Protocol Amendment 3

A Phase II, randomised, observer-blind, placebo controlled multi-country study to assess the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women aged 18 to 40 years and infants born to vaccinated Mothers

NCT ID: NCT04126213
EudraCT number: 2019-001991-12

Amendment 3 Final: 30 September 2020

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209544 (RSV MAT-004)
Protocol Amendment 3 Final

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

Primary Study vaccine and number	• GlaxoSmithKline (GSK) Respiratory Syncytial Virus (RSV) Maternal Vaccine (RSVPreF3) (GSK3888550A)
Other Study vaccines/products	• Placebo (buffered saline)
eTrack study number and abbreviated title	209544 (RSV MAT-004)
EudraCT number	2019-001991-12
Date of protocol	Final Version 1: 09 July 2019
Date of protocol amendment/ administrative change	Administrative change 1 Final: 08 October 2019 Amendment 1 Final: 27 January 2020 Amendment 2 Final: 19 May 2020 Amendment 3 Final: 30 September 2020
Title	A Phase II, randomised, observer-blind, placebo controlled multi-country study to assess the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women aged 18 to 40 years and infants born to vaccinated mothers
Short title	A Phase II observer-blind study to assess safety, reactogenicity, and immunogenicity of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women and infants born to vaccinated mothers
Coordinating author	• PPD Lead Science Writer
Contributing authors	• PPD, Clinical & Epidemiological Project Lead • PPD, Clinical Research and Development Lead • PPD, Lead Statistician; PPD, Study statistician

eTrack study number and abbreviated title	209544 (RSV MAT-004)
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Contributing authors (Cont.)	• PPD, PPD, PPD and PPD, Study Delivery Leads • PPD, Study Delivery Lead, Synteract Contractor for GSK Biologicals • PPD, Clinical Trial Supply manager • PPD, Clinical Read-Out Team Leader • PPD, Clinical Laboratory Sciences Study Manager, Business & Decision Life Sciences Contractor for GSK Biologicals • PPD, Safety Physician • PPD and PPD, Oversight Data Managers • PPD, Regulatory Affairs Representative

GSK Biologicals' Protocol WS v 17 pilot

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Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209544 (RSV MAT-004)
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Sponsor signatory	Ouzama Henry, MD MSc Clinical and Epidemiology Project Lead, RSV Maternal
Signature	
Date	

Protocol Amendment 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccine/product and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- 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 investigational vaccine/product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 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 other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	209544 (RSV MAT-004)
EudraCT number	2019-001991-12
Date of protocol	Final Version 1: 09 July 2019
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Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

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

GSK Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.3.1

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

5. GSK Biologicals' Helpdesk for Emergency Unblinding

Refer to protocol section 6.3.4.1

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES TABLE

Document history

Document	Date
Amendment 3	30-SEP-2020
Amendment 2	19-MAY-2020
Amendment 1	27-JAN-2020
Administrative Change 1	08-OCT-2019
Original Protocol	09-JUL-2019

Amendment 3: 30-SEP-2020

Overall rationale for the current Amendment:

This protocol amendment has been amended to take into account that as of analysis 2, the study is no longer considered observer blind; This amendment was developed because, following analysis 2 the possibility of inadvertent unblinding with the IB update my occur.

In addition, this amendment outlines measures to implement a plan for additional contacts for safety monitoring in the event of problems with ERT.

Changes pertaining to these changes in the amendment are listed below

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Table 6 4.2.5 Study blinding 6.3.4 Blinding and unblinding 9.5.1.1 First analysis 9.5.1.12 Second analysis 9.5.1.3 Third analysis 10.3.8 Recording and follow-up of AEs, SAEs, AESIs and subsequent pregnancies	Observer blind removed following 2nd analysis	After the second analysis, the study will not be considered observer blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study.
Section 8, Study Procedures during special circumstances 8.4.2. Surveillance	New language pertaining to special circumstances has been added.	Outlines measures that may be taken in case ERT portal/ alerts are not functioning, contacts will be conducted at least weekly until NB4/V8. Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local laws and best practice.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

RSV MAT-004 will evaluate, for the first time:

- The safety, reactogenicity, and immunogenicity of the investigational RSV maternal vaccine when administered to healthy women in the third trimester of pregnancy, and
- The effects of maternal immunization on the infants born to these vaccinated women.

A Phase I/II study of this vaccine is underway in healthy *non-pregnant* women (study RSV MAT-001; NCT02753413). The 2 dose levels considered to have the highest immunogenicity associated with an acceptable safety profile in RSV MAT-001 (60 and 120 µg) will be further investigated in the current study (RSV MAT-004).

RSV MAT-004 will only be initiated after a favorable evaluation of all available safety data from completed/ongoing non-clinical studies and from the ongoing RSV MAT-001 study.

Objectives and Endpoints are presented in Table 5**.**

1.2. Schema

This is a multi-center, randomized, observer-blinded, placebo-controlled study. ***Up to*** 300 healthy maternal subjects 18 to 40 years of age (inclusive, at the time of informed consent) will be assigned to one of 3 study groups, and will receive a single intramuscular injection between 28 $^{0/7}$ to 33 $^{6/7}$ weeks of gestation (inclusive) as follows:

- RSVPreF3, 60 µg (N up to ~ 100),
- RSVPreF3, 120 µg (N up to ~ 100), or
- Saline placebo (N up to ~ 100).

Maternal subjects will participate for approximately 9 months (from informed consent until 6 months after delivery), and will be evaluated for reactogenicity, safety, and humoral immune response (including maternal – infant RSV-specific antibody transfer). Infant subjects will be followed for 12 months after birth and will be evaluated for safety and RSV-specific antibody levels. All safety data will be reviewed by a blinded Safety Review Team (SRT) and an unblinded Independent Data Monitoring Committee (IDMC) on an on-going basis.

Section 4.1 provides an overview of the study design; Section 8.2.3 presents additional information about study holding rules and safety monitoring.

1.3. Schedules of Activities (SoA)

For maternal subjects, Table 1 presents the Schedule of Activities (SoA) and Table 2 describes the allowed study visit intervals. For infant subjects, Table 3 presents the SoA and Table 4 describes the allowed study visit intervals.

Whenever possible, the investigator should arrange study visits within the allowed study visit intervals. Immunogenicity data from blood samples collected outside an allowed interval may not be considered in the associated per protocol set (PPS) for analysis.

Please note:

- Study visits, assessments and procedures do not replace local standards of care. If local standard of care recommends additional visits/medical evaluations (for maternal subjects or their infants), subjects should comply with these local recommendations.
- Any adverse event / potential adverse event identified during a study visit or procedure should be treated according to local standards of care or by referral to an appropriate health care provider
- When a maternal subject completes Visit 1 (enrolment), and again at Visit 5 (delivery), site staff should ensure all site study obstetrician(s) and pediatrician(s) are informed. This will help to ensure that study pediatrician(s) and/or staff are aware of the maternal subject's approximate date of delivery and potential enrolment of the neonate.
- Maternal subject Visits 2 (day 8), 3 (day 31), 4 (Day 61), 7 (Day 121 post delivery) and 8 (Day 181 post delivery) and infant subject Visits 1-NB through 5-NB (birth to 12 months after birth) may be conducted through a home visit by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).
- Respiratory tract illness (RTI) assessment visits and event-driven safety visits may take place at the investigator's clinical facility or another medical facility, or via a home visit by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).
- The visit location must have appropriate infrastructure and logistics to support completion of all study procedures. Blood samples must be centrifuged within 1 hour after collection if used to assess biochemistry, or within 2 hours of collection if used to assess hematology or immune response.
- Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local best practice. If the study site is the subject's primary healthcare facility, contact with study personnel may also be made in the context of a visit for routine or event-driven care.
- Refer to Section 8 for information about special circumstances (e.g., the COVID 19 pandemic) and their impact on study activities.

Table 1 Schedule of activities for maternal subjects

Epochs	Epoch 001	Epoch 002											Additional Information
			May be replaced by V5, depending on delivery date				*To coincide with infant visits 2-NB, 3-NB, 4-NB*				*Event Driven*		
Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**											
Visit Day	**D-28 – D-1**	**D1**	**D8**	**D31**	**D61**	**Delivery D1PD**	**D43 PD**	**D121 PD**	**D181 PD**				
Informed consent	●												Section 10.1.3
Check Inclusion/exclusion criteria	●	O											Sections 5.1.1, 5.2.1
Assign maternal subject study number	●												Section 6.3.1
Assign infant subject study number		O											
Record Demographic data and lifestyle characteristics	●												Section 8.2.1.1.1
Review & collect Medical and vaccination history	●	O											Section 8.2.1.1.2
Record outcome of Level 2 ultrasound (also known as a fetal anomaly ultrasound scan or fetal morphology assessment)	●												
Record obstetric history from past and current pregnancies	●												

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Epochs	Epoch 001	Epoch 002											Additional Information
			May be replaced by V5, depending on delivery date				*To coincide with infant visits 2-NB, 3-NB, 4-NB*				*Event Driven*		
Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**											
Visit Day	**D-28 – D-1**	**D1**	**D8**	**D31**	**D61**	**Delivery D1PD**	**D43 PD**	**D121 PD**	**D181 PD**				
Record Travel history to or living in Zika virus endemic countries/regions	●	●	●	●	●	●							During the current pregnancy only
General and obstetrical examination	●	●	●	●	●	●	●	●	●		O	O	General exam is symptom directed at V7, V8, & event-driven visits. Vaginal exams are symptom directed. See Section 8.2.1.2
Pre-vaccination body temperature		●											Preferred location for measurement will be the oral cavity. "Fever" = temperature ≥38.0°C/100.4°F regardless of the location of measurement.
Urine sample	●	●	●	●	●								Table 11

Epochs	Epoch 001	Epoch 002											Additional Information
			May be replaced by V5, depending on delivery date				*To coincide with infant visits 2-NB, 3-NB, 4-NB*				*Event Driven*		
Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**											
Visit Day	**D-28 – D-1**	**D1**	**D8**	**D31**	**D61**	**Delivery D1PD**	**D43 PD**	**D121 PD**	**D181 PD**				
Blood sample (hematology / biochemistry, ~ 5.5 ml)	●	●	●								●		Table 11 If screening sample ≤ 15 days before V1, then V1 sample not required. During an event-driven safety visit, additional samples are per investigator's discretion and standard of care and to be tested locally.
Blood sample (hematocrit: ~ 3.0 ml)				●		●	●						Table 11
Blood sample (immunogenicity ~ 10 ml)		●		●		●	●						
Cord blood (~ 5 to 10 ml)						●							
Nasal swab												●	
Check contraindications to and criteria for temporary delay for vaccination		O											Sections 5.2.1 and 7.1.1

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Epochs	Epoch 001	Epoch 002											Additional Information
			May be replaced by V5, depending on delivery date				*To coincide with infant visits 2-NB, 3-NB, 4-NB*				*Event Driven*		
Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**											
Visit Day	**D-28 – D-1**	**D1**	**D8**	**D31**	**D61**	**Delivery D1PD**	**D43 PD**	**D121 PD**	**D181 PD**				
Allocate maternal study group, intervention number		O											Sections 6.3.2 and 6.3.3
Assign cohort for blood sampling of infants		O											
Administer Intervention (study vaccine/product)		•											Sections 6.1 and 6.2
Record administered intervention number		•											
Observe for 60 minutes post-dose		O											
Distribute maternal subject card	O	O											At screening or at Visit 1 as per local practice. Section 8.3.4
Record Labor / Delivery information						•							
Record pregnancy / delivery outcomes						•							Submit Expedited AE report for an adverse pregnancy outcome (Section 8.3.3)
Train maternal subject /LAR on use of e-diary device		O	O										Sections 8.4.2 and 10.3.8

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Epochs	**Epoch 001**	**Epoch 002**											**Additional Information**
			May be replaced by V5, depending on delivery date				*To coincide with infant visits 2-NB, 3-NB, 4-NB*				*Event Driven*		
Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**											
Visit Day	**D-28 – D-1**	**D1**	**D8**	**D31**	**D61**	**Delivery D1PD**	**D43 PD**	**D121 PD**	**D181 PD**				
Distribute e-diary device to maternal subject / LAR.		O											
Review e-diary results		O	O	O	O	O	O	O	O				
Return e-diary device									O				At V8 or infant Visit 4-NB, whichever is last.
Concomitant medications / vaccinations		●	●	●	●	●	●	●	●	●	●	●	Sections 6.5.1, 6.5.3
Solicited administration site & systemic events (Days 1 to 7)		●	●										Sections 10.3.3, 10.3.8
All unsolicited AEs (Days 1 to 30)		●	●	●						●	●		Sections 10.3.4, 10.3.8
Pregnancy-related AESIs		●	●	●	●	●	●			●	●	●	Sections 8.3.3.2, 10.3.8
Suspected, probable and confirmed cases of COVID-19 infection		●	●	●	●	●	●	●	●	●	●	●	Section 8.3.2.1
MAEs		●	●	●	●	●	●	●	●	●	●		Sections 8 and 10.3.9.3
MA-RTI signs, symptoms and corresponding (S)AEs										●		●	Sections 8.3.3, 8.4

Epochs	**Epoch 001**	**Epoch 002**											**Additional Information**
			May be replaced by V5, depending on delivery date				*To coincide with infant visits 2-NB, 3-NB, 4-NB*				*Event Driven*		
Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**											
Visit Day	**D-28 – D-1**	**D1**	**D8**	**D31**	**D61**	**Delivery D1PD**	**D43 PD**	**D121 PD**	**D181 PD**				
SAEs, and AEs leading to study withdrawal		●	●	●	●	●	●	●	●	●	●		Sections 7.2, 10.3.8
SAEs related to study participation or concurrent GSK medication/vaccine	●	●											Sections 8.3.3, 10.3.8
Subsequent pregnancies							●	●	●	●	●		Section 10.3.8
Record interest in joining future extension study								O	●				Request at Visit 7, confirm at Visit 8; Section 6.7
Screening conclusion	●												
Investigator sign-off on eCRF before analysis	●			●			●		●				
Study conclusion									●				Section 4.4

The timing of an event-driven site visit (e.g., to further evaluate a potential AE or MA-RTIs) cannot be defined with precision in the protocol. Event-driven visits may occur throughout the study. **Note:**. ● 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. V = visit; D = day; GA = gestational age; MA-RTI = medically attended respiratory tract illness; PD = post delivery; Hct = hematocrit.

Table 2 Intervals between study visits – maternal subjects

Interval	Optimal interval	Allowed interval	Additional Information
Screening → V1	4 days	1– 28 days	The screening interval extends from Day -28 to Day -1 (the day before dosing). If a subject is screened but not vaccinated within the allowed interval, a re-screening can be done to establish the subject's eligibility. Please make sure the subject's gestational age is still within the allowed range, refer to Section 10.7 for guidance on gestational age assessment.
V1 → V2	7 days	7 – 14 days	
V1 → V3	30 days	20 - 45 days	
V1 → V4	60 days	50–75 days	
V5 (delivery)	0 days	1 day before to 3 days post delivery	Collect maternal blood sample at any point from the day before up to delivery. If blood is not collected during delivery, collect maternal blood sample no later than 3 days after delivery. A cord blood sample should be collected at the time of each delivery. If cord blood cannot be collected at delivery, a blood sample should be collected from the infant subject as soon as possible and no later than 3 days after birth.
V5 → V6	42 days	40 – 60 days	
V5 → V7	120 days	110 -140 days	Visit may coincide with infant subject's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule)
V5 → V8	180 days	165 – 200 days	
Monthly contacts	Approximately every 25 – 35 days		Monthly until Visit 8. May occur more often between Visit 5 and Visit 6 at the discretion of study personnel. Contacts are additional to and do not replace protocol specified Visits.

V=Visit

Table 3 Schedule of activities for infants

Epochs	Epoch 002						Epoch 003		Additional Information
Visit / Contact		*To coincide with maternal visits 6, 7, 8*				*Event-Driven*			
	V1-NB	**V2-NB**	**V3-NB**	**V4-NB**	**Monthly contacts**	**RTI Visit**	***C1-NB***	**V5-NB**	NB=Newborn *Monthly Contacts* coincide with maternal monthly contacts. *RTI Visit:* Sections 8.4.3 and 8.4.5.
Age of infant		**6 weeks**	**4 months**	**6 months**			**9 months**	**12 months**	
Visit Day	**Birth**	**D43**	**D121**	**D181**			**D271**	**D365**	Table 4
Check Inclusion / exclusion criteria	●								Sections 5.1.2, 5.2.2
Re-consent if required by local regulations	●								
Record infant subject study number	●								
Record subcohort for immunogenicity blood sampling	●								Section 6.3.3
Distribute infant's subject card	O								Section 8.3.4
Demographic data and lifestyle characteristics	●	●	●	●			●	●	Section *8.2.2.1*, Record at Visit 1-NB and if changes in lifestyle characteristics thereafter
Apgar score	●								At 1, 5 and 10 minutes, if available
Weight, length, head circumference, physical examination	●	●	●	●				●	Section *8.2.2.2*
Blood sample if no cord blood ~2.5 ml	●								Adjust volume if weight ≤ 2.5 Kg. Refer to Table 12.
Blood sample (immunology, infants) ~2.5 ml		●	●	●					1 sample at one of these visits, as per infant's assigned subcohort. Adjust volume if weight ≤ 2.5 Kg. Refer to Table 12
Concomitant medications / vaccinations	●	●	●	●	●	●	●	●	Sections 6.5.2, 6.5.3
Neonatal AESIs	●	●							Sections 8.3.3, 10.3.8. Must submit an Expedited AE Report
Suspected, probable and confirmed cases of COVID-19 infection	●	●	●	●	●	●	●	●	

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Epochs	Epoch 002						Epoch 003		Additional Information
Visit / Contact		*To coincide with maternal visits 6, 7, 8*				*Event-Driven*			
	V1-NB	**V2-NB**	**V3-NB**	**V4-NB**	**Monthly contacts**	**RTI Visit**	***C1-NB***	**V5-NB**	NB=Newborn *Monthly Contacts* coincide with maternal monthly contacts. *RTI Visit:* Sections 8.4.3 and 8.4.5.
Age of infant		**6 weeks**	**4 months**	**6 months**			**9 months**	**12 months**	
Visit Day	**Birth**	**D43**	**D121**	**D181**			**D271**	**D365**	Table 4
MAEs	●	●	●	●	●		●	●	Sections 8 and 10.3.9.3
SAEs and AEs leading to study withdrawal	●	●	●	●	●	●	●	●	Sections 7.2, 10.3.8
Train maternal subject/LAR on use of electronic diary device	O								Sections 8.4.2 and 10.3.8
Distribute electronic diary device to maternal subject/LAR	O								
Review electronic diary results		O	O	O		O			
Return eDiary device				O					At maternal Visit 8 or infant Visit 4-NB, whichever is last
Symptom-directed physical examination (includes RTI signs, symptoms)						●			Section 8.4.5
Nasal swab						●			Sections 8.1.1, 8.4.5.2, Table 12
Study conclusion								●	Section 4.4
Investigator sign-off on eCRF before analysis		●		●				●	

The timing of an event-driven visit cannot be defined with precision in the protocol. **Note:** ● indicates a study procedure that requires documentation in the individual eCRF. ○ indicates a study procedure that does not require documentation in the individual eCRF. LAR = legally acceptable representative; V=visit; D=day; NB = newborn.

Table 4 Intervals between study visits – infant subjects

Interval	Optimal interval	Allowed interval	Additional Information
Birth → V1-NB	0 days	0 - 3 days (for blood sample collection)	If no cord blood was obtained, a blood sample should be collected at this visit. If consent is not obtained within the allowed interval, but the parent(s) /LAR(s) still wish the infant to participate, consent may be obtained at any time until the Day 43 visit. Refer to the SPM for additional details.
Birth → V2-NB	42 days	28 – 60 days	
Birth → V3-NB	120 days	110 -140 days	Visit may coincide with infant subject's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule
Birth → V4-NB	180 days	165 – 200 days	
Monthly Contacts	Approximately every 25 – 35 days from birth through Visit 4-NB.		May occur more often between Birth and Visit 2-NB at the discretion of study personnel. Should coincide with Monthly post-delivery contacts described in Table 1 and Table 2. Contacts are additional to and do not replace protocol specified Visits.
Birth → C1-NB	270 days	256 – 286 days	
Birth → V5-NB	365 days	330 - 400 days	

V= Visit;NB=Newborn

2. INTRODUCTION

2.1. Study Rationale

GSK Biologicals is developing an investigational Respiratory Syncytial Virus (RSV) vaccine for administration to pregnant women, with the aim of preventing RSV-associated lower respiratory tract illnesses (LRTIs) in their infants by transfer of maternal antibodies. The vaccine candidate is based on a recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation (RSVPreF3).

A Phase I/II study of this candidate vaccine is underway (study RSV MAT-001; NCT 03674177). In this study, healthy non-pregnant women received a single intramuscular (IM) dose of either 30, 60 or 120 µg of the candidate vaccine, or saline placebo. The GSK Biologicals iSRC responsible for monitoring the safety data in RSV MAT-001 and the Independent Data Monitoring Committee (IDMC) who will oversee safety monitoring in RSV-MAT-004 will review the unblinded safety data from all subjects, (i.e. ~375 active vaccine and ~125 saline placebo recipients) up to 90 days post vaccination. The current study will only be initiated after a favorable evaluation of all available safety data from completed/ ongoing non-clinical studies and from the ongoing RSV MAT-001 clinical study.

In the current (RSV MAT-004) study, a single IM dose of the candidate vaccine will be administered for the first time to pregnant women in the third trimester. Two dose levels were selected for evaluation; the selection criteria are described in Section 4.3. Subjects will be vaccinated year-round and will not be limited to seasonal enrollment.

Safety, reactogenicity and immunogenicity of the candidate vaccine (at 2 dose levels) will be evaluated in maternal subjects for up to 6 months after delivery; safety evaluation will include assessment of pregnancy outcomes and pregnancy-related and neonatal adverse events of special interest (AESIs). The study will also evaluate the transfer of RSV-specific antibodies from vaccinated maternal subjects to the infants, the incidence of medically attended RSV-associated respiratory tract illnesses (MA-RTI) in maternal subjects, the incidence of RSV-associated respiratory tract / lower respiratory tract illnesses (RTI/LRTI) in infants for up to 6 months after delivery/birth, and the incidence of medically attended and serious adverse events for up to 12 months, in infants born to vaccinated mothers.

2.2. Background

Please refer to the current Investigator's Brochure (IB) for background information on RSV infection, the rationale for the maternal immunization approach described in this protocol, information regarding the pre-clinical and clinical studies of the RSV Maternal (RSVPreF3) vaccine**.**

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of the RSV Maternal (RSVPreF3) vaccine can be found in the IB.

The balance of anticipated benefits and apparent risks associated with the RSV maternal (RSVPreF3) vaccine continues to be acceptable following ongoing systematic review of the safety data.

3. OBJECTIVE(S) AND ENDPOINT(S)

Table 5 Study objectives and endpoints

Primary Safety objectives	Primary Safety endpoint(s)
To evaluate the safety and reactogenicity of a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery	Occurrence of solicited administration site and systemic events) during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).
	Occurrence of any hematological (complete blood count with differential and platelet count) or biochemical (alanine amino-transferase, aspartate amino-transferase, creatinine, blood urea nitrogen) laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs (MAEs) from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).
To evaluate pregnancy outcomes and pregnancy-related AESIs after a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery (Visit 6).	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include live birth with no congenital anomalies, live birth with congenital anomalies, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with congenital anomalies, elective/therapeutic termination with no congenital anomalies and elective/therapeutic termination with congenital anomalies.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, cesarean scar pregnancy, uterine rupture), postpartum hemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.*
To evaluate the safety of the study vaccine, including neonatal AEs of special interest, in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 weeks after birth.	The occurrence of neonatal AEs of special interest (reported up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia.*
	Occurrence of SAEs, AEs leading to study withdrawal and MAEs from birth up to 6 weeks after birth.

Primary Immunogenicity objectives	**Primary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects at Day 31 and at Delivery.	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).
To evaluate RSV-specific antibody levels in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine at birth	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A. Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained).
To evaluate the transfer of RSV-specific antibodies from maternal subjects vaccinated with a single IM dose of study vaccine to their infants at the time of delivery.	The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations *or an infant blood sample collected within 3 days after birth (if no cord blood sample can be obtained).
Secondary Safety objectives	**Secondary Safety endpoints**
To evaluate the safety of a single IM dose of study vaccine in maternal subjects, up to 6 months after delivery	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs, and AEs leading to study withdrawal.
To evaluate the safety of the vaccine in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 1 year of age	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs.
To estimate the incidence of RSV-associated, medically attended RTIs (MA-RTIs) in maternal subjects vaccinated with a single IM dose of study vaccine, from vaccination up to 6 months post-delivery (Visit 8).	Occurrence of RSV-associated MA-RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)
To estimate the incidence of RSV-associated lower respiratory tract illness (LRTI), severe LRTI and very severe LRTI and RSV-associated hospitalization in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, from birth up to 6 months of age.	From birth to 6 months (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions).
Secondary immunogenicity objectives	**Secondary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibodies against RSV-A at Day 43 after Delivery (Visit 6).	RSVPreF3 IgG-specific antibody concentration Neutralizing antibody titers against RSV-A Measured on the blood sample collected at Day 43 post- delivery (Visit 6).
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSV-B neutralizing antibodies at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).	Neutralizing antibody titers against RSV-B Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).

Secondary immunogenicity objectives	**Secondary Immunogenicity endpoints**
To evaluate RSV-specific antibodies in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 months after birth.	RSVPreF3 IgG-specific antibody concentration Neutralising antibody titres against RSV-A Neutralising antibody titres against RSV-B For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective). For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to treatment study intervention.
Tertiary objectives: To further evaluate the humoral response to the RSV maternal vaccine, which may include RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints. To evaluate the presence of other respiratory viruses in nasal swabs collected from maternal subjects and their infants (via an Allplex Respiratory Viruses Panel or alternative, performed for RSV A/B-positive samples and if deemed necessary for RSV A/B-negative samples.)	

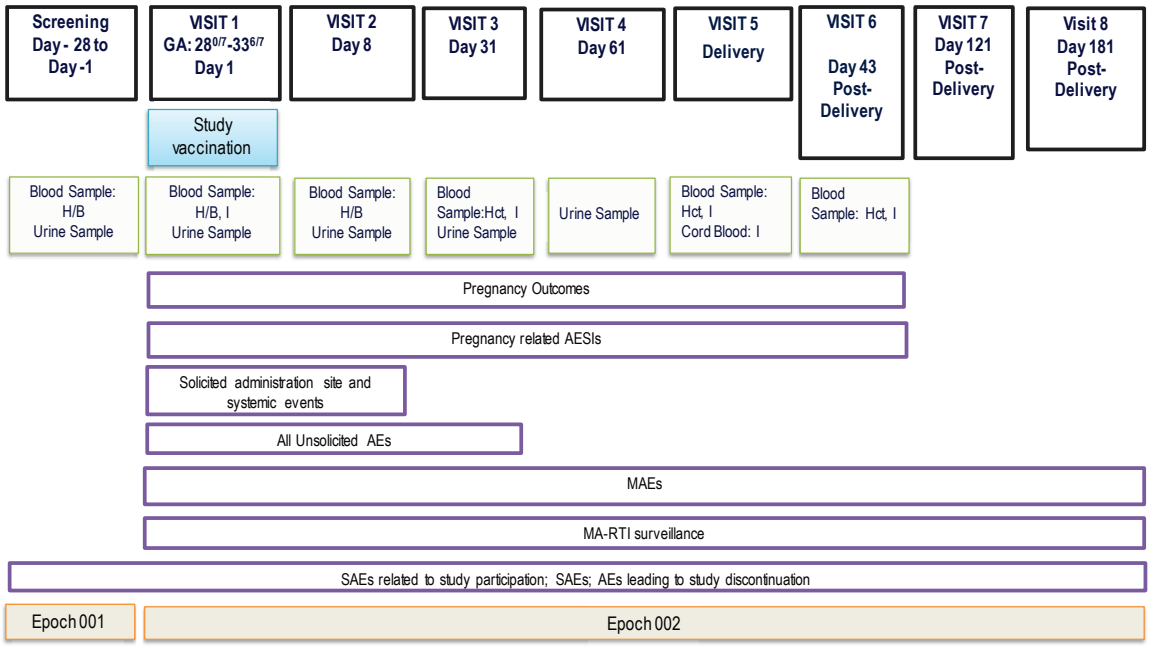
*Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with GAIA assessment and level of diagnostic certainty when applicable. Of note, some adverse events of special interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category."

4. STUDY DESIGN

4.1. Overall design

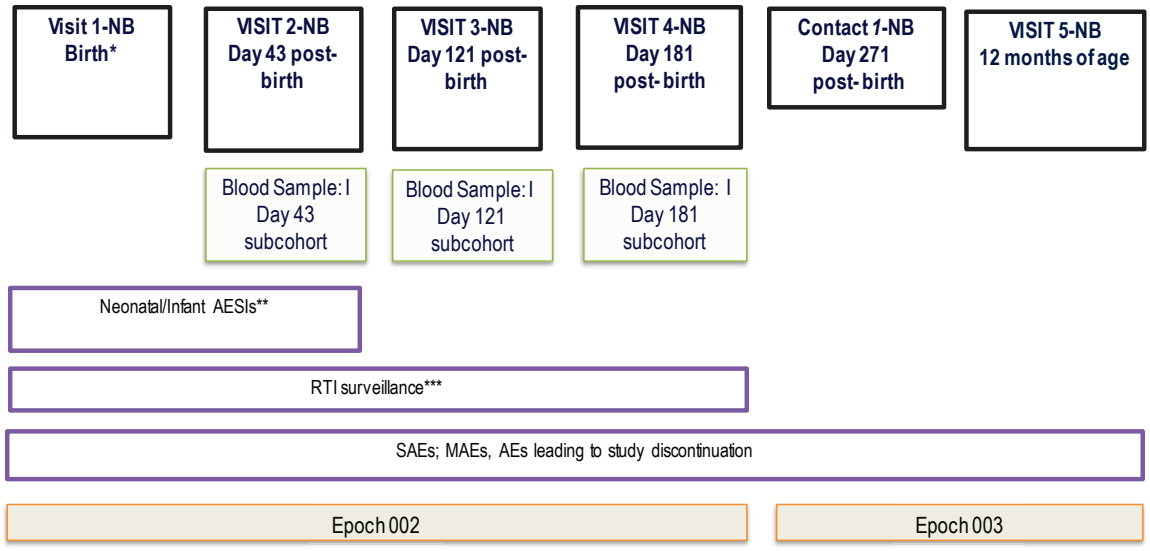
Figure 1 and Figure 2 provide overviews of the study design for maternal and infant subjects, respectively. Section 1.3 provides Schedules of Activities (SoAs) for maternal and infant subjects. Section 9.5.1 describes the sequence of analyses for maternal and infant subject data.

Figure 1 Overall design – maternal subjects



H/B= hematology/biochemistry, Hct- hematocrit; I= humoral immune response
If Screening blood sample collected ≤ 15 days before Visit 1, hematology/biochemistry not required at Visit 1
Subjects will be vaccinated year-round and will not be limited to seasonal enrolment
*Pregnancy-related AESIs identified after Day 43 will continue to be reported as such.

Figure 2 Overall design– infant subjects



NB = Newborn; I=humoral immune response: infants will be randomized 1:1:1 to **one** of the 3 subcohorts shown.
*Blood sample to be collected within 3 days after birth **ONLY** if a cord blood sample is not collected
**Neonatal AESIs identified after Day 43 (e.g., congenital anomalies) will continue to be reported as such.
***Infant subjects' parent(s)/LAR(s) will be contacted at least monthly to ensure RTI eDiary compliance.
Safety and disease surveillance data collected *after* Visit 4-NB will be reported in the database *in Epoch 003*.

- Study Type: self-contained.
- Experimental design: Phase II, observer-blind, randomised, placebo controlled, multi-centric, multi-country study with 3 parallel groups.
- Study Duration: Approximately 9 months (including the screening visit) for participating pregnant women; approximately 1 year after birth for participating infants.
- Control: Placebo.
- Epochs 001, 002 and 003 begin and end as described in Table 6.
- Blinding is as described in Table 6.
- Randomized intervention allocation is described in Section 6.2.
- Study (intervention) groups are described in Table 6.

Table 6 Study groups, subcohorts, interventions, epochs and blinding foreseen in the study (Amended 30-SEP-2020)

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	**Approximate Number of maternal subjects**	**Age of maternal subject at enrolment (Min/Max)**	**Interven-tion name**	**Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)**	**Approximate Number of infant subjects**	**Study groups for randomization (Allocation 1:1:1:1:1:1:1:1:1)**	**Epoch 001 Maternal subjects Only (Screening)**	**Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind)***	**Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)**
RSV MAT 60	Up to 100	18 – 40 years	RSVPreF3_60	BS1_60	Up to 33	RSVMAT60_BS1	●	●	●
				BS2_60	Up to 33	RSVMAT60_BS2		●	
				BS3_60	Up to 33	RSVMAT60_BS3		●	
RSV MAT 120	Up to 100	18 – 40 years	RSVPreF3_120	BS1_120	Up to 33	RSVMAT120_BS1	●	●	●
				BS2_120	Up to 33	RSVMAT120_BS2		●	
				BS3_120	Up to 33	RSVMAT120_BS3		●	
Control	Up to 100	18 – 40 years	Control	BS1_C	Up to 33	Control_BS1	●	●	●
				BS2_C	Up to 33	Control_BS2		●	
				BS3_C	Up to 33	Control_BS3		●	

M=maternal subject; I=infant; Control = Placebo; Blood sampling subcohorts are abbreviated "BS1;" "BS2;" BS3" and correspond to visits 2-NB (Day 43), 3-NB (Day 121) and 4-NB (Day 181), respectively.

* After the second analysis, the study will not be considered observer blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study.

- Data collection: standardized Electronic Case Report Form (eCRF). Electronic diaries (e-diaries) for solicited event data, and notifications regarding occurrence of unsolicited events (including medically attended events and SAEs), and symptoms of respiratory tract illnesses in infant subjects.
- Safety monitoring: Refer to section 8.2.3 for detailed description of holding rules and safety monitoring.

4.2. Scientific rationale for study design

4.2.1. Study population

The study population mirrors that of the intended indication: healthy women in the third trimester of pregnancy.

4.2.2. Rationale for the use of placebo

The placebo group serves as a control for safety, reactogenicity, and immunogenicity assessments.

4.2.3. Safety considerations

As this is the first time the RSV maternal (RSVPreF3) vaccine will be administered to pregnant women, enrolment will be limited to 10 subjects per day across all sites until the first 30 subjects have been dosed. Within any given study site, these subjects will be vaccinated sequentially and at least 60 minutes apart.

In addition, throughout the study:

- All subjects will be required to remain at the site for 60 minutes following vaccination, and
- The data will be reviewed by a safety review team (SRT) and by an independent data monitoring committee (IDMC), and
- Holding rules will be applied.

The risk of Enhanced Respiratory Disease related to boosting pre-existing maternal antibody and transfer of vaccine-induced neutralizing antibodies from mother to infant is considered negligible. However, as data evaluating this risk are expected before vaccinating larger numbers of pregnant women, surveillance and evaluation (Section 8.4) of all RTIs in infants and medically attended-RTIs in mothers through 6 months post-delivery has been implemented.

4.2.4. Sub-cohorts for blood sampling in infants

Sub-cohorts for blood sampling have been defined to limit discomfort and risk to infants while ensuring enough observations to support robust evaluation of immune response (see Figure 4 and Table 6).

4.2.5. Study blinding (Amended 30-SEP-2020)

The RSV maternal vaccine and the placebo differ in appearance. In addition, the RSV maternal vaccine formulations must be reconstituted before administration, whereas the placebo does not. Therefore, double blinding is not feasible and the study will be conducted in an observer-blinded manner until the second analysis is conducted, as described in Section 6.3.4. After the second analysis, the study will not be considered

observer-blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study.

Please refer to the Glossary of terms for the definition of "observer-blind."

4.2.6. Case Definitions

Cases will be classified (during data analyses) according to the definitions that follow. Case definitions should not be confused with the definitions study personnel use during RTI surveillance (Section 8.4).

4.2.6.1. Maternal, medically attended respiratory tract illness (MA-RTI)

Table 7 MA-RTI case definitions for data analysis in maternal subjects

RSV-MA-RTI	Medically attended visit for RTI symptoms AND Confirmed RSV infection [1, 2]
RSV hospitalization	Confirmed RSV infection AND Hospitalized for acute medical condition [3]
All-cause MA- RTI	Medically attended visit for RTI symptoms

[1] Confirmed RSV infection defined in Section 4.2.6.3
[2] RSV (nasal swab) sampling and testing as specified in Table 11.
[3] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

4.2.6.2. Respiratory tract illness (RTI) / Lower respiratory tract illness (LRTI) in infants

Table 8 RTI/LRTI case definitions for data analysis in infants

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

Definitions based on [Modjarrad, 2016]
RTI = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.
[1] Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnea).
[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.
[3] RR increase defined as:
> 60/minute (< 2 months of age)
> 50/minute (2 to < 12 months of age)
> 40/minute (12 to 24 months of age)
[4] Confirmed RSV infection defined in Section 4.2.6.3
[5] RSV (nasal swab) sampling and testing as specified in Table 12.
[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

4.2.6.3. RSV infection

The sponsor will analyze nasal swabs by quantitative reverse transcription polymerase chain reaction (qRT-PCR) for the presence of RSV A/B. A positive (RSV A or B) test result constitutes a case of RSV infection. Refer to Table 11, Table 12 and Section 8.1.

4.3. Justification for dose

Two formulations (containing 60 and 120 µg of the RSVPreF3 antigen, respectively) have been selected from RSV MAT-001 for evaluation in the current study, RSV MAT-004, as they elicited a more robust immune response than the 30µg dose. Selection of the doses for RSV MAT-004 was based on the review of safety data through 90 days and immunogenicity data through 30 days post-vaccination for all 500 subjects enrolled and dosed, and safety data through 180 days and immunogenicity data through 90 days for the first 60 subjects enrolled and dosed. This data will be included in the Investigator Brochure to support RSV MAT-004. Evaluating 2 dose levels supports efforts to determine if there is a dose response relationship in the maternal antibody response to the vaccine and placental transfer of antibodies to the fetus.

Because re-infection with RSV occurs throughout an individual's lifetime, it is extremely unlikely that an adult (in this case, a maternal subject) *would not* have been naturally infected with RSV before. Therefore, a single dose of the study vaccine should be sufficient to boost the neutralizing antibodies induced by previous natural infections.

The study vaccine will be administered at $28^{0/7}$ - $33^{6/7}$ weeks of gestation. This gestational age range is considered optimal for both immunogenicity and safety. It allows enough time to (a) induce high neutralizing antibody levels in maternal subjects before delivery and (b) ensure these antibody levels are elevated during the period of greatest placental antibody transfer to the fetus. Moreover, it is after the critical period for organogenesis (i.e. after the period when most congenital abnormalities develop).

4.4. End of study definition

A subject is considered to have completed the study if he/she returns for the last visit (Visit 8 for maternal subjects / Visit 5-NB for infant subjects) as described in the protocol.

The Primary Completion Date (PCD) occurs on completion of the Day 43 post-delivery visit in Epoch 002 (Visit 6 for the maternal subjects and Visit 2-NB for the infant subjects).

End of study (EoS) occurs with the last (infant) subject last visit (LSLV; Visit 5-NB).

Refer to the Glossary of terms for the definitions of PCD and EoS.

5. STUDY POPULATION

5.1. Inclusion criteria for enrolment

Adherence to these criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardise the scientific integrity or regulatory acceptability of the study or subject safety.

5.1.1. Maternal subjects

Maternal subjects must satisfy all the following criteria at study entry:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the electronic diaries, return for follow-up visits).
- Subjects who give written or witnessed/thumb printed informed consent after the study has been explained according to local regulatory requirements, and before any study specific procedure are performed. The informed consent given at screening should (consistent with local regulations / guidelines) either:
  - include consent for both the maternal subject's participation and participation of the infant after the infant's birth, or
  - include consent for the maternal subject's participation and expressed willingness to consider permitting the infant to take part after the infant's birth (if local regulations/guidelines require parent(s) to provide an additional informed consent after the infant's birth).
  - Both mother and father should consent if local regulations/guidelines require it.
- Age 18 to 40 years, inclusive, when informed consent is given (i.e., at enrolment).
- Pre-pregnancy BMI (based on subject's report) 18.5 to 34.9, inclusive
- Healthy as established by medical history and clinical examination before entering into the study.

- At 28 $^{0/7}$ to 33 $^{6/7}$ weeks of gestation at the time of study vaccination (Visit 1), as established by last menstrual period (LMP) date corroborated by first or second trimester ultrasound examination (U/S).

  * If LMP and U/S do not correlate, default to U/S gestational age assessment. The level of diagnostic certainty of the gestational age should be established by using the Global Alignment of Immunisation safety Assessment in pregnancy (GAIA) gestation age assessment tool (Section 10.7)

- Subject satisfying screening requirements
- Singleton pregnancy
- HIV negative, as assessed by local standard of care serologic tests conducted during the current pregnancy and before enrolment (Visit 1).
- No fetal genetic abnormalities (based on genetic testing, if performed).
- No significant congenital malformations (such as abnormal fetal morphology, abnormal amniotic fluid levels, significant abnormalities in placenta or umbilical cord), as assessed by level 2 ultrasound (also known as a fetal anomaly ultrasound scan or fetal morphology assessment) conducted after 18 weeks of gestation
- Willing to provide cord blood
- Willing to have the infant followed-up after delivery for a period of 12 months
- Does not plan after delivery to give the infant for adoption or place the infant in care

Note that women whose pregnancies resulted from Assisted Reproductive Technologies may be enrolled if they meet all inclusion criteria and none of the exclusion criteria.

5.1.2. Infant subjects

Infant subjects must satisfy all the following criteria at study entry:

- Live-born from the study pregnancy.
- Re-signed (confirmed) written or witnessed/thumb printed informed consent for study participation of the infant obtained from the infant's mother and/or father and/or LAR, as applicable by local law, before performing any study specific procedure.

5.2. Exclusion criteria for enrolment

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardise the scientific integrity or regulatory acceptability of the study or safety of the subject.

The following criteria should be checked at the time of study entry. The potential subject MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Maternal subjects

5.2.1.1. Medical conditions

- History of allergic disease or reactions likely to be exacerbated by any component of the RSV vaccine
- Hypersensitivity to latex
- Significant (as per Investigator's judgement) complications in the current pregnancy such as:
  - Gestational hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation in the absence of proteinuria in a woman with a previously normal blood pressure [ACOG, 2019a]
  - Gestational diabetes which is not controlled by diet and exercise (Gestational diabetes is defined as absence of pre-gestational diabetes and hyperglycemia during pregnancy, which is not due to other known causes, confirmed based on positive oral glucose tolerance test or based on fasting plasma glucose levels in venous or capillary blood samples [Kachikis, 2017].)
  - Pre-eclampsia (defined as Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure and proteinuria or, in the absence of proteinuria, the new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema or headache unresponsive to medication [ACOG, 2019a]
  - Eclampsia (defined as occurrence of new-onset seizures, in the absence of other causative conditions, in a woman with a hypertensive disorder of pregnancy) [ACOG, 2019a] during current pregnancy
  - Intrauterine growth restriction (defined as sonographically estimated fetal weight that is less than the 10th percentile for gestational age) [ACOG, 2019b]
  - Placenta previa (unless there is documented sonographic evidence that the placenta has moved up before enrolment),
  - Placental abruption, placenta accreta/percreta/increta, chorioamnionitis or any abnormalities that in the opinion of Investigator can impair the maternal-fetal circulation
  - Polyhydramnios (defined as either a deepest vertical pocket of ≥8 cm or an amniotic fluid index of ≥24 cm on ultrasound examination) [Dashe, 2018]
  - Oligohydramnios (defined as a maximum vertical pocket shorter than 2 cm or amniotic fluid index ≤ 5 cm on the ultrasound examination) [Reddy, 2014]
  - Cervical suture in place
  - Preterm labour or history of preterm labour in the current pregnancy
  - Ongoing medical intervention to prevent preterm delivery or medical treatment for suspected preterm delivery

  - Cholestasis (defined as unexplained pruritus and/or abnormal liver function tests and/or raised bile acids, based on investigator's clinical judgement) [RCOG, 2011]
  - Other pregnancy-related complications that in the Investigator's judgement would preclude participation of the subjects in an investigational vaccine trial or might pose risk to the subject due to participation in the study

- Significant (as per Investigator's judgement) structural abnormalities of the uterus or cervix.
- History of prior stillbirth or neonatal death
- History of preterm birth (< 37 weeks gestation)
- History of ≥2 spontaneous abortions.
- Known or suspected HBV or HCV infection, based on medical history and clinical presentation (no laboratory testing is required)
- Known or suspected infection during the current pregnancy with Toxoplasma, Parvovirus B19, Syphilis, Zika, Rubella, Varicella, CMV or primary genital Herpes Simplex, based on medical history and clinical presentation (no laboratory testing is required).
- Active infection with tuberculosis, based on medical history and clinical presentation (no lab testing is required).
- Known or suspected impairment of the immune system or autoimmune disorder (based on medical history and physical examination; no laboratory testing required).
- Lymphoproliferative disorder or malignancy within 5 years before vaccination (excluding effectively treated non-melanoma skin cancer).
- Any clinically significant grade 1 haematological and/or biochemical laboratory abnormalities identified at screening. The investigator should use clinical judgement to decide which abnormalities are clinically significant based on reference ranges for pregnant women in the second and third trimester, as provided in [Sheffield, 2013] and the SPM for this study.
- Grade ≥ 2 haematological and/or biochemical laboratory abnormalities identified at screening based on reference ranges for pregnant women in the second and third trimester, as provided in [Sheffield, 2013] and the SPM for this study.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality or poorly controlled pre-existent co-morbidities or any other clinical conditions, as determined by physical examination or laboratory screening tests, that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study
- Any conditions that, in the investigator's judgement, may interfere with subject's ability to comply with study procedures or receipt of prenatal care, such as behavioral or cognitive impairment or neuropsychiatric illness.
- Any condition which, in the investigator's opinion, would increase the risks of study participation to the unborn infant.

5.2.1.2. Prior/Concomitant therapy

- Prior receipt of a COVID-19 vaccine.
- Prior receipt of an RSV vaccine.
- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine(s)/product(s) during the period beginning 29 days before the dose of study vaccine/product (Day -28 to Day 1), or planned use during the study period.
- Planned administration/administration of any vaccine within 29 days before study vaccine administration (Day -28 to Day 1) and through delivery (Visit 5), except seasonal influenza vaccines and dTpa/Tdap or tetanus, which may be administered according to standard of care ≥ 15 days before or after study vaccination

  Note that if public health authorities organize an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) outside the routine immunisation program, then the intervals described above can be reduced if necessary for that mass vaccination vaccine, provided the vaccine is licensed and used according to its Product Information.
- Administration of immunoglobulins, blood products (except anti-Rh0D IG) or plasma derivatives within 3 months before study vaccination or planned administration through Visit 5 (the delivery visit).
- Administration of immune-modifying therapy within 6 months before the study vaccine/product dose, or planned administration through delivery. This includes but is not limited to:
  - Azathioprine, mycophenolate mofetil, 6-mercaptopurine, cyclosporine, tacrolimus, monoclonal or polyclonal antibodies;
  - Prednisone ≥ 5 mg/day or equivalent for ≥ 14 days. Topical steroids are allowed. Inhaled steroids are allowed if ≤ 500µg/day of beclomethasone or fluticasone, or ≤ 800µg/day of budesonide.

5.2.1.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).

5.2.1.4. Other exclusions

- Alcoholism or substance use disorder within the past 24 months based on the presence of two or more of the following abuse criteria: hazardous use, social/interpersonal problems related to use, neglected major roles to use, withdrawal tolerance, use of larger amounts or longer, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use, activities given up to use, craving (based on the DSM-5 criteria, [Hasin, 2013])

- A local condition that in the opinion of the Investigator precludes injection of the study drug or precludes assessment of local (administration site) reactogenicity.
- Consanguinity of maternal subject and her partner (second degree cousins or closer)
- Any study personnel or their immediate dependants, family, or household members

5.2.2. Infant subjects

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).
- Child in care (Please refer to the Glossary of terms for the definition of child in care)

5.3. Lifestyle considerations

For lifestyle considerations pertaining to inclusion /exclusion criteria, refer to Sections 5.1 and 5.2. For data collection pertaining to lifestyle characteristics, refer to Section 8.2.1.1.1.

5.4. Screen failures

Screen failures are subjects who consent to participate in this study but are not subsequently randomly assigned to a study intervention.

Limited data for screening failures (including reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

6. STUDY INTERVENTION

A ‘study intervention’ is defined as a set of investigational or marketed product(s) or placebo intended to be administered to a subject during the study.

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

6.1. Study Intervention(s) administered

After completing all prerequisite pre-dosing procedures and confirming the maternal subject’s eligibility, 1 dose of study vaccine/product will be prepared and administered as shown in Table 9.

Note that the active vaccines (RSVPreF3_60 and RSVPreF3_120) must be reconstituted before administration.

Table 9 Study interventions administered

Study intervention name:	**RSVPreF3_60**		**RSVPreF3_120**		**Placebo**
Study intervention formulation:	RSVPreF3 (60 µg)	Sodium chloride (NaCl) (0.9%); Water for injections q.s, 0.5 mL	RSVPreF3 (120 µg)	Sodium chloride (NaCl) (0.9%); Water for injections q.s, 0.5 mL	Sodium chloride (NaCl) (0.9%); Water for injections q.s, 0.5 mL
Presentation:	Powder for suspension for injection, vial	Solution for injection; vial	Powder for suspension for injection, vial	Solution for injection; vial	Solution for injection; vial
Route of administration:	Intramuscular use		Intramuscular use		Intramuscular use
Administration site:					
• **Location**	Deltoid		Deltoid		Deltoid
• **Laterality ***	Non-Dominant		Non-Dominant		Non-Dominant
Number of doses to be administered:	1		1		1
Volume to be administered:	0.5 ml		0.5 ml		0.5 ml
Packaging, labelling and TM:	Refer to the SPM		Refer to the SPM		Refer to the SPM
Manufacturer:	GSK Biologicals		GSK Biologicals		GSK Biologicals

*****The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

Maternal subjects must be observed closely for at least 60 minutes after administration of the study vaccine/product. Appropriate medical treatment must be readily available in case of anaphylaxis and syncope.

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

6.2. Preparation/Handling/Storage/Accountability

The study vaccine(s)/product(s) must be stored in a safe, locked place at the temperature specified on the vaccine/product label. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Only authorised study personnel should be allowed access to the study vaccine/product. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study vaccine(s)/product(s).

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Subject identification

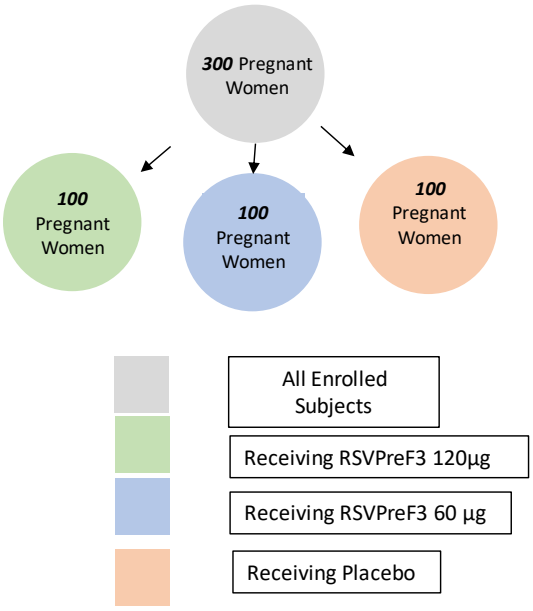
Maternal identification numbers will be assigned sequentially to pregnant women who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center.

When a maternal subject is randomized at Visit 1, an identification number will be assigned to her (as yet unborn) infant. Maternal and infant identification numbers will be linked.

6.3.2. Randomisation to study intervention

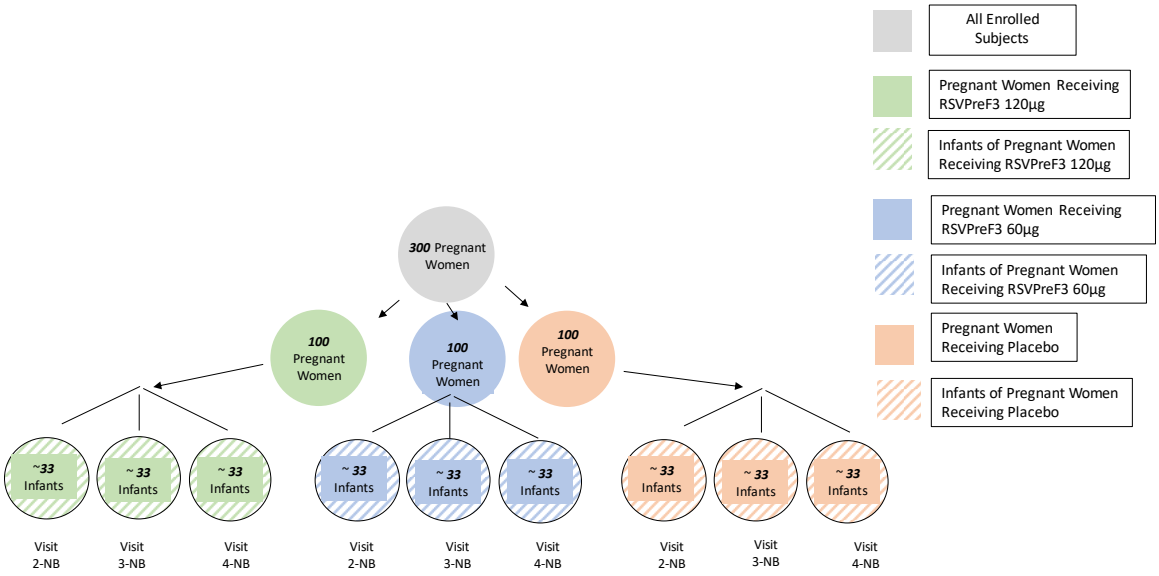
Up to 300 eligible pregnant women will be randomly assigned to 3 study (intervention) groups in a 1:1:1 ratio and at the same time, their (as yet unborn) infants will be randomly assigned to 3 blood sampling subcohorts (also in a 1:1:1 ratio). This yields up to 100 pregnant women per group and up to 33 infants per blood sampling subcohort within each group, for an overall allocation of 1:1:1:1:1:1:1:1:1. Refer to Table 6, Figure 3 and Figure 4.

Figure 3 Allocation of maternal subjects to study (intervention) groups



*Numbers are approximate and represent maximum subject enrolment.

Figure 4 Allocation of infant subjects to blood sampling subcohorts



*Numbers are approximate and represent maximum subject enrolment.

The randomisation of supplies within blocks will be performed at GSK, using MATerial EXcellence (MatEx), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, USA) by GSK. Entire blocks will be shipped to the study centres/warehouse(s).

To allow GSK to take advantage of greater rates of recruitment in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

6.3.3. Intervention allocation to the subjects

Upon providing the maternal subject identification number, an automated internet based system (SBIR) will allocate the maternal subject to an intervention number and her (as yet unborn) infant subject to a blood sampling subcohort. The system's randomisation algorithm will use a minimisation procedure accounting for maternal age at the time of vaccination (≥18 and <35 years of age or ≥ 35 years of age), gestational age at the time of vaccination ($28^{0/7}$-$31^{0/7}$; $31\ ^{1/7}$-$33^{6/7}$) and center. Minimisation factors will have equal weight in the minimisation algorithm.

When the automated Internet-based system (SBIR) is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about intervention number allocation.

6.3.4. Blinding and unblinding (Amended 30-SEP-2020)

Data will be collected in an observer-blind manner. To do so, vaccine/product will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or entry of any study endpoint (i.e., reactogenicity, safety, efficacy).

The laboratory in charge of the sample testing will be blinded to the intervention assignment. Codes will be used to link the subject and study (without any link to the intervention attributed to the subject) to each sample.

Investigators will remain blinded to each subject's assigned study intervention until the second analysis. After the second analysis, the investigator's brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments.

6.3.4.1. Emergency unblinding

Unblinding a subject's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the subject.

A subject may continue in the study if that subject's intervention assignment is unblinded.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the subject's individual study intervention via an automated Internet-based system (SBIR).

As a back-up process, the investigator has the option of contacting a GSK Biologicals' Helpdesk (refer to Table 10) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

A non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Biologicals' Helpdesk (back up process). The maternal and infant subject cards list contact information for both the investigator and GSK Biologicals' Helpdesk.

Table 10 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Phone: PPD Phone (Canada, US and Puerto Rico): PPD Fax: PPD E-mail: PPD

6.3.4.2. Emergency unblinding before regulatory reporting of SAEs

GSK policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccine(s)/product(s), prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the intervention assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 10.3.10).

In addition, GSK VCSP staff may unblind the intervention assignment for any subject with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a Serious Adverse Event that is fatal or life threatening. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study intervention compliance

Subjects will be dosed at the site by qualified unblinded study personnel. Before dosing, 2 qualified, unblinded members of the study staff will confirm that the intervention number is correct. The intervention number administered, and the administration date and time will be recorded in the source documents. Unblinded monitors and, in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study intervention records at the site(s) to verify that randomisation/dispensing has been done accurately.

6.5. Concomitant therapy

At each study visit/contact, the investigator or delegate should question the maternal subject and/or the infant subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

The Local Medical Lead (LML) should be contacted if there are any questions about concomitant (or prior) therapy.

6.5.1. Maternal subjects

- **All folate and iron supplements** beginning the month before the estimated date of conception and continuing through delivery (i.e., through Visit 5). These supplements should be reported when taken independently and/or when included in a multivitamin mineral supplement.
- All concomitant **vaccines** beginning the month before the estimated date of conception and throughout the study (i.e., through Visit 8).
- **Prophylactic medication** related to the effects (actual or anticipated) of study vaccine/product administration (e.g., medication administered either in the absence of ANY symptom and in anticipation of a reaction to the dose, or to prevent re-occurrence of one or more post-dose AEs such as headache).
- Any concomitant **medications/products** associated with a solicited event or with an unsolicited adverse event, beginning at Visit 1 and ending at Visit 3 (Day 1 to Day 31).
- Any concomitant **medications/products** associated with a medically attended adverse event (MAE) (and/or an MA-RTI) beginning at Visit 1 and ending at Visit 8 (Day 1 to Day 181 post delivery).

6.5.2. Infant subjects

- Vaccinations administered from Birth (Visit 1-NB) through the 12-month visit (Visit 5-NB)
- Medications/products administered in relation to RTIs/LRTIs from Birth (Visit 1-NB) through the six-month visit (Visit 4-NB).
- Medications/products administered in relation to MAEs from Birth (Visit 1-NB) through the 12-month visit (Visit 5-NB).

6.5.3. Maternal and Infant subjects

- Any concomitant medications/products/vaccines leading to a subject's non-eligibility (Sections 5.2.1 and 5.2.2) or potential non-evaluability (Section 9.3.3.1), or to a subject's withdrawal from the study.
- Any concomitant medications/products/vaccines relevant to an SAE/Adverse Event of Special interest (AESI) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI. Concomitant medications relevant to SAEs / AESIs must be recorded on the Expedited Adverse Event report.

6.6. Dose modification

Not applicable.

6.7. Intervention after the end of the study

At Visit 7 the investigator will ask each maternal subject if she is interested in participating in a study of a second (booster) dose of the RSV maternal vaccine, to be administered within 3 years after the study pregnancy. At the study conclusion visit (Visit 8), the investigator will confirm whether the subject is interested and record the subject's response in the eCRF.

Among maternal subjects interested in joining such a study:

- Those who become pregnant again within 3 years may be invited to receive a booster dose while pregnant. They will be followed (along with the infant, when delivered) in a manner similar to that described in this protocol.
- Those who do not become pregnant again may be invited to receive a booster dose and be followed for safety and immune response.

For maternal subjects who are not interested, the reason for refusal will be documented, when available, in the subject's eCRF

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Criteria for discontinuation of study vaccines / products do not apply since this is a single dose study. However, administration of the study's single dose may be *delayed* if the criteria presented in Section 7.1.1 are met.

7.1.1. Criteria for temporary delay of study vaccination

Vaccination may be postponed within the permitted time interval until transient circumstances cited below have been resolved:

- Clinically significant Grade 1 hematological/biochemical values, *if* expected to be temporary. Subjects may be re-screened at a later date within the allowed time interval (Table 2). Reference ranges are as provided in [Sheffield, 2013] and in the SPM.
- Acute disease and/or fever within 48 hours before study vaccination. Fever is defined as temperature ≥38ºC by any age appropriate route (oral route preferred). Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator

- Use of systemic antibiotic or antiviral treatment within 7 days before study vaccination.
- Use of antipyretics and/or analgesics within 3 days before study vaccination.

7.1.2. Contraindications to subsequent vaccine administration

Not applicable.

7.2. Subject discontinuation/withdrawal from the study

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

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not return for the concluding visit/was not available for the concluding contact foreseen in the protocol.

Investigators will attempt to contact those subjects who do not return for scheduled visits or follow-up.

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

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

- Adverse events requiring expedited reporting to GSK (Section 8.3.3)
- Unsolicited non-serious adverse event
- Solicited adverse event (maternal subjects)
- Protocol deviation
- Withdrawal by maternal subject / infant subject's parent(s)/LAR(s), not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*If a maternal or infant subject is withdrawn from the study because the maternal subject / infant subject's parent(s)/LAR(s) has withdrawn consent and provided the reason for its withdrawal, the investigator will document this reason in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will

follow subjects who are withdrawn from the study as result of an SAE/AE until resolution of the event (see Section 10.3.8).

7.3. Lost to follow-up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

Please refer to the SPM for a description of the actions to be taken before considering the subject as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES (AMENDED 30-SEP-2020)

Study procedures and their timing are summarised in the SoAs (Section 1.3). Information not provided in the SoAs follows.

Readers are reminded that study visits /contacts, assessments and procedures *do not* replace local standards of care, and that any adverse event / potential adverse event identified during a study visit/contact or procedure should be treated according to local medical practice or by referral to an appropriate health care provider.

Adherence to the protocol is essential and required for study conduct.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

The investigator is not allowed to do testing on samples outside of what has been agreed upon by the IEC/IRB.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team is aware of them.

All screening evaluations must be completed and the results reviewed before confirming that potential subjects meet all eligibility criteria.

The investigator will maintain a screening log of all subjects screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. hematologic profiles) and obtained before the subject signed the Informed Consent Form (ICF) may be used for screening and/or for establishing a clinical baseline, provided the procedure met protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).

The SPM provides the investigator and site personnel with administrative and detailed technical information that does not impact subject safety.

Study Procedures During Special Circumstances: COVID-19 pandemic

- During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For the duration of such special circumstances:

- Enrolment of ADDITIONAL maternal subjects may be placed on hold. Decisions on re-starting enrolment to achieve the planned sample size will be made in a manner consistent with guidance from public health and other competent authorities.
- The following measures may be implemented for enrolled participants:
  - If it is not possible to conduct a protocol-specified, scheduled or event-driven visit as described in Section 1.3, the visit may be replaced with a contact conducted by telephone, videotelephony or telemedicine. SMS and email are not allowed.
  - Biological samples may be collected at a different location* other than the study site or the subject's home. Biological samples should not be collected if they cannot be obtained within the visit interval (Table 2, Table 4), processed in a timely manner or appropriately stored until the intended use.
    - Nasal swabs and blood samples for assessment of immune response should only be collected using centrally provided supplies.
    - Hematocrit and dipstick urinalysis may be evaluated locally, using local supplies, if collection using centrally provided supplies is not feasible.
  - If hematocrit is evaluated locally, date, result and normal range should be recorded in the eCRF in the Comment section for the relevant visit.
  - If any other missing data were collected during a visit for standard care in the appropriate interval (Table 2 for maternal subjects; Table 4 for infant subjects), and if the medical records for this visit are accessible to site staff (as allowed by local law), then the data from the medical record may be recorded in the subject's study source document and entered into the eCRF.
- "Medically attended visits" will include actual visits to or from medical personnel and instances where, due to the special circumstances, the subject cannot seek medical advice for symptoms/an illness by visiting a medical facility or arranging for a home visit, and seeks this advice instead via telephone, SMS, email, videotelephony or telemedicine, or other means.
- The eDiary device provided to the maternal subject may be returned to the site by conventional mail after Day 181 post-delivery/birth, if the Day 181 post- delivery / birth visits (Visit 8 / Visit 4-NB) cannot be performed.

*It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location

should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March 2020) for more details. The impact of measures taken during special circumstances on the per protocol set for immunogenicity will be determined on a case by case basis.
Study Procedures During Special Circumstance: E-diary failure • In case ERT portal/ alerts are not functioning, contacts will be conducted at least weekly until Visit 8 (maternal subjects) / 4-NB (infant subjects). Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local laws and best practice.

8.1. Efficacy and/or immunogenicity assessments

Collected biological samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to prior IEC/IRB approval if required per local legislation.

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

Sample testing will be done in accordance with the recorded consent of the individual maternal subject/ infant subject's parent(s)/LAR(s).

If additional testing is performed, the marker priority ranking given in Section 8.1.3 may be changed.

Collected samples will be stored for a maximum of 20 years. This storage period begins when the last subject performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with subject consent. These extra requirements need to be communicated formally to, and discussed and agreed with GSK.

8.1.1. Biological samples

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

Table 11 Biological samples – maternal subjects

Maternal Sample type	Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information
Whole Blood	Hematology, Biochemistry	~5.5	ml	Screening	As needed to achieve up to 300 eligible subjects at Visit 1.
	Hematology, Biochemistry Immune response	~15.5*	ml	Visit 1 (Day 1)	Hematology, chemistry: ~5.5 ml. This sample is NOT required if the screening sample was collected ≤15 days before Visit 1. Immune response: ~10 mL. Must be collected at Visit 1 before dosing. *Volume of sample collected to assess immune response may be reduced to ~5 ml at investigator's discretion. Refer to the Laboratory Manual.
	Hematology, Biochemistry	~5.5	ml	Visit 2(Day 8)	
	Hematocrit Immune response	~13*	ml	Visit 3 (Day 31)	Hematocrit: ~3 mL Immune response: ~10 ml. *Volume of sample collected to assess immune response may be reduced to ~5 ml at investigator's discretion. Refer to the Laboratory Manual.
		~13*	ml	Visit 5 (Delivery)	
		~13*	ml	Visit 6 (Day 43 post delivery)	
		~65.5	**ml**	**Minimum Total, not including repeat or unscheduled samples**	
Cord blood	Immune Response	~5, up to ~10	ml	Visit 5 (Delivery)	
Urine	Protein, Glucose	Dipstick	NA	Screening	As needed to achieve ***up to*** 300 eligible subjects at Visit 1.
				Visit 1 (Day 1)	
				Visit 2 (Day 8)	
				Visit 3 (Day 31)	
				Visit 4 (Day 61)	
Nasal Swab	Presence of:RSV A / B	-	-	MA RTI Assessment Visit	Collect a nasal swab from any maternal subject who reports a medically attended (MA) RTI
		-	-	RTI hospitalization	Collect a nasal swab (if possible) from any subject hospitalized with a RTI (or soon after discharge, as long as symptoms are ongoing). NOTE: Collection of a nasal swab for sponsor testing is additional to and DOES NOT REPLACE any specimen collection (per local standard of care) for testing by the local laboratory to establish a fast and accurate diagnosis for the hospitalization. In the case of hospitalization, local testing for RSV infection should be performed if feasible. If other specimens are collected and tested locally as per local standard of care, results will be recorded in the eCRF. However, only the sponsor laboratory results will be used when applying the case definitions for data analysis in Section 4.2.6 Thus, where mandated by the protocol, every effort should be made to obtain samples that can be analyzed by the sponsor (or sponsor-designated) laboratory.

Table 12 Biological samples – infant subjects

Infant Sample type	Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information	
Blood	Immune response	~2.5	ml	Visit 1-NB (Within 3 days after birth	**ONLY** if cord blood **cannot** be collected.	Volume must be reduced if weight ≤ 2.5 kg. [Trial-related blood loss for infant subjects should be ≤ 1 % at each timepoint. Total blood volume is estimated at 80 to 90 ml/kg body weight, and venipuncture should not exceed ~ 1.6 ml for a 2kg baby or 2.0 ml for a 2.5 kg baby.] **Refer to the Laboratory Manual for additional information.**
		~2.5*	ml	Visit 2-NB (Day 43)		
		~2.5*	ml	Visit 3-NB (Month 4)		
		~2.5*	ml	Visit 4-NB (Month 6)		
		~ **2.5** **~5.0**	**ml**	Minimum TOTAL, assuming body weight > 2.5 kg and cord blood (Table 11) collected Minimum TOTAL, assuming body weight > 2.5 kg and cord blood NOT collected		
Nasal swab	Presence of RSV A / B	-	-	Assessment Visit (Infant RTI)	Collect **at least one** nasal swab for each RTI reported A nasal swab should be collected at the **first RTI** assessment visit **and** at the **first follow-up** RTI assessment visit (if criteria for follow-up are met – see Sections 8.4.4.2 and 8.4.7 If more than one follow-up assessment visit is conducted, additional nasal swabs may be collected at the Investigator's discretion.	
		-	-	RTI hospitalization	Collect (if possible) from any subject hospitalized with a RTI (or soon after release, as long as symptoms are ongoing). Collection of a nasal swab for sponsor testing is additional to and **DOES NOT REPLACE** any specimen collection (per local standard of care) for **testing by the local laboratory** to establish a fast and accurate diagnosis for the hospitalisation. In the case of hospitalization, local testing for RSV infection should be performed if feasible. If other specimens are collected and tested locally as per local standard of care, results will be recorded in the eCRF. However, only the sponsor laboratory results will be used when applying the case definitions for data analysis in Section 8.4.7. Thus, where mandated by the protocol, every effort should be made to obtain samples that can be analyzed by the sponsor (or sponsor-designated) laboratory.	

*Only from infant subjects in the sample collection subcohort for the visit. Each infant is assigned to a single subcohort.

8.1.2. Laboratory assays

Assays performed to evaluate immune response / the presence of RSV infection are listed below.

Table 13 Antibody determination

System	Component	Method	Laboratory
SERUM	RSV-A NAb (RSV-A Neutralizing Antibody)	NEUT	GSK Biologicals** or GSK designated lab
SERUM	RSV-B NAb (RSV-B Neutralizing Antibody)	NEUT	GSK Biologicals** or GSK designated lab
SERUM	Respiratory Syncytial Virus PreF3 Ab.IgG (RSVPreF3 IgG antibody concentration)	ELISA	GSK Biologicals** or GSK designated lab

ELISA = enzyme-linked immunosorbent assay**; NEUT** = Neutralization;** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) facilities in Rixensart, Belgium, Marburg, Germany and Wavre, Belgium.

Table 14 Molecular Biology

System	Component*	Method	Unit	Laboratory
NASMUC (Nasal swab)	Respiratory Syncytial Virus A RNA	QRTPCR	Copies/mL	GSK Biologicals or GSK designated lab**
NASMUC (Nasal swab)	Respiratory Syncytial Virus B RNA	QRTPCR	Copies/mL	GSK Biologicals or GSK designated lab**

* RSV-A/B quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.5. To evaluate tertiary objectives, an Allplex Respiratory Viruses Panel or alternative may be performed for RSV A/B-positive samples, and (if deemed necessary) for RSV A/B-negative samples
** GSK Biologicals laboratory refers to Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium, Marburg, Germany.

Additional testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These additional tests may not be represented in the objectives/endpoints of the study protocol.

Additional tests that may be performed on remaining blood samples to explore tertiary study objectives include, but are not limited to: evaluation (in blood samples) of RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints. Additional tests that may be performed on remaining nasal swab specimens to explore tertiary study objectives include, but are not limited to: evaluation for the presence of other respiratory viruses, via Allplex Respiratory Viruses Panel or alternative, in RSV A/B-positive samples, and if deemed necessary, in RSV A/B negative samples.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

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

8.1.3. Immunological read-outs

Table 15 Immunological read-outs

Blood sampling timepoint		No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint			
Maternal subjects				
V1 (Day 1)	pre vaccination	up to 300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V3 (Day 31)	post vaccination	up to 300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V5 (Delivery) (venous blood and cord blood)*	delivery	up to 300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V6 (Day 43 post-Delivery	post delivery	up to 300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
Infant subjects				
V1-NB (Birth)*	birth (only if cord blood cannot be collected)	Event-driven	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V2-NB (Day 43)	post birth 1	up to 100	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V3-NB (Day 121)	post birth 2	up to 100	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V4-NB (Day 181)	post birth 3	up to 100	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2

V = Visit; RSV-A/B: respiratory syncytial virus subtype A/B; **NA**: Not applicable; **NB**: Newborn. **IgG**: immunoglobulin G;
* Refer to Table 11 and Table 12

Table 16 Molecular biology tests

Nasal swab sampling timepoint		No. subjects	Component***
Type of contact (timepoint)	**Sampling timepoint**		
Maternal MA-RTI *	Event driven	Event-driven*	Respiratory Syncytial Virus A RNA
			Respiratory Syncytial Virus B RNA
Infant RTI**	Event driven	Event-driven*	Respiratory Syncytial Virus A RNA
			Respiratory Syncytial Virus B RNA

*Includes maternal RTI hospitalizations
**Includes infant RTI hospitalizations
***Quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.5. To evaluate tertiary objectives, an Allplex Respiratory Viruses Panel or alternative may be performed for RSV A/B-positive samples, and (if deemed necessary) for RSV A/B-negative samples

8.1.4. Clinical safety laboratory assessments

Refer to Section 10.2 for the list of clinical laboratory tests for safety assessments required by the protocol. These tests must be conducted according to the clinical laboratory manual and the SoA (Section 1.3).

8.1.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigen(s) used in the RSV maternal (RSVPreF3) vaccine.

8.2. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE, or AESI. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study intervention or participation in the study, are AESIs, or that caused the subject to discontinue the study.

Surveillance for / evaluation of respiratory tract illness is described in Section 8.4.

Electronic diary use is also described in Section 8.4.

8.2.1. Procedures for maternal subjects

8.2.1.1. Pre-vaccination procedures

8.2.1.1.1. Demographic data and lifestyle characteristics

Demographic data may include (but are not limited to) geographic ancestry (race)*, ethnicity*, month of birth (if allowed per local regulation) and year of birth.

Lifestyle characteristics may include (but are not limited to) highest level of education, smoking status/exposures, household environment, and other factors that could place them at risk of adverse study outcomes.

*Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013] have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry (race) and ethnicity will be collected for all subjects participating in this study.

8.2.1.1.2. Medical/vaccination history

Obtain the maternal subject's medical/vaccination history by interviewing her and/or reviewing her medical records. Record any pre-existing maternal subject conditions, signs and/or symptoms present before the study vaccination in the eCRF.

- Record outcome of Level 2 ultrasound (also known as a fetal anomaly ultrasound scan or fetal morphology assessment). Please see the Glossary of terms for a description. If results are not available at screening, then the ultrasound can be performed as a study procedure under certain conditions. Refer to the SPM for further details. If abnormal, subjects will be referred per local standard of care.
- Information from additional antenatal / medical evaluations (external to study visits/procedures) may be collected before, during, or after a scheduled study visit but should only be recorded in the additional antenatal/medical evaluations eCRF.
- Record number of past pregnancies, their outcome(s) and any pregnancy-related complications.
- For the current pregnancy, record:
  - the subject's pre-pregnancy weight (i.e., weight during the months before the subject became pregnant). This information can be obtained either via medical record review or subject interview.
  - gestational age, along with GAIA level of certainty as defined in Section 10.7
  - expected date of delivery (EDD) and method of estimation
  - number of prenatal visits attended up to the date of the study Screening visit,
  - approximate date of first prenatal visit,
  - results of any clinically significant, abnormal pregnancy screening laboratory tests,
  - any pregnancy-related complications
  - results of any procedures intended to screen for congenital anomalies.

8.2.1.2. Procedures carried out pre- and post-vaccination

8.2.1.2.1. Physical examination (General and obstetric examination)

Screening and Visits 1 through 6

General examination should include:

- Height (only at screening)
- Weight, temperature, and systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest (at screening and at Visits 1 through 6). At Visit 1, temperature need only be measured once, pre-vaccination.
- Pulmonary examination including measurement of blood oxygen saturation (by pulse oximetry) and chest auscultation (at screening and at Visits 1 through 6).

Obstetric examination should include:

- Fetal heart tones, fetal movement and fundal height (at screening and visits 1-5)
- Presence of edema (at screening and visits 1 – 5)
- Symptom directed vaginal examinations (speculum and and/or manual). If performed, results (normal/abnormal: specify) will be recorded.

Visits 7 and 8, and all unscheduled visits

General and obstetric examination should be symptom-directed.

Any unscheduled visit for a medically attended respiratory tract illness **must** include the maternal subject assessments listed in Section 8.4.5.

8.2.1.2.2. Pulse oximetry

Measurement of blood oxygen saturation by trained site personnel, using pulse oximeters provided by GSK, is strongly preferred. The SPM presents additional information about GSK-provided pulse oximeters and their use.

8.2.2. Procedures for infant subjects

8.2.2.1. Demographic data and lifestyle characteristics

Demographic data may include (but are not limited to) geographic ancestry (race)*, ethnicity*, month of birth (if allowed per local regulation) and year of birth.

Lifestyle characteristics may include but are not limited to living environment, household composition, breastfeeding (breastfeeding only / breastfeeding with supplementation / no breastfeeding), passive smoking, and extent of contact with children less than 6 years of age.

*Refer to Section 8.2.1.1.1 for additional information about collection of geographic ancestry (race) and ethnicity.

8.2.2.2. Physical examination at Visits 1-NB through 5-NB

A physical examination will be performed at each protocol-specified visit (Visits 1-NB through 5-NB).

The examination will include (but need not be limited to) assessment of the following:

- Weight, length, head circumference
- Temperature, heart rate and respiratory rate.
- Age-appropriate organ system examination including (but not limited to): eyes, ears, musculoskeletal, pulmonary (chest auscultation), cardiovascular, neurological and genitourinary.
- Presence of congenital anomalies.

8.2.3. Study holding rules and safety monitoring

8.2.3.1. Limitation on number of doses administered per day (first 30 maternal subjects)

Dosing will be limited to 10 maternal subjects per day across all sites until the first 30 maternal subjects have been dosed. During this period, within any given study site, subjects will be dosed sequentially and at least 60 minutes apart.

Additional enrolment and dosing may not proceed without written authorization. After this authorization has been provided, enrolment and dosing may continue without limitation on the number of subjects dosed per day or the time between consecutive subjects dosed at a given study site.

As noted in Section 6.1, all (up to 300) maternal subjects must be closely observed at the study site for at least 60 minutes after dose administration.

8.2.3.2. Outcomes of safety evaluations

Safety evaluations will include those performed by investigators, by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, independent data monitoring committee external to GSK (IDMC). **Details** regarding SRT and IDMC safety evaluations **are provided in a separate IDMC charter**.

- If no safety signal is observed after the first 30 maternal subjects have been enrolled and dosed, this will be documented. GSK will provide investigators with written authorization to enroll and dose the remaining ~ 270 maternal subjects.
- If the IDMC'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 IDMC Chair (or his/her representative) will notify the study CRDL. The study CRDL will be accountable for notifying investigators in writing of the IDMC's decision(s).

8.2.3.3. Study holding rules

8.2.3.3.1. Holding rules assessed by the investigator

The investigator and /or designees will assess on an ongoing basis whether any of the holding rules in Table 17 have been met, irrespective of the number of subjects enrolled and/or timing of the event relative to dosing.

Table 17 Holding rules assessed by the investigator

Holding Rule	Event	Number of mothers/infants
1a	**Maternal death** or any **life-threatening SAE**, or **fetal death** or unexplained **neonatal/infant death** up to 1 year of age	≥ 1
1b	Any non-life-threatening **SAE** that cannot be reasonably attributed to a cause other than vaccination (applies to both maternal subjects and infants of vaccinated mothers).	≥ 1
1c	Any **withdrawal** from the study (by the investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination.	≥ 1
1d	Any solicited administration site or systemic event leading to **hospitalization**, or **fever > 40°C** (104°F) (oral route) or necrosis at the injection site, within the 7-days (Day 1-7) post-vaccination period.	≥ 1

If the investigator becomes aware of a holding rule (e.g., 1a-1d in Table 17) being met, he/she will suspend enrolment and study vaccine/product administration and inform GSK as soon as possible (no later than within 24 hours).

The investigator is not permitted to start the administration of the next dose or enrol additional subjects until provided with written documentation of the favourable outcome of the safety evaluation, and written authorization to proceed.

Refer to Table 23 for contact information.

The below flow of communication must be followed.

- Investigator (or a designee) informs their local sponsor contact as soon as possible (no later than within 24 hours). (Table 23).
- The local sponsor contact informs the central sponsor contact (e.g., the SDL; the CRDL) as soon as possible (no later than within 24 hours).
- The central sponsor team ensures that SBIR is blocked, all sites administering study vaccine/product are informed, and all country or region- specific regulatory authorities are informed.
- Study sites confirm that they have been notified and have taken appropriate action, providing appropriate documentation to their local sponsor contact.
- The GSK Vaccine Safety Monitoring Board evaluates the case after receipt of the IDMC's recommendations / and takes the decision to stop or to restart dose administration.

- Where required per local / regional regulation, the central sponsor team submits a substantial amendment to the local/regional authority requesting authorization to re-start the study.
- When all required authorizations to re-start the study in a country / region have been provided, the central sponsor team provides written notification to local sponsor contacts; local sponsor contacts then provide written notification to study sites.

8.2.3.3.2. Holding rules assessed during IDMC evaluations

The Holding rules in Table 18 will be assessed by the IDMC during safety evaluations of unblinded data.

Note that these rules have been written under the assumption that the safety data from all expected subjects will be available. If the data from all subjects are not available (i.e. in case a subject is lost to follow-up), then the holding rules will be assessed on a pro-rata basis.

Further note that the IDMC may recommend that the study be placed on hold for reasons not covered by the holding rules if deemed necessary. Any available safety data may be reviewed as requested by the IDMC to allow for an overall assessment of the benefit/risk ratio of vaccination.

If the study is placed on hold, the investigator must suspend enrolment and study vaccine/product administration. As noted in Section 8.2.3.3.1, the investigator is not permitted to start the administration of the next dose or enrol additional subjects until provided with written documentation of the favourable outcome of the IDMC evaluation, and written authorization to proceed.

Table 18 Holding rules assessed during IDMC evaluations

Holding Rule	Event	Number of mothers/infants[1]
2a	Any **Grade 3 solicited administration site event** lasting 48h or more in an investigational RSV group, within the 7-days (Day 1-7) post-vaccination period.	≥ 4 subjects and ≥ 25% across active vaccine groups
2b	Any **Grade 3 solicited systemic event** lasting 48h or more in an investigational RSV group, within the 7-days (Day 1-7) post-vaccination period.	≥ 4 subjects and ≥ 25% across active vaccine groups
2c	Any **Grade 3 unsolicited AE** in an investigational RSV group that cannot be reasonably attributed to a cause other than vaccination, within the 7-days (Day 1-7) post-vaccination period. OR Any Grade 3 abnormality in pre-specified hematological or biochemical **laboratory parameters** in an investigational RSV group, at Day 8 post-vaccination[2].	≥ 4 subjects and ≥ 25% across active vaccine groups

[1] Across active vaccine groups, both conditions need to be achieved together: at least 4 subjects with the corresponding symptoms and at least 25% of subjects with the corresponding symptoms.
[2] Grading of laboratory parameters will be based on reference ranges as provided in [Sheffield, 2013] and in the SPM for this study.

GSK will inform the investigator of any holding rules in Table 18 (2a-2c) that are met.

The below flow of communication must be followed.

- IDMC Chair (or his/her representative) notifies the Clinical Research & Development Lead (CRDL).
- CRDL informs local sponsor contacts / Local Medical Leads (LMLs) and ensures that SBIR is blocked.
- The central sponsor team ensures that all country or region- specific regulatory authorities are informed.
- LMLs inform study sites to place a hold on screening activities and dose administration.
- Informed study sites confirm to their local sponsor contact(s) that action has been taken, providing appropriate documentation to their local GSK sponsor contact.
- The GSK Vaccine Safety Monitoring Board evaluates the case after receipt of the IDMC's recommendations and takes the decision to stop or to restart dose administration.
- Where required per local / regional regulation, the central sponsor team submits a substantial amendment to the local/regional authority requesting authorization to re-start the study and will not re-start the study until approval of the substantial amendment.
- When all required authorizations to re-start the study have been provided, the CRDL / central sponsor team provides written notification to local sponsor contacts; local sponsor contacts then provide written notification to study sites.

8.2.3.3.3. Overview of IDMC reviews

The IDMC will receive an unblinded report approximately monthly, once enrolment has started. For each report, the IDMC will be provided with available safety data, including but not limited to SAEs, pregnancy outcomes, pregnancy-related and neonatal adverse events of special interest, medically attended RTIs in maternal subjects and RTI/LRTIs in infants. Continuous monthly monitoring throughout the study will allow for ad-hoc data review meetings if deemed necessary by the IDMC.

In addition, there will be 5 planned IDMC data review meetings:

- The first planned meeting will take place once 75 maternal subjects have been dosed;
- Additional meetings will occur to coincide with release of results from each of the analyses described in Section 9.5.1.

For each review, the IDMC will be provided with unblinded safety data as described above.

The IDMC will also review all safety data on infant subjects through 1 year of age.

As part of ongoing review, the IDMC will monitor the rates of pregnancy-related outcomes and pregnancy-related and neonatal AESIs. Observed rates of outcomes and of AESIs for active vaccine recipients that are **higher** than rates reported in the placebo group or expected in the general population may trigger enhanced scrutiny of the cases by the IDMC. *Examples* based on a 2-fold higher reporting rate in vaccine recipients as compared to the general population are listed in Table 19. For example, with 16 maternal infant pairs followed through delivery, no more than 2 cases of pre-term birth should be expected among the vaccinated group. If that number is 4 or greater, it could be an early indication that vaccination may be harmful and would prompt further scrutiny by the IDMC, including the possibility to hold further vaccination. Depending on the nature and severity of the outcome or AESI, enhanced scrutiny may be triggered even if there is a less than 2-fold increase in reporting rate in vaccine recipients compared to that expected in the general population or seen in the placebo group.

Table 19 Examples of rates for AESIs

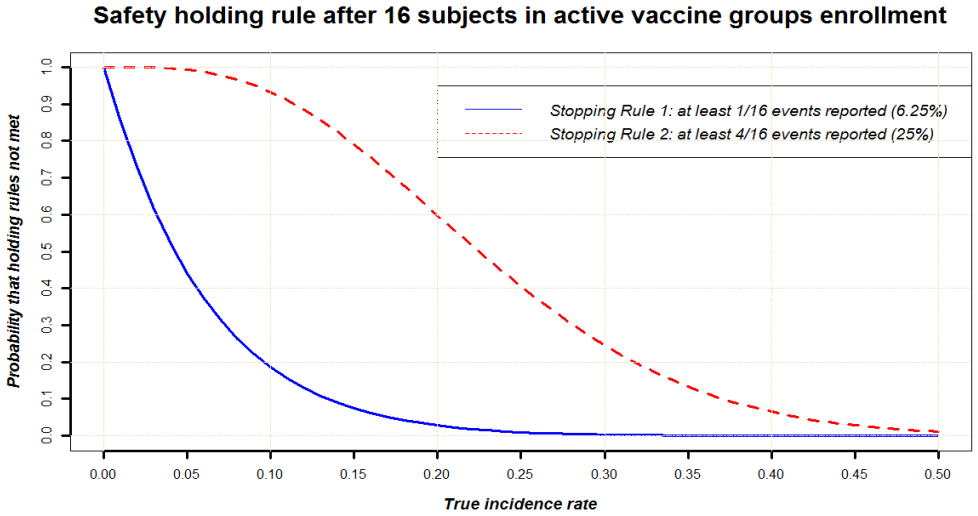
Event of Special Interest	Reported Rate in general population	Rate that could trigger additional safety concern (for the active vaccine groups combined)		
		% of subjects	Number of subjects in vaccinated groups at IDMC meeting 1	Number of subjects in vaccinated groups at IDMC meeting 2
Gestational hypertension	8%	16%	3	16
Gestational diabetes	6-7%	14%	3	14
Small for gestational age	10%	20%	4	20
Non-reassuring fetal status	15%	30%	5	30
Preterm Birth	12%	24%	4	24
Low birth weight	8%	16%	3	16
Respiratory distress/asphyxia	10%	20%	4	20
Antenatal bleeding	4-5%	10%	2	10
Intrauterine growth restriction	3-7%	14%	3	14

Enhanced scrutiny of the cases by the IDMC can be triggered at any point during the study depending on the observed rate of an AESI or any other safety concern.

8.2.3.4. Risk assessment

Figure 5 illustrates the probability of not meeting holding rule 1 and 2 for 16 active vaccine recipients at the first planned IDMC meeting.

Figure 5 Evaluations based on 16 active recipients - Risk assessment curve for one formulation based on the proposed safety holding rules across active groups



Thus, with 16 active vaccine recipients across study groups:

- Each holding rule 1a-1c has a more than 90% chance of not being met for vaccination with a true incidence rate below 1% and has a more than 80% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 2a-2c has a more than 90% chance of not being met for vaccination with a true incidence rate below 10% and a more than 80% chance of being met for vaccination with a true incidence rate above 35%.

The risk of ERD related to boosting pre-existing maternal antibody and transfer of vaccine-induced neutralizing antibodies from mother to infant, is considered negligible. However, as data evaluating this risk are expected before the vaccination of larger numbers of pregnant women, surveillance and evaluation of all RTIs in infants and medically attended-RTIs in mothers (Section 8.4) has been implemented.

To assess the ability of the study to demonstrate with 90% power that the progression rate from RSV infection to severe disease or hospitalization is lower than the 80% rate seen in the historical formalin-inactivated vaccine, the accrual of at least 5 cases of RSV infection among infants will be needed. With a one-sided 5% type one error rate and assumption of a 10% rate of infection progressing to severe disease or hospitalization, 5 infections can provide at least 90% statistical power to demonstrate the progression rate from RSV infection to severe disease or hospitalization is less than 80%.

Table 20 shows examples of the rate of progression to more severe disease or hospitalization and their corresponding upper 95% confidence intervals when 5 or 10 cases of RSV among infants are accrued. Where the upper limit of the 95% confidence interval is above 80%, this suggests a rate of severe disease that is equivalent to the historical formalin-inactivated vaccine. Where the upper limit is less than 80%, this would suggest that the current vaccine is not equivalent to the historical vaccine in terms of progression to more severe RSV disease.

Table 20 Rates of progression to more severe RSV disease or RSV associated hospitalization

		Rate of hospitalization or severe disease	
Observed number of infected infant subjects	Observed Number of hospitalizations or severe disease	Actual	Upper 95% CI
5	1	20%	71.6%
5	2	40%	85.3%
10	1	10%	45%
10	2	20%	56%
10	3	30%	65.2%
10	4	40%	73.8%
10	5	50%	81.3%

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other events of interest

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

Table 21 provides an overview of the protocol-required reporting periods for safety (as well as RTI) information.

Table 21 Timeframes for collecting and reporting safety (and RTI) information

		Before Delivery*						Delivery / Birth	Post-Delivery*				
Timepoint		D-28	D1	D7	D8	D31	D61		D 43	D121	D181	D271	12 months
Maternal subject visits		Pre-**	V1		V2	V3	V4	V5	V6	V7	V8		
Infant visits								V1-NB	V2-NB	V3-NB	V4-NB	C1-NB	V5-NB
Event	Administration site and systemic solicited events		M										
	Unsolicited AEs		M		M								
	Subsequent Pregnancies***							M					
	AEs/SAEs leading to Withdrawal from the study		M					I					
	SAEs and MAEs		M					I					
	AESIs*****		M					I					
	Medically attended RTI RTI/LRTI		M					I					
	SAEs related to study participation or concurrent GSK medication or vaccine	M											

* Approximately monthly contacts pre- and post-delivery also occur within the timeframes described above and are described in Section 1.3. **i.e. consent obtained. Pre = pre-vaccination; V=visit; C = contact; D= Day. *** if subsequent pregnancy occurs during the study, follow-up extends up to 8 weeks post birth of the infant If subsequent pregnancy occurs after Visit 8, report adverse pregnancy outcomes / other SAEs experienced by mother / infant, if known. ****AESIs include adverse pregnancy outcomes, pregnancy related AEs of special interest and neonatal AEs of special interest. Neonatal AEs of special interest identified after V2-NB (e.g., congenital anomalies) will continue to be reported as such

The investigator or designee will record and immediately report all SAEs (including RTIs associated with hospitalization of a maternal or infant subject and all adverse pregnancy outcomes), as well as all pregnancy related AESIs and neonatal AESIs to the sponsor or designee via the Expedited AE Reporting Form. This reporting should under no circumstances occur later than 24 hours after the investigator becomes aware of the event, as indicated in Section 10.3.10. The investigator will submit any updated data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 21. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine(s)/product(s), the investigator will promptly notify the Study Contact for Reporting SAEs mentioned in Table 23.

8.3.2. Method of detecting AEs, SAEs, other events of interest, and subsequent pregnancies

Methods of detecting and recording AE/SAE/AESI/subsequent pregnancies are detailed in Section 10.3.8. The assessment of AE/SAE intensity, causality and outcome are provided in the Section 10.3.9.

Open-ended and non-leading verbal questioning of the maternal subjects/infant subjects' parent(s)/LAR(s) is the preferred method of acquiring information related to an AE/SAE/AESI/subsequent pregnancy.

8.3.2.1. COVID-19 Infection

COVID-19 cases identified within the existing framework of the study will be captured and reported using standard AE, medically-attended AE or SAE criteria, as outlined in Section 10.3.

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

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

8.3.2.2. Clinically significant abnormal laboratory findings

The investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE Section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- All clinically significant abnormal laboratory test values during the study or within 8 days after the last dose of study intervention should be repeated until the values return to normal or baseline, or are no longer considered significantly abnormal by the investigator or LML. Refer to Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AEs or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, subsequent pregnancies, and other events

Once an investigator (or designee) becomes aware that a study subject has experienced an SAE/AESI/subsequent pregnancy, he/she must report it to GSK using the documentation and within the timeframes mentioned in Table 22. This is essential for meeting legal obligations and ethical responsibilities for the subject safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator will always provide an assessment of causality at the time of the initial report as defined in Section 10.3.9.2.

Local regulatory requirements and sponsor policy for the preparation of an investigator safety report for Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has a legal responsibility to notify local authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/AESIs/subsequent pregnancies

Table 22 Timeframes for submitting serious adverse event, subsequent pregnancy and other event reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs (including adverse protocol pregnancy outcomes)	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
AESIs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Maternal subjects: MA-RTIs Infant subjects: RTIs/LRTIs	3 days*	eCRF	1 week	eCRF
Subsequent Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once investigator determines event meets protocol definition of an AESI.
‡ The investigator will be required to confirm review of SAE/AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AESI

8.3.3.1. Contact information for reporting of serious adverse events (SAEs), AESIs, subsequent pregnancies and study holding rules

Table 23 Contact information for reporting of serious adverse events (SAEs), AESIs, subsequent pregnancies and study holding rules

Study contact for questions regarding SAEs, AESIs, subsequent pregnancies Refer to the local study contact information document	**Study contact for reporting of study holding rules** As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the Local Medical Lead (LML).
Back-up study contact for reporting SAEs, AESIs, subsequent pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD Email address: PPD US sites only: Fax: PPD Canadian sites only: Fax: PPD	**Back-up study contact for escalation of holding rules** Refer to the local study contact information document.

8.3.3.2. Additional Reporting Guidance for the Study Pregnancy

A medical complication that requires an unplanned caesarian section or an emergency induction of vaginal delivery may be reported as an SAE/AESI (as applicable), using the corresponding Expedited AE report form.

All congenital anomalies (minor and major) are to be reported as serious adverse events (SAEs). To confirm if a medical condition is a congenital anomaly the WHO/CDC/ICBDSR birth defects surveillance manual [WHO/CDC/ICBDSR, 2014], available online, can be reviewed.

Only major congenital anomalies meet the criteria for the GAIA case definition of neonatal AESI. To assess if a congenital anomaly is major and should be reported as an AESI, the same website can be consulted.

8.3.4. Subject card

The investigator (or designee) must provide the maternal subjects/infant subjects' parent(s)/LAR(s) with a "subject card" containing information about the clinical study. One card will be provided to each maternal subject who enters the study. Another card will be provided for each infant subject who enters the study.

Maternal subjects/ infant subjects' parent(s)/LAR(s) must be instructed to keep these subject cards in his/her/their possession at all times throughout the study.

In an emergency, the cards serve to inform the responsible attending physician that the maternal / infant subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.4. Respiratory tract illnesses (RTIs)

The definitions provided in Sections 8.4.1.1 and 8.4.1.2 are for use by site personnel. They are designed to provide GSK Biologicals with the information needed to apply case definitions during data analyses. They are related but not identical to the case definitions themselves (Section 4.2.6). For additional details regarding maternal MA-RTI and infant RTI surveillance and assessment, refer to the SPM.

8.4.1. Definitions

8.4.1.1. Medically attended respiratory tract illnesses (MA-RTIs) in maternal subjects

A maternal MA-RTI occurs when the maternal subject visits a healthcare professional (e.g., a General Practitioner) for any respiratory symptom, including (but not limited to) cough, sputum production and difficulty breathing.

8.4.1.2. Respiratory tract illnesses (RTIs) in infant subjects

RTI symptoms include:

- Nasal discharge running freely out of the infant's nose (runny nose),
- Breathing through the mouth because the infant's nose is blocked (blocked nose),
- Regular bursts of cough,
- Difficulty in breathing (fast breathing, poor feeding, working hard to breathe, or making unusual sounds when breathing), and
- Wheezing (a whistling sound when the infant breathes out, and thus another sign of difficulty in breathing).

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

8.4.2. Surveillance (Amended 30-SEP-2020)

MA-RTI surveillance begins when a maternal subject enters the study and ends 6 months after delivery (Visit 8). RTI surveillance in infant subjects begins at birth (Visit 1-NB) and ends 6 months after birth (Visit 4-NB).

An electronic Diary (e-Diary) device will be provided to the maternal subject/LAR at Visit 1.

As noted in Section 10.3.8, maternal subjects/LARs will use the e-Diary to capture the occurrence of maternal medically attended RTIs and RTIs in infant subjects. Maternal subjects/LARs will also use the e-Diary to capture solicited administration site or systemic events, the occurrence of unsolicited adverse events 30 days post vaccination, and medically attended adverse events (additional to maternal medically attended RTIs).

Maternal subjects/LARs will keep the e-Diary device until the last surveillance visit (Visit 8 for the maternal subject or Visit 4-NB for the infant subject), whichever comes last, has been completed.

During surveillance, the maternal subject/LAR will:

- Complete the eDiary daily, and
- Contact site personnel if:
  - The maternal subject/LAR encounters any difficulty with eDiary entry, or
  - The maternal subject has respiratory symptoms for which she visits (or plans to visit) a healthcare professional, or for which she is hospitalized, or
  - The infant subject has any new or worsening RTI symptoms, or
  - The maternal subject/LAR intends to seek medical care because of concern about the infant's respiratory tract illness, or general health in the context of the infant's respiratory tract illness, or
  - The maternal subject experiences severe solicited administration site or systemic events in the 7 days post-vaccination, or
  - The maternal subject has any new symptoms or medical problems, whether related or unrelated to her pregnancy.
- Site personnel will:
  - Review the e-Diary web portal on a regular basis,
  - Promptly follow up on any maternal subject/LAR initiated or e-Diary generated alert,
  - Initiate planned scripted contacts with the maternal subject/LAR as described in Table 2 and Table 4. During these contacts, site personnel will reinforce the maternal subject's/LAR's understanding of the eDiary, elicit information as described in Table 1 and Table 3, and determine whether the maternal subject/LAR has visited a healthcare provider not affiliated with the study (for the maternal or infant subject's care).
  - In the event that ERT portal/ alerts are not functioning, the site should contact subjects at least weekly until Visit 8 (maternal subjects) / 4-NB (infant subjects) to complete surveillance questions and collect information about adverse events. Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local best practice.

If the maternal subject visited / the infant subject was taken to a healthcare provider not affiliated with the study, site personnel should (if permitted by local regulation) contact that healthcare provider to obtain the medical record(s) for the visit.

Three attempts should be made within the week of a scheduled contact. If these attempts are unsuccessful, that monthly contact is considered a missed contact. The next scheduled contact will be made the following month). Note, contacts may occur more often between Visit 5 and Visit 6 (See Table 2).

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

8.4.3. Treatment of adverse events

Any medication administered for the treatment of an SAE/AESI should be recorded in the Expedited Adverse Event Report of the subject's eCRF screen (refer to Section 10.3.10.1).

8.4.4. When to conduct an assessment visit

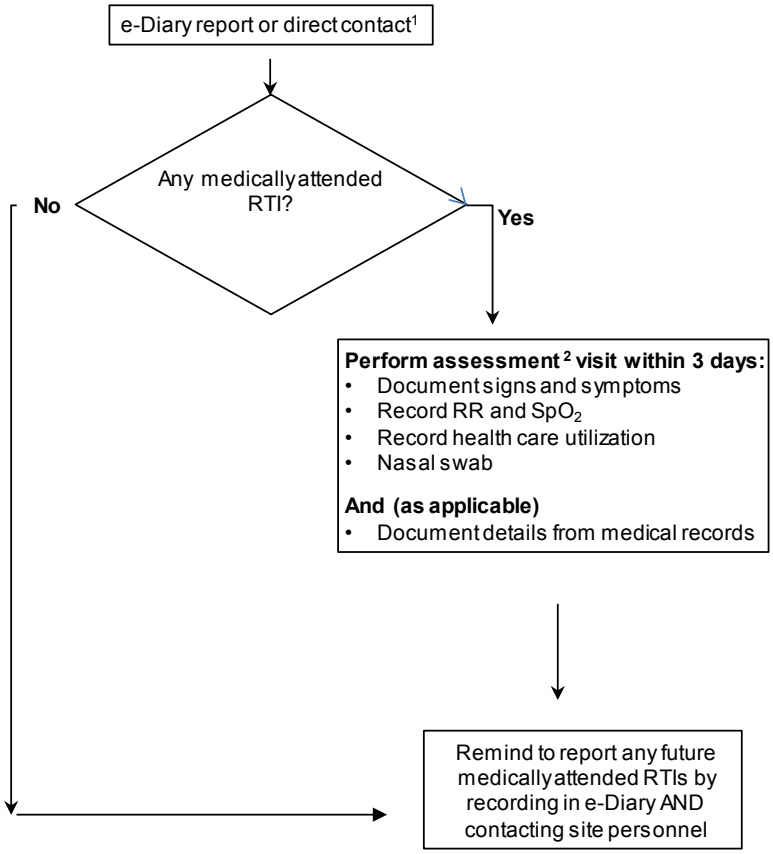
8.4.4.1. For a maternal MA-RTI

Conduct an assessment visit (Section 8.4.5), ideally within 3 calendar days after a medically attended visit due to RTI symptoms occurs during the surveillance period. However, a visit may be conducted *even if beyond this window if* symptoms are ongoing.

If a maternal subject informs the site that she has RTI symptoms and would see / have seen a physician for them if she was not already scheduled for a study visit, then the site should perform the MA-RTI assessment visit procedures (including nasal swab) during the already scheduled study visit.

A decision tree is provided in Figure 6. Refer to the SPM for additional details regarding maternal MA-RTI surveillance.

Figure 6 Decision Tree for site personnel – maternal surveillance and assessment



RR: Respiratory rate: **SpO_2**: Blood oxygen saturation by pulse oximetry.
[1]Details regarding Surveillance are provided in Section 8.4.2 and the SPM.
[2]Details regarding the RTI assessment visit are provided in Section 8.4.5 and the SPM.

8.4.4.2. For an infant RTI

Conduct an assessment visit, as described in Section 8.4.5, as soon as possible after at least one of the following has been reported during the surveillance period:

- Cough,
- Runny nose (if new),
- Blocked nose,
- Difficulty in breathing,
- Wheezing.

If reported symptoms include difficulty in breathing or wheezing, the visit should (ideally) take place within 24 hours; otherwise the visit should (ideally) take place within 3 calendar days. However, a visit may be conducted *even if beyond the specified ideal window* provided symptoms are ongoing.

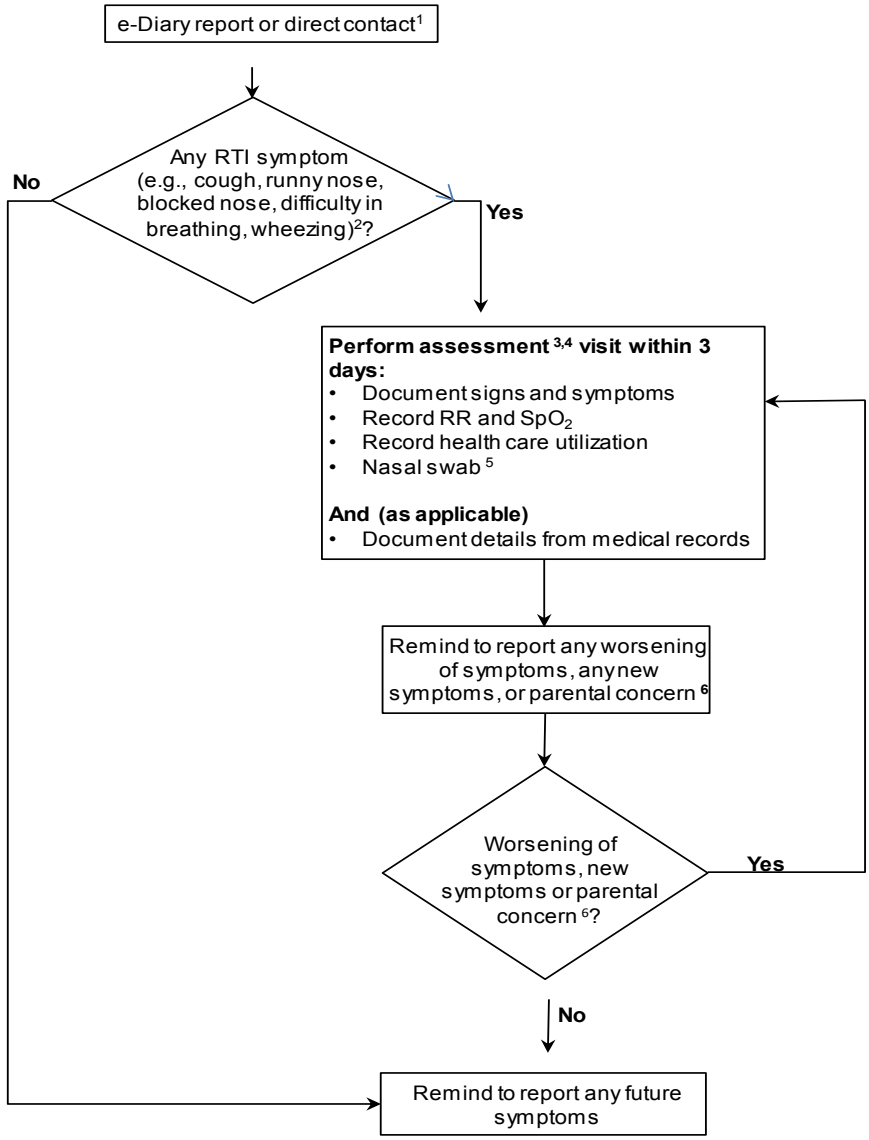
After the first assessment visit, site personnel should use the RTI eDiary data and results of any unscheduled contacts to assess the development of new and worsening of previously reported symptoms.

- Site personnel should conduct a **follow-up** assessment **visit** as soon as possible after learning:
  - that any symptom present at the first assessment visit has worsened, OR
  - that there are new symptoms, OR
  - that there is parental concern in the context of the respiratory tract illness.

The timing of the follow-up visit should be consistent with the guidance given above; i.e., ideally within 24 hours if difficulty breathing or wheezing is reported; ideally within 3 calendar days otherwise.

A decision tree is provided in Figure 7. Refer to the SPM for additional details regarding infant RTI surveillance.

Figure 7 Decision Tree for site personnel - infant surveillance and assessment



RR: Respiratory rate: **SpO_2**: Blood oxygen saturation by pulse oximetry.
[1]Details regarding Surveillance are provided in Section 8.4.2 and the SPM.
[2]Cough, runny nose, blocked nose, difficulty in breathing, wheezing are described in Section 8.4.4.2
[3]Details regarding the RTI assessment visit are provided in Section 8.4.5 and the SPM.
[4] Post-visit follow up is described in Sections 8.4.7 and in the SPM.
[5]If a follow-up assessment visit is conducted, collection of additional nasal swabs is as described in Table 12.
[6]Parental concern *in the context of an RTI*

8.4.5. Assessment visit procedures

The purpose of each assessment visit is to objectively document signs and symptoms of a respiratory tract illness by an appropriately qualified person (i.e. medical or nursing), provide medical advice or referral as appropriate, and collect specimens for detection of RSV infection:

An assessment visit may take place at the investigator's clinical facility or another medical facility, or via a home visit by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).

Unless otherwise specified, assessment visit procedures will be the same for maternal subjects with MA-RTIs and for infant subjects with RTIs.

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

8.4.5.1. Clinical evaluation

At every assessment visit, the investigator/study staff/designated third party will evaluate the clinical signs and symptoms of the RTI. Data to be collected and recorded include (but are not limited to):

For maternal subjects:

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (Section 8.2.1.2.2), in room air, if feasible
- Results of chest auscultation
- Signs of difficulty in breathing (wheezing and tachypnoea in maternal subjects)

For infant subjects:

- Temperature
- Respiratory rate
- Blood oxygen saturation (measured by pulse oximetry (Section 8.2.1.2.2), in room air, if feasible
- Results of chest auscultation
- Presence of cough, runny nose or blocked nose
- Signs of difficulty in breathing (wheezing, tachypnoea, nasal flaring, chest in-drawing and apnea)
- Irritability/agitation
- Lethargy/excessive sleepiness
- Cyanosis
- Feeding poorly

8.4.5.2. Nasal swab collection

Refer to Table 11 (maternal subjects) and Table 12 (infant subjects). Additional details are provided in the SPM.

8.4.5.3. Missed assessment visit

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

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

8.4.6. RTI hospitalization during the surveillance interval

Whenever a subject is admitted to hospital for observation or treatment of an acute respiratory illness during the surveillance interval for that subject, a nasal swab should be collected using GSK Biologicals -provided supplies, and sent to GSK Biologicals for analysis as described in Table 11 and Table 12**.**

8.4.7. Follow-up of infant respiratory tract illnesses

Any infant RTI documented as ongoing at a previous visit/contact will be reviewed at subsequent visits/contacts during the surveillance interval until (a) all symptoms have resolved (except runny nose, often chronic in infants), or (b) the subject completes Visit 4-NB or (c) the subject is lost to follow up.

8.5. Treatment of overdose

Not applicable.

8.6. Pharmacokinetics

Not applicable.

8.7. Pharmacodynamics

Not applicable.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

Not applicable.

8.10. Health outcomes

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

All analyses will be descriptive.

9.2. Sample size determination

Up to 300 subjects will be randomised to achieve up to 270 evaluable subjects for an estimated total of up to 90 evaluable maternal subjects per study group.

Assessments of both safety and immunogenicity data were considered when determining sample size for this study.

Withdrawals will not be replaced.

9.2.1. Safety

A sample size of 50 maternal subjects per group will provide a probability of 78%, 92% or 99% to observe at least one AE, if the true AE rate is 3%, 5% or 10%, respectively.

A sample size of 100 maternal subjects per group will provide a probability of 95%, 99% or >99.9% to observe at least one AE, if the true AE rate is 3%, 5% or 10%, respectively.

Table 24 illustrates the precision one can expect on the percentage of subjects with symptoms following vaccination, considering sample sizes of 150 vaccinated women and 300 vaccinated women (50 and 100, respectively, in the placebo control group; 50 and 100, respectively, in each active vaccine group).

There is 95% confidence that the true incident rate is within (0, 7.1%) if no AE is observed in a single vaccine group with 50 subjects. The true incident rate will be within (0, 3.6%) if no AE is observed across both active vaccine groups with 100 subjects.

There is 95% confidence that the true incident rate is within (0, 3.6%) if no AE is observed in a single vaccine group with 100 subjects. The true incident rate will be within (0, 1.8%) if no AE is observed across both active vaccine groups with 200 subjects.

Table 24 Exact 95% confidence interval on the percentage of subjects with adverse events following vaccination per group

50 subjects in an RSV vaccine group			100 subjects in an RSV vaccine group		
Number (%) of subjects with an AE	Exact 95% Confidence Interval		Number (%) of subjects with an AE	Exact 95% Confidence Interval	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
50 (100)	92.9	100.0	100 (100)	96.4	100
45 (90)	78.2	96.7	90 (90)	82.4	95.1
40 (80)	66.3	90	80 (80)	70.8	87.3
35 (70)	55.4	82.1	70(70)	60	78.8
30 (60)	45.2	73.6	60 (60)	49.7	69.7
25 (50)	35.5	64.5	50 (50)	39.8	60.2
20 (40)	26.4	54.8	40 (40)	30.3	50.3
15 (30)	17.9	44.6	30 (30)	21.2	40
10 (20)	10	33.7	20 (20)	12.7	29.2
5 (10)	3.3	21.8	10 (10)	4.9	17.6
0 (0)	0.0	7.1	0 (0)	0	3.6

Exact 95% CI computed based on Clopper/ Pearson formula

9.2.2. Immune response

Assuming a 10% rate of non-evaluable subjects, approximately 90 subjects per group will be evaluable for the analysis of RSV specific antibody titer/concentration.

The two active vaccine groups will be compared at Day 31 using a one-sided two sample T-test with significance level of 5%. Table 25 includes the power to detect a fold change greater than 1 given that the alternative hypothesis of fold changes between 1.4- to 2.0 between two vaccine groups is true, assuming the standard deviation of RSV-A neutralizing antibody titers of 0.25, 0.3, 0.35 and 0.4 on its log 10 scale.

Table 25 Effect of dose: Power and fold increase in terms of RSV-A neutralizing antibody titers with sample sizes of 45 and 90 subjects per group at significance level of one- sided 5%

Standard Deviation*	Fold change	No. of Subjects per group	Power	No. of Subjects per group	Power
0.25	1.4	45	86.5	90	98.8
	1.5	45	95.2	90	99.9
	1.6	45	98.6	90	>99.9
	1.7	45	99.6	90	100
	1.8	45	99.9	90	100
	1.9	45	≥99.9	90	100
	2	45	≥99.9	90	100
0.3	1.4	45	74.1	90	94.6
	1.5	45	86.8	90	98.9
	1.6	45	94	90	99.8
	1.7	45	97.5	90	>99.9
	1.8	45	99.1	90	>99.9
	1.9	45	99.7	90	100
	2	45	99.9	90	100
0.35	1.4	45	62.5	90	87.3
	1.5	45	76.5	90	95.7
	1.6	45	86.4	90	98.8
	1.7	45	92.6	90	99.7
	1.8	45	96.3	90	>99.9
	1.9	45	98.2	90	>99.9
	2	45	99.2	90	>99.9
0.4	1.4	45	52.9	90	78.6
	1.5	45	66.5	90	90.2
	1.6	45	77.5	90	96.1
	1.7	45	85.6	90	98.6
	1.8	45	91.2	90	99.6
	1.9	45	94.9	90	99.9
	2	45	97.1	90	>99.9

*Standard deviation on log10 transformed RSV-A neutralizing antibody titer based on previous studies on PreF2 vaccine. **PASS: One sided two-Sample T-Test with alpha 5%

9.3. Populations for analyses

For purposes of analysis, the following analysis sets are defined:

9.3.1. Maternal Subjects

	Description
Analysis Set	**Maternal subjects**
Enrolled	All maternal subjects who completed the informed consent process and signed the informed consent form. Refer to the glossary of terms for the definition of 'enrolled'
Exposed	All maternal subjects who received at least 1 dose of the study intervention. The allocation in a group is done in function of the administered intervention.
Full Analysis	All maternal subjects in the Exposed set who have post-vaccination immunogenicity data.
Per Protocol	All maternal subjects who received at least 1 dose of the study intervention to which they were randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion.
Unsolicited Safety	All maternal subjects who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety	All maternal subjects in the Exposed Set who have solicited safety data

9.3.2. Infant subjects

	Description
Analysis Set	
Exposed	Infants live-born to exposed maternal subjects, whose parents/LARs completed the informed consent process and signed the informed consent form
Full Analysis	All infant subjects in the Exposed set who have post-delivery/birth immunogenicity data.
Per Protocol	All infant subjects in the Full Analysis set minus those who (a) were born less than 4 weeks post- maternal subject vaccination and/ or (b) have protocol deviations that lead to exclusion.
Unsolicited Safety	All infants in the exposed set for whom unsolicited AEs /not having unsolicited AEs are reported

9.3.3. Criteria for elimination from analysis

The Statistical Analysis Plan (SAP) will provide a complete list of criteria for elimination from per protocol analyses. Criteria may include, but are not limited to, those in Section 9.3.3.1 and 9.3.3.2.

9.3.3.1. Intercurrent medical conditions and concomitant medications/products/vaccines that may lead to elimination of a subject from per-protocol analyses

9.3.3.1.1. Maternal subjects

- Any of the medications listed in Section 5.2.1.2 if administered up to Day 43 post-delivery (Visit 6).

9.3.3.1.2. Infant subjects

- Systemic immunosuppressants or other immune-modifying drugs administered chronically (i.e. for more than 14 consecutive days) up to Day 43 post birth (Visit 2-NB), or Day 121 post birth (Visit 3-NB), or Day 181 post-birth (Visit 4-NB) depending on the relevant (visit-specific) sub-cohort for blood sampling.
  - For corticosteroids, this will mean prednisone or equivalent, ≥ 0.5 mg/kg/day.
  - Topical steroids are allowed.
  - Inhaled steroids are allowed if used in accordance with local labelling information (e.g. for budesonide).
- Immunoglobulins and/or any blood or plasma derivatives administered up to Day 43 post birth (Visit 2-NB), or Day 121 post birth (Visit 3-NB), or Day 181 post-birth (Visit 4-NB), depending on the infant's assigned sub-cohort for blood sampling.

9.3.3.1.3. Maternal and Infant subjects

- Diagnosis during the study with an immunological disorder or occurrence during the study of a condition (other than the study pregnancy) capable of altering immune response. For evaluation of immunogenicity endpoints in maternal and infant subjects, this includes RSV infection confirmed either locally or by GSK Biologicals during the specified analysis interval.
- Any investigational or non-registered product (drug or vaccine) other than the study vaccine/product administered during the specified analysis interval.

9.3.3.2. Other situations that may lead to elimination of a subject from per-protocol analyses

- Protocol violation(s) linked to the inclusion/ exclusion criteria, including age.
- Study vaccine/product not administered as specified by the protocol.
- Failure to comply with the post-vaccination immunogenicity blood sampling schedule at a given time-point (Table 2, Table 4).

9.4. Statistical analyses

9.4.1. General considerations

The statistical analysis plan (SAP) will be finalized before database lock and will include a more technical and detailed description of the statistical analyses to be performed. This section summarizes planned statistical analyses of primary and secondary endpoints.

The SAP describes how missing data will be handled during analyses.

9.4.1.1. Safety

Safety analyses in **maternal subjects** will include summaries by study group and age category (18 - < 35 years of age; ≥35 years of age; overall) of hematology and biochemistry results by grade and per time point, solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, , MA-RTIs,, RSV-associated MA-RTIs, AEs leading to study withdrawal, pregnancy outcomes and pregnancy related AESIs.

Safety analyses in **infant subjects** will include summaries by study group and gestational age at birth (> 37 weeks or ≤ 37 weeks) of neonatal AESIs, MAEs, SAEs, AEs leading to study withdrawal, and the occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations. Case definitions for RSV associated LRTIs are based on those described in [Modjarrad, 2016] and are described in Section 4.2.6.

All safety analyses will be performed on the Solicited Safety, Unsolicited Safety and Exposed sets.

9.4.1.2. Immunogenicity

The primary analysis will be based on the Per Protocol set for analysis of immunogenicity. If, in any study group and at any timepoint, the percentage of vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set will be performed to complement the Per Protocol analysis.

9.4.2. Subject disposition

Number of screened, randomised, vaccinated and withdrawn maternal subjects in each group and overall will be described.

Number of infants enrolled and withdrawn (by group and subcohort, and overall) will be described. Additional analyses by country and/or by site may be performed.

9.4.3. Primary endpoints

9.4.3.1. Safety

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal subjects	Occurrence of Solicited administration site and systemic events during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).	The number and percentage with exact 95% CI of maternal subjects reporting each **Solicited administration site event** (any grade, each grade,) and **solicited systemic event** (any, each grade) during the 7-day (days 1 to 7) follow-up period after vaccination will be tabulated by maximum intensity per subject for each study vaccine group. **For fever** during the 7-day follow-up period after vaccination, the number and percentage of maternal subjects reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments, any Grade 3 fevers, will be reported. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited and unsolicited**), with at least one **systemic AE** (**solicited and unsolicited)** and with **any AE** during the 7-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).
	Occurrence of any protocol-specified hematological or biochemical laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)	The number and percentage of subjects with hematology and biochemistry results outside central laboratory normal ranges will be tabulated to show Day 8 versus baseline. The maximum grading as described in [Sheffield, 2013] and in the SPM from Screening up to Day 8 will also be tabulated.
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).	The number and percentage of maternal subjects with **unsolicited** symptoms within 30 days after vaccination with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited symptoms, for any causally related unsolicited symptoms, for Grade 3 related unsolicited symptoms and for MAEs.
		The number and percentage of maternal subjects with at least one **administration site AE** (**solicited and unsolicited**), with at least one **systemic AE** (**solicited and unsolicited)** and with **any AE** during the 30-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for MAEs.
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs from Visit 1	The number and percentage of maternal subjects with • at least one SAE; • at least one MAE

	Primary Safety Endpoints	Statistical Analysis Methods
	(Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).	from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). Outcomes are listed in Section 3.	The number and percentage of maternal subjects with each pregnancy outcome will be tabulated with its exact 95% CI by group. By subject listings of adverse pregnancy outcomes will be prepared but will not be released until the final, unblinded analysis has been completed.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post delivery; Visit 6**).** These events are listed in Section 3**.**	The number and percentage of maternal subjects with each pregnancy-related AESI will be tabulated with its exact 95% CI by group. By subject listings of pregnancy-related AESIs will be prepared but will not be released until the final, unblinded analysis has been completed.
Infant subjects	The occurrence of neonatal AESIs (reported up to 6 weeks after birth). These events are listed In Section 3. Occurrence of SAEs, AEs leading to study withdrawal and medically attended AEs from birth up to 6 weeks after birth.	The number and percentage of infant subjects with each neonatal AESI will be tabulated with its exact 95% CI by group. By-subject listings of neonatal AESIs will be prepared, but will not be released until the final, unblinded analysis has been completed. The number and percentage of infant subjects with • at least one SAE; • at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).

9.4.3.2. Immunogenicity

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).	For each assay, at each timepoint and by study group and age category (18 - <35 years; ≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at baseline, at day 31 and at delivery will be explored using scatter plots of individual values. Between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A will be performed at Day31 and at Delivery using a mixed effect model on the $logarithm_{10}$ transformation of the concentrations/titers, and including the pre-vaccination $logarithm_{10}$ transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, and the interval between vaccination and delivery as covariates if needed.
Cord blood/ placental transfer	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A	For each assay, the following analysis will be performed by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • The distribution of RSV-A and RSVPreF3 IgG-specific antibody titres/concentration from cord blood will be tabulated • For each assay, relationship between maternal antibody titers and infant antibody titers at the time of delivery will be evaluated graphically using scatter plots of individual results.
	• The ratio between cord blood and maternal RSVPreF3 IgG-specific antibody concentrations	• Geometric mean of placental transfer will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer ≥ 1 will be tabulated with exact 95 % CI by study group.

Primary Immunogenicity Endpoints		Statistical Analysis Methods
	• All 3 endpoints measured on blood samples collected from maternal subjects at delivery and either cord blood, or (if cord blood cannot be collected) infant blood samples collected within 3 days after birth	Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks; ≤ 37 weeks), and the interval between vaccination and delivery as covariates if appropriate. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at delivery will be explored using scatter plots of individual values.

9.4.4. Secondary endpoints

9.4.4.1. Safety

Secondary Safety Endpoints		Statistical Analysis Methods
Maternal subjects	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs and AEs leading to study withdrawal. Occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)	The number and percentage of maternal subjects with at least one SAE, AE leading to study withdrawal, MAE from Day 1 up to 6 months after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared (but will not be released until the final, unblinded, analysis has been completed). The number and proportion of subjects with at least one RSV-associated MA- RTI (with 95 % CI) will be calculated and tabulated.
Infant subjects	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and medically attended AEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs	For each category: • SAE, • AE leading to study withdrawal, • MAEs The number and proportion of infant subjects who experienced at least one event from birth up to 6 months after birth and the number and proportion of infant subjects who experienced at least one event from birth up to 1 year after birth will be tabulated with 95% CI by group. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared.
	From birth to 6 months (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions in Section 4.2.6)	For each category: • RSV-associated LRTI, • Severe LRTI, • Very severe LRTI • RSV-associated hospitalization The number and proportion (with 95% CI) of subjects with at least one event will be calculated and tabulated by group.

9.4.4.2. Immunogenicity

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and • Neutralizing antibody titers against RSV B • For RSV-A: Measured on the blood sample collected Day 43 post- delivery (Visit 6). • For RSV-B: Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post delivery (Visit 6).	For each assay, at each timepoint and by study group and age category (18 - <35 years ;≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at baseline, at day 31, at delivery and at day 43 post-delivery will be explored using scatter plots of individual values. In addition, between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A and RSV-B will be performed at Day31, , at Delivery and at Day 43 post-delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, and the interval between vaccination and delivery if available as covariates if needed.
Infant subjects	• RSVPreF3 IgG-specific antibody concentration • Neutralising antibody titres against RSV-A • Neutralising antibody titres against RSV-B For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will	For each assay, at each timepoint and by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. In addition, analyses will include exploratory evaluation of the persistence of RSV specific antibodies in infants through time, and half-life analysis modelling of logarithm transformed RSV antibody concentrations/titers over time. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery, and on blood samples collected at 6 weeks, 3-4 months and 6 months post-birth using a mixed effect model on the

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
	be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to intervention For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective).	logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks ; ≤ 37 weeks), and the interval between vaccination and delivery as covariates if appropriate and needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at delivery will be explored using scatter plots of individual values.

9.4.5. Tertiary / exploratory endpoints

9.4.5.1. Immunogenicity

Tertiary Immunogenicity Endpoints	Statistical Analysis Methods
Tertiary endpoints for maternal and infant subjects may include: • Humoral immune response in terms of RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints • The presence of other respiratory viruses in nasal swabs (assessed via an Allplex Respiratory Viruses Panel or alternative; performed for RSV A/B-positive samples and if deemed necessary for RSV A/B-negative samples).	To be described in a separate Statistical Analysis Plan.

9.4.5.2. Exploratory endpoints

Biomarker exploratory analyses and any other analysis (as applicable) will be described in a separate statistical analysis plan.

9.4.6. Other analyses

9.4.6.1. Demography and baseline characteristics

These analyses will be performed on the Exposed set and on the Per protocol set for immunogenicity.

For all maternal subjects, demographic characteristics (e.g., age at vaccination (18 - <35; ≥ 35 years), gestational age at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), geographic ancestry) will be summarized by group using descriptive statistics. The interval in days between maternal vaccination and delivery will be calculated and summarized by group using descriptive statistics. For their infants, demographic characteristics (e.g., gestational age at time of delivery (> 37 weeks; ≤ 37 weeks), sex, weight, length, head circumference, geographic ancestry, apgar score), and lifestyle characteristics (e.g., living environment, household composition, breastfeeding, passive smoking and and extent of contact with children less than 6 years of age) will be summarised by group, and for each immunogenicity sub-cohort within each group, using descriptive statistics.

- Frequency tables will be generated for categorical variable such as geographic ancestry.
- Mean, median, standard deviation and range will be provided for continuous data such as age.

9.4.6.2. Dose Characterization

The characterization of the doses and the choice of the dose to be carried over to subsequent studies will be based on the totality of safety, reactogenicity and immunogenicity data from the analyses above with a focus on maximizing cord blood titers. The vaccine dose that demonstrates the highest immunogenicity in pregnant women and in cord blood in terms of GMTs/GMCs at Day 31 and delivery, that is associated with an acceptable safety profile will be considered for subsequent trials. As variability in titers is expected to be lower at Day 31 than in the cord blood, power calculations for dose characterization are based on anticipated standard deviations at Day 31. If immune response is similar in the active vaccination groups, additional analyses using a generalized ROC (Receiver Operating Characteristics) method [Yu, 2018] will be performed.

Additional details will be provided in the SAP.

9.4.6.3. Case accruals

Rules for MA-RTI and RTI case accountability will be described in the Statistical Analysis Plan.

9.5. Interim analyses

No interim analyses are planned. However, analyses to evaluate objectives and endpoints will be performed in steps. The sequence of analyses is described below.

9.5.1. Sequence of analyses

9.5.1.1. First analysis

The **first analysis** will be conducted after approximately 75 maternal subjects have completed Visit 3 (Day 31) and approximately 24 maternal subjects and their infants have completed Visit 5 / Visit 1-NB (Delivery/Birth).

By-study-group safety and immunogenicity analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

Immunogenicity analyses will include all available test results at:

- Visit 1 (Day 1) and Visit 3 (Day 31);
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.

Safety analyses will be performed by blinded treatment group, with the letters "A," "B," and "C" replacing treatment-specific group identifiers in all results summaries. Steps will be taken to minimize the risk of unblinding (e.g., events that happen in a single group will be masked by adding the same amount of counts to other groups). Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.

Safety analyses will include all available data for:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

A report summarizing these ***safety and immunogenicity*** results will be prepared but will not be made available to investigators.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

9.5.1.2. Second analysis (Amended 30-SEP-2020)

The **second analysis** will be performed after approximately 24 maternal subjects and their infants have completed Visit 7 / Visit 3-NB (Day 121 post-delivery / birth).

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results, at:

- Visit 1 (Day 1) and Visit 3 (Day 31).

- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.
- Visit 6 / Visit 2-NB (Day 43 post delivery).
- Visit 3-NB (Day 121 post-delivery).

By-study-group safety analyses will include the following data from those subjects who have reached the Day 43 post-delivery visit:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified). Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.

Blinded SAE and AESI listings for all subjects will also be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

9.5.1.3. Third analysis (Amended 30-SEP-2020)

The **third analysis** will be performed after approximately 150 maternal and infant subjects have completed Visit 8/Visit 4-NB (Day 181 post-delivery/birth).

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project.

By-study-group immunogenicity analyses will include all available test results at:

- Visit 1 (Day 1) and Visit 3 (Day 31);
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.
- Visit 6 / Visit 2-NB (Day 43 post delivery);
- Visit 3-NB (Day 121 post-delivery)
- Visit 4-NB (Day 181 post-delivery)

By-study-group safety analyses will include the following data from all ***vaccinated*** subjects who have reached the Day 43 post-delivery visit:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified). Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases. In addition, blinded SAE and AESI listings for all subjects will be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

9.5.1.4. Final analysis

The **final** analysis will evaluate all data pertaining to primary and secondary safety and immunogenicity endpoints. It will be performed by the GSK Biologicals biostatistics team when all primary and secondary endpoint data up to study end (last Visit 5-NB) are available.

Results will be presented in a clinical study report. This report will include results summarized by study group as well as individual (by subject) data / data listings and will be made available to investigators.

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

9.5.2. Statistical considerations for interim analysis

The first 3 analyses will be descriptive. Therefore, the conduct of these analyses has no impact on interpretation of study results.

9.6. Data Monitoring Committee (DMC)

An unblinded, independent data monitoring committee external to GSK (IDMC) will review the data for this study. **Details** concerning the IDMC's structure and processes **are provided in a separate IDMC charter**.

The analysis plan for IDMC reviews will be detailed in a separate SAP. These unblinded analyses will all be done by an independent statistician from an Independent Data Analysis Center (IDAC) outside GSK to maintain the study blind and will be documented in a statistical analysis report.

Only the outcomes of the IDMC reviews will be communicated to the study team (no potentially unblinding safety signal details).

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:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF) or Informed Assent Form (IAF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - 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/EC.
  - Notifying the IRB/IEC of SAE(s) 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 financial interest information prior initiation of the centre and at the end of the study. Investigators are responsible for providing a

Financial Disclosure update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject / subject's parent(s) or his/her LAR(s) and answer all questions regarding the study.

Subjects/subjects' parent(s)/LAR(s) must be informed that their participation is voluntary.

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

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written or witnessed/thumb printed informed consent was obtained before the subject was enrolled in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects / subjects parent(s) / LAR(s) must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's parent(s)/LAR(s).

Subjects who are rescreened are required to sign a new ICF.

10.1.4. Data protection

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject / subject's parent(s)/LAR(s) must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The subjects/subjects' parent(s)/LAR(s) must be informed of their rights regarding the use of their personal data in accordance with the data privacy Section of the ICF.

The subject / subject's parent(s)/LAR(s) must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure protection of the personal data of the investigator and site staff which will be collected within the framework and for the purpose of the study in accordance with the Data Privacy Notice that will be sent to the site staff.

10.1.5. Committees structure

Safety oversight will be provided by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, independent data monitoring committee external to GSK (IDMC). Details regarding SRT and IDMC safety evaluations are provided in a separate IDMC charter.

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 the GSK Clinical Study Register in compliance with the 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 trial 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. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this trial 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 trial subjects are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential trial documents may be added or removed where justified (in advance of trial initiation) based on their importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies.

All subject data relating to the study will be recorded on printed or electronic CRF 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 eCRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). The safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source 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 Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer 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 subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data 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, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

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

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

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

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

10.1.10. Publication policy

GSK aims to submit for publication the results of these studies in searchable, peer reviewed scientific literature within 18 months from Last Subject Last Visit (LSLV) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

10.2. Appendix 2: Clinical laboratory tests

Study-required laboratory assessments detailed in Table 26, except urinalysis, should be performed by a central laboratory. During special circumstances, hematocrit may be performed locally if it is not possible to collect a blood sample for central analysis using GSK-provided supplies (see Section 8).

Table 26 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Leukocytes (White Blood Cells)
	Lymphocytes
	Neutrophils
	Eosinophils
	Platelets
	Erythrocytes (Red Blood Cells)
	Hematocrit
	Hemoglobin
	Erythrocyte Mean Corpuscular Volume (MCV)
	Aspartate Aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Alanine Aminotransferase (ALT) / Serum Glutamic-Pyruvic Transaminase (SGPT)
	Creatinine
	Urea nitrogen
Urinalysis by dipstick	Glucose
	Protein

Assessment of eligibility and grading of laboratory parameters will be based on reference ranges described in [Sheffield, 2013] and the SPM for this study.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an Adverse Event (AE)

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

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Significant or unexpected worsening or exacerbation of the condition/indication under study. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study vaccine(s)/product(s) administration even though they may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s)/product(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).

- Signs or symptoms temporally associated with study vaccine(s)/product(s) administration.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits)
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant prior to the study vaccination. These events will be recorded in the medical history Section of the eCRF.
- Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline.
- Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen.
- Disease-related events (DRE), typically associated with the disease under study. These events will be recorded in the participant's eCRF and will be monitored by the IDMC on a routine basis.

However, if 1 or both of the following conditions apply, then the event should be reported promptly to GSK as an SAE (see Section 10.3.8):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or
- The investigator considers that there is a reasonable possibility that the event was related to the administration of the study vaccine/product

10.3.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:
a. Results in death
b. Is life-threatening Note: 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, had it been more severe.
c. Requires hospitalisation or prolongation of existing hospitalisation Note: In general, hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered as AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred, or was necessary, the AE should be considered serious.
d. Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Other situations Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 27 Solicited administration site events

All age groups
Pain
Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 28 Solicited systemic events

Adult/Child (≥6 years)
Fatigue
Fever
Nausea
Vomiting
Diarrhea
Abdominal pain
Headache

Note: maternal subjects will be instructed to measure and record the (preferably) oral temperature at least once each day, at approximately the same time each day. Should additional temperature measurements be performed at other times of day, subjects will be instructed to record the highest temperature in the electronic Subject Diary (e-Diary).

10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a maternal subject/infant subjects' parent(s)/LAR(s) who has/have signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The subject's/ subject'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 subject/ parental /LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by the maternal subject/infant subject's parent(s)/LAR(s) will be collected during interview with the maternal subjects/ infant subjects' parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

AESIs include adverse pregnancy outcomes, pregnancy-related adverse events of special interest (newly occurring or worsening of existing condition), and neonatal adverse events of special interest. Refer to Section 10.8 for additional details.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as an AESI. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as AESIs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of **a** diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments the investigator considers clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2**).**

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Subsequent Pregnancy

All maternal subjects will be in the third trimester of pregnancy at enrolment and are expected to deliver while participating in the study. Maternal subjects who become pregnant again after completing the study pregnancy may continue the study at the discretion of the investigator.

While subsequent pregnancy itself is not considered an AE or SAE, any abnormal subsequent pregnancy outcome or complication or elective termination of a subsequent pregnancy for medical reasons will be recorded and reported as an AE or a SAE. Please refer to the Section 10.3.2 for the definition of a SAE.

10.3.8. Recording and follow-up of AEs, SAEs, AESIs and subsequent pregnancies (Amended 30-SEP-2020)

The maternal subjects/infant subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they/their parent(s) / LAR(s) perceive as serious.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an

AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all maternal and infant subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

An Electronic Diary (eDiary) hereafter referred to as the Subject Diary will be used in this study to capture solicited administration site or systemic events, as well as the occurrence of unsolicited adverse events 30 days post vaccination, medically attended adverse events (including medically attended RTIs in maternal subjects), and RTIs in infant subjects. The maternal subject should be trained on how and when to complete each field of the Subject Diary. In case ERT portal/ alerts are not functioning, contacts will be conducted at least weekly until NB4/V8. Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local laws and best practice.

Any individual(s) who will perform the measurements of administration site or systemic events and who will enter the information into the Subject Diary should be trained on the use of the Diary. This training must be documented in the maternal subject's source record. If any individual other than the maternal subject is making entries in the Subject Diary, their identity should be documented in the Subject Diary/maternal subject's source record.

Refer to the SPM for more information regarding the use of eDiaries.

10.3.8.1. Time period for collecting and recording AEs, SAEs, AESIs, and subsequent pregnancies and other events of interest

Refer to Section 8.3.1.

10.3.8.2. Where to record AEs, SAEs, AESIs, subsequent pregnancies and other events of interest

All solicited AEs that occur during the 7 days following administration of the study vaccine/product (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity or whether or not they are considered vaccination-related.

Details regarding all other AEs should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

10.3.8.3. Follow-up of AEs, SAEs, AESIs, subsequent pregnancies and other events of interest

10.3.8.3.1. Follow-up during the study

After the initial AE/SA/AESI/subsequent pregnancy or any other event of interest for the study, the investigator is required to proactively follow each subject at subsequent visits/contacts.

The investigator will follow participants with SAEs/AESIs (serious or non-serious) subsequent pregnancy or subjects withdrawn from the study because of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or until the participant is lost to follow-up.

Non-serious medically attended AEs must be followed until recovered / resolved, or until the subject's last study visit, or until the subject is lost to follow-up.

Other non-serious AEs (maternal subjects) must be followed until 30 days after study vaccine/product administration or until the subject is lost to follow-up (if this occurs before Visit 3 (Day 31)).

If a maternal or infant subject dies during participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.3.2. Follow-up after the subject is discharged from the study

The investigator will provide any new or updated relevant information on previously reported SAEs, AESIs, subjects withdrawn from the study because of an AE and subsequent pregnancies to GSK using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

10.3.8.3.3. Follow-up of subsequent pregnancies

Maternal subjects who became pregnant again while participating in the study will be followed to determine the outcome of the subsequent pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the subsequent pregnancy outcome is a SAE, it should always be reported as a SAE

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND this is considered by the investigator to be reasonably related to the study vaccine(s)/product(s), he/she has to report this information to GSK as described in Section 10.3.10.

10.3.8.4. Updating of SAE, AESI and subsequent pregnancy information after removal of write access to the subject's eCRF

When additional SAE, AESI or subsequent pregnancy information is received after removal of write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to Table 23) or to the GSK Clinical Safety and Pharmacovigilance department within the defined reporting time frames specified in Table 22).

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

The intensity of the following solicited events will be assessed as described:

Table 29 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F (with 1 decimal) Temperature will be analysed in 0.5°C increments from ≥ 38.0°C /100.4°F) Grade 3 fever is defined as > 39.0°C /102.2°F
Headache		
Fatigue	0	Normal
Nausea	1	Mild: Easily tolerated
Vomiting	2	Moderate: Interferes with normal activity
Diarrhea	3	Severe: Prevents normal activity
Abdominal pain		

*Refer to the SoA for the definition of fever and the preferred location for temperature measurement.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0 : ≤ 20 mm
1 : > 20 mm to ≤ 50 mm
2 : > 50 mm to ≤ 100 mm
3 : > 100 mm

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in Section 10.3.2.

10.3.9.2. Assessment of causality

All solicited administration site and systemic events will be considered causally related to vaccination. The complete list of these events is provided in Table 27 and Table 28.

The investigator must assess the relationship between study vaccine(s)/product(s) and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine(s)/product(s) will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study vaccine/product?

YES	:	There is a reasonable possibility that the study vaccine(s)/product(s) contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s)/product(s). There are other, more likely causes and administration of the study vaccine(s)/product(s) is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine(s)/product(s), if applicable.
- Erroneous administration.
- Other cause (specify).

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

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

10.3.9.4. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

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

10.3.10. Reporting of SAEs, AESIs, subsequent pregnancies, and other events

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in a study subject, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. The report must then be dated and signed by the investigator (or designee).

Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated GSK WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to Table 22 for the details on timeframes for reporting of SAEs/AESIs/subsequent pregnancies.

The investigator will be required to confirm the review of the SAE causality by ticking the ‘reviewed’ box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

Refer to Section 10.3.10.2 for the back-up system in case the electronic reporting system does not work.

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

In rare circumstances if the electronic reporting system does not work, the investigator (or designee) must fax a completed, dated and signed paper Expedited Adverse Events Report to the Study Contact for Reporting SAEs (refer to the SPONSOR INFORMATION) or to the GSK Clinical Safety and Pharmacovigilance department within 24 hours.

The Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours once the electronic reporting system is working again. information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of subsequent pregnancy information

Contraceptive guidance does not apply in this study. Refer to Sections 10.3.7, 10.3.8 and 10.3.10 for further information on detection, recording, reporting and follow-up of subsequent pregnancies.

10.5. Appendix 5: Country-specific requirements

10.5.1. France

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

10.5.1.1. Concerning the "SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA"

- Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the Informed Consent Form. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.
- According to French Public Health Code law (L.1121-16 and R.1121-16), the following people must be registered in National File ("Fichier National"):
  - Healthy volunteer;
  - Subjects if the aim of the study is not linked to their disease;
  - Subjects on request of the Ethics Committee regarding study risks and constraints.
- The following details will be described:
  - Reference of the study
  - Surname and first name
  - Date and place of birth
  - Gender
  - Dates of beginning and termination of the study
  - Exclusion period during which the subject cannot participate to another study (French Public Health Code law L.1121-12)
  - The total amount of compensation
- The subjects' registration in National File ("Fichier National") should be documented in the source document - subject notes and monitored by the CRA.
- The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.
- A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study if authorised by the Ethics Committee).

- It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:
  - is either affiliated to or beneficiary of a social security category;
  - has got an authorisation by the Ethics Committee.

10.5.1.2. Concerning the "STATISTICAL CONSIDERATIONS AND DATA ANALYSES" and specially in the "SAMPLE SIZE ASSUMPTIONS"

The expected number of subjects to be recruited in France is declared to the French regulatory authority.

10.5.1.3. Concerning the "REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process"**
  - Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:
    - French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.
  - Concerning the **process for obtaining** subject informed consent:
    - **if the subject is minor,** the following text is added:

      The informed consent of the holders of parental authority must be obtained before the beginning of the study. The consent of the child will be also sought when he/she is old enough to express his/her opinion. His/her refusal or the revocation of his/her consent cannot be disregarded. If there is only one holder of parental authority, the investigator will ask the present person to file, date and sign the parental certificate indicating their situation regarding the parental authority. A copy of this parental certificate is joined to each consent form.

      If these directives are not followed, the subject inclusion could be considered as a protocol violation and the data of this case won't be taken into account.
  - Concerning the management of the Patient Informed Consent Forms, the following text is added:
    - French Patient Informed Consent Form is in duplicate (triplicate for minor subject).
    - The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

10.5.1.4. NOTIFICATION TO THE HOSPITAL DIRECTOR

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

10.5.1.5. INFORMATION TO THE HOSPITAL PHARMACIST

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

10.5.1.6. Concerning the "DATA MANAGEMENT" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment (intervention) number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GlaxoSmithKline data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Data Protection French Law n° 78-17 of 6th January 1978, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

DEMOGRAPHIC DATA

In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 – article 8, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

TESTING OF BIOLOGICAL SAMPLES

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

10.5.1.7. SAE

TRANSMISSION OF THE SAE REPORTS:

The notification of all serious adverse events and all serious adverse reactions is done promptly (and at the latest within 24 hours) by the investigator to GlaxoSmithKline as explained in Section 8.3.3 of study protocol.

GlaxoSmithKline has a legal responsibility to promptly notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation and this is applicable for all the study sites where the study is planned to be conducted. As sponsor of the study, GlaxoSmithKline has in place processes meant to communicate any issue (including : suspicions of unexpected serious adverse reactions (SUSAR) occurring in France and outside the national territory, expected serious adverse reactions and serious adverse events occurring in France, new facts and urgent security measures) as soon as possible to the ANSM in order to safeguard the subjects enrolled in the clinical trials in accordance with the national reporting requirements in France (Article R1123-54 and Article R1123-46 of the French Public Health Code). This communication applies as soon as the sponsor has the following information:

- Suspected investigational product
- Patient/subject who presents with the effect/event
- Reporter
- Single identification number for the research/number of the protocol
- Causality assessment if applicable.

In case of paper notification, the SAE Reports have to be transmitted to the GlaxoSmithKline France Drug Safety Department, which name, address and phone number are:

Département de Pharmacovigilance
Laboratoire GlaxoSmithKline
23, rue François Jacob
92 500 Rueil-Malmaison
Tel : PPD
Fax : PPD
Email : PPD

10.5.1.8. Monitoring visits

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that

the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc …). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

10.5.1.9. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

The Health Institution and the Investigator undertake:

1. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
2. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
3. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
4. To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
5. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
6. To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

10.5.1.10. CTR publication

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registered (CTR) including the registration of all the clinical trials conducted by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

10.5.1.11. Data Protection French Law of 6th January 1978 (CNIL)

In accordance with the Data Protection French Law of 6 January 1978 updated the 20th of June 2018, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. Personal information can be transferred or be accessed to/by other entities of GLAXOSMITHKLINE Group, what the Investigator agrees by the signature of the present Protocol.

10.6. Appendix 6: Abbreviations and Glossary of terms

10.6.1. List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
BMI	Body mass index
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
eCRF	electronic Case Report Form
EoS	End of Study
FU	Follow-Up
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Acceptable Representative

LLOQ	Lower Limit of Quantification
LMP	Last Menstrual Period
LRTI	Lower Respiratory Tract illness
LSLV	Last Subject Last Visit
MAE	Medically attended adverse event
NB	Newborn
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
RBC	Red Blood Cell
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SPM	Study Procedures Manual
SpO2	Blood oxygen saturation as measured by pulse oximetry
WBC	White Blood Cell
WHO	World Health Organization

10.6.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.

	In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the intervention assignment. In a single-blind study, the investigator and/or his staff are aware of the intervention assignment but the subject is not.
Body Mass Index	A key index for relating weight to height. Calculated as follows: Weight (kg) / (Height (m))^2
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child	A young human being below the legal age of majority (generally < 18 years of age).
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	EoS must be achieved no later than 8 months after the last infant subject last visit (LSLV; Visit 5-NB). End of study (EoS) cannot be achieved **BEFORE** the last (infant) subject last visit (LSLV; Visit 5-NB).
Enrolled	'Enrolled' means a subject's/parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to Section 9.3 for the definition of 'enrolled' applicable to the study.
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomisation, study intervention, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardised term to replace: period, cycle, phase, stage.

Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK Biologicals' tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 9.3 for details on criteria for evaluability).
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy. A project that aims to improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in low to middle income countries.
Gestational age:	A measure of the age of a pregnancy where the origin is the first day of the woman's last normal menstrual period, or the corresponding age as estimated by other methods. Gestational age will be described in weeks of pregnancy completed + number of days completed of the following week. For example: 28 0/7 means completed 28 weeks of pregnancy + 0 days of the 29th week and 28 6/7 means completed 28 weeks of pregnancy + 6 days of the 29th week.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Infant	A child younger than 1 year of age
Intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Investigational vaccine/product:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

	The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. The terms legal representative or legally authorised representative are used in some settings.
(**Level 2 ultrasound** also known as a **f**etal anomaly ultrasound scan **or fetal morphology** assessment**)**	Comprehensive, detailed evaluation of fetal anatomy and development that is usually performed at approximately 20 weeks of gestational age. In addition to standard ultrasound parameters such as fetal heart activity and gestational age estimation, a Level 2 ultrasound usually includes assessment of amniotic fluid levels; assessment of the condition of the placenta, cervix, and uterus; and detection of fetal anomalies.
Local healthcare provider	A healthcare provider who provides subjects with medical care per local standards. This individual may or may not be a member of the study staff.
Neonatal adverse events of special interest	Clinically significant events that occur from birth through 28 days of age. They include but are not limited to preterm birth, neonatal death, congenital anomaly, low birth weight, small for gestational age, and neonatal infections, encephalopathy, sepsis, respiratory distress/asphyxia, and failure to thrive/growth deficiency.
Neonate (or Newborn)	An infant 28 days old or younger.
Parental concern	The parent(s) / Legally Acceptable Representative(s) are concerned about the infant’s respiratory tract illness (or general health in the context of the respiratory tract illness) and intend to seek medical care
Pregnancy outcomes	These include live birth with no congenital anomalies, live birth with congenital anomalies, fetal death/still birth with no congenital anomalies, fetal death/still birth with congenital anomalies, elective/therapeutic termination with no congenital anomalies and elective/therapeutic termination with congenital anomalies.
Pregnancy related adverse events of special interest	Clinically significant events that occur up to 42 days after delivery. They include but are not limited to the pregnancy related adverse events of special interest listed as primary safety endpoints in Table 5.

Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial/ pharmaco-epidemiological study was concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Randomisation:	Process of random attribution of study intervention to subjects to reduce selection bias.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorised use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.

Study population:	Sample of population of interest.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine/product or as a control.
Subject number:	A unique identification number assigned to each subject consenting to participate in the study.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.7. Appendix 7: Gestational Age Assessment

10.7.1. 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 immunisation 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, or • 1st trimester U/S
Level 2A	• Certain LMP WITH 2nd trimester U/S*, or • Certain LMP WITH 1st trimester physical examination**
Level 2B	Uncertain LMP WITH 2nd trimester U/S
Level 3A	• Certain LMP WITH 3rd trimester U/S***, or • Certain LMP WITH confirmatory 2nd trimester FH, or • Certain LMP WITH birth weight, or • Uncertain LMP WITH 1st trimester physical examination

Level	Description
Level 3B Lowest level of certainty	• Uncertain LMP WITH FH, or • Uncertain LMP WITH neonatal physical assessment (New Ballard score), or • Uncertain LMP WITH birth weight

grey highlights: applicable for enrollment in this study.
1st trimester U/S: ≤$13^{6/7}$ weeks, 2nd trimester U/S: $14^{0/7}$ to $27^{6/7}$ weeks, 3rd trimester U/S: ≥