteria
1b	Clinical Definition A AND Confirmation via histopathology or culture AND Gestational age ≥ 22–0/7 weeks by ANY GAIA gestational age criteria
2a	Clinical Definition A OR Chorioamnionitis via histopathology or culture AND Gestational age ≥ 22–0/7 weeks by GAIA gestational age level 1–2 criteria
2b	Clinical Definition B AND Gestational age ≥ 22–0/7 weeks by GAIA gestational age level 1–2 criteria
2c	Clinical Definition A or B OR Chorioamnionitis via histopathology or culture AND Gestational age ≥22–0/7 weeks by any GAIA gestational age criteria
3a	Clinical definition A or B with report of fever or maternal feeling of ‘‘feverishness.’’ AND Gestational age ≥ 22–0/7 weeks by any GAIA gestational age criteria
3b	Clinical definition B without fever (documented or reported) AND Gestational age ≥ 22–0/7 weeks by any GAIA gestational age criteria

[1]W.A. Blanc Pathology of the placenta, membranes, and umbilical cord in bacterial, fungal, and viral infections in man. Monogr Pathol, 22 (1981), pp. 67-132

[2]R.W. Redline, O. Faye-Petersen, D. Heller, F. Qureshi, V. Savell, C. Vogler Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatric Dev Pathol: Off J Soc Pediatric Pathol Paediatric Pathol Soc, 6 (5) (2003), pp. 435-448

[3]C.M. Salafia, C. Weigl, L. Silberman The prevalence and distribution of acute placental inflammation in uncomplicated term pregnancies. Obstet Gynecol, 73 (3 Pt 1) (1989), pp. 383-389

Reference ***[Kachikis, 2019]***: Kachikis, A, Eckart L, Walker C et al. Chorioamnionitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2019; 7610–7622

Table 24 Standard Definitions for Maternal Events of interest not defined as events in GAIA

Event of Interest	Definition
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 pocket 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 institute.

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.

MAP = mean arterial pressure; qSOFA = quick SOFA; SOFA = Sequential [Sepsis-related] Organ Failure Assessment
</td></tr>
</table>

References ***[Ko, 2006; Geenes, 2016; Bonet, 2017]***:

[1] Geenes V. Williamson C, Chappell L. Intrahepatic cholestasis of pregnancy. The Obstetrician and Gynecologist. 2016; 18:273-81.

[2] Ko H, Yoshida E. Acute Fatty Liver of Pregnancy. Can J Gastroenterol. 2006; 20:25-30.

[3] Bonet M, Pileggi V, Rijken M et al. Towards a concensus definition of maternal sepsis: results of a systematic review and expert consultation. Reproductive Health. 2017; 14:67.

Table 25 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: – 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 – First trimester ultrasound
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 exam
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
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

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, 2017]***: 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 26 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	Newborn infant weighed within 24 hours of birth AND Use electronic scale which is graduated to 10 grams AND Scale is calibrated at least once a year AND Scale placed on level, hard surface AND Scale tared to zero grams AND Weight recorded as <2500 grams OR Birth weight recorded as <2500 grams AND Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 5 above.
2	Newborn infant weighed within 24 hours of birth AND Scale (electronic/spring) is graduated to at least 50 grams AND Scale is calibrated at least once a year, or more often if moved AND Scale tared to zero grams or 0.00kg AND Weight recorded as <2500 grams OR Birth weight recorded as <2500 grams AND 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 color-coded scale)
3	Newborn infant weighed on day 1 or 2 of life (first 48 hours of life) AND Weight measured using dial/spring/color-coded scale AND Weight assessed as <2500 grams
4	Newborn weight assessed between day 1 and 2 of life (first 48 hours) AND Proxy measure (newborn foot length, chest circumference, mid upper arm circumference) of birth weight used AND Weight CATEGORY assessed as <2500 grams

Reference ***[Cutland, 2017]***: 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 27 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, 2017]***: 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 28 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 trimester or 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 (e.g. 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 (e.g. 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 (e.g. 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 (e.g. 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 measurement at 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 (e.g. 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, 2017]***: 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. 2017;35:6472 – 6482.

Table 29 Major Congenital anomalies

Congenital anomalies, also commonly referred to as birth defects, congenital disorders, congenital malformations, or congenital 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, 2016]***: 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 30 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	Live born infant AND • Gestational age <22 weeks (GA level of certainty = 1) OR • Birth weight <500 g AND Death of infant in first 28 days of life AND Medically-confirmed death
2	Live born infant AND Gestational age/size of newborn assessed as at least one of: • Gestational age <22 weeks (GA Level of Certainty = 1 OR 2) • Birth weight <500 g AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
3	Live born infant AND Gestational age <5 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
Neonatal death in an extremely preterm live birth	
Level	**Description**
1	Live born infant AND • Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1) OR • Birth weight ≥500 g but <1000 g AND Death of infant in first 28 days of life AND Medically-confirmed death
2	Live born infant AND Gestational age/size of newborn assesses as one or more of: • Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1 OR 2) • Birth weight ≥500 g but <1000 g AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death

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

Neonatal death in a term live birth (continued)	
Level	**Description**
2	Live born infant AND Gestational age/size of newborn assesses as one or more of: • Gestational age ≥37 weeks (GA Level of Certainty = 1 OR 2) • Birth weight ≥2500 g AND Death of infant in first 28 days of life AND 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 Lower Middle Income Countries) 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, 2016]***: 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 31 Neonatal Infections

Neonatal bacteremia and sepsis (of early or late onset), meningitis, pneumonia and other respiratory infections such as bronchiolitis, caused by bacteria, parasites, viruses or fungi. Localized 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	Recognized 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
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	Recognized 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 Recognized 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 • Recognized virus identified using a validated assay from an upper respiratory sample OR • Recognized 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, 2016]***: Vergnano S, Buttery J, Cailes B, et al. Neonatal infections: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34 (49):6038-6046.

Table 32 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, 2017]***: 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 33 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, 2016]***: Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6047-6056.

Table 34 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 Bare weights obtained using an appropriate electronic baby scale AND At least 2 such weights, measured at least 4 weeks apart AND Weight for age or weight for length/height falling by two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time [2,3,4]
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 two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time
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 two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time
3b	Infants with no weight available AND Physical examination consistent with FTT[5] AND MUAC[6] indicative of severe wasting

[1]This case definition is limited to infants up to 12 months of age.
[2]Homan GJ, Failure to Thrive: A Practical Guide. Am Fam Physician. 2016; 94(4):295-9
[3] 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.
[4] 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.
[5] 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.
[6] 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, 2017]***: 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 35 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).

10.7. Appendix 7: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 2 (21 Jun 2023)

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall rationale for the Amendment:

This amendment is being done to include details pertaining to the exclusion criteria for women of nonchildbearing potential, the timeframe for the primary and secondary objectives and the Phase of the study (Phase 3b). It also includes updated information indicating that all the prior studies listed are collectively called as 'prior RSV MAT studies' for both cohorts, to allow participants from any of the prior RSV MAT studies who are pregnant at enrollment to be enrolled in the prospective cohort. It further clarifies the method and source of data collection in the retrospective and prospective cohorts.

Additional updates were made in the objectives and endpoints section, schedule of activities, study design section, participant discontinuation/withdrawal from the study section, safety section, statistical considerations, and appendix.

The list of abbreviations and references were updated, additional information from the current protocol template were included, and some minor edits were made for clarity wherever applicable. Some minor typographical and grammatical corrections were also made in this amendment.

Summary of changes table of previous amendments (Protocol Amendment 1):

Section # and Name	Description of Change	Brief Rationale
10.5.1. GAIA Gestational age assessment form	Removed highlighted text (bold text) in the form and deleted relevant footnotes	To correct an error where GAIA gestational age assessment should not be an enrollment criterion.
Section 7.2 Participant discontinuation/withdrawal from the study Section 7.3 Lost to follow-up	Text in these sections were edited to clarify the criteria to consider for participant discontinuation, withdrawal and lost to follow-up.	To clarify the criteria for participant discontinuation, withdrawal and lost to follow-up.
Table 6 Collection and reporting of safety information	Error in column header corrected	Initial pregnancy contact was incorrectly stated as Visit 2. This has been corrected.
Section 8.4.10 COVID-19 infection	Clarification for capture of COVID-19 related information added	Clarification for COVID-19 data collection added
Table 13 95% CI on the percentage of participants with event(s) of interest	Number of events for sample size of 650 study participants updated.	To correct typos in initial calculation.
Section 8.4.5.1. List of AESIs	Add pathways to preterm birth: insufficient cervix to list of pregnancy AESIs	As this study will collect pregnancy data before 24 weeks gestation, this pathway to

Section # and Name	Description of Change	Brief Rationale
		preterm birth will be relevant as an AESI for this study.
Table 17 Antenatal Bleeding Table 22 Pathways to preterm birth	Removed references to conditions ineligible for this study, add details on insufficient cervix.	To correct errors where specific conditions are referenced as ineligible, as absence of those conditions are not part of enrollment eligibility criteria.

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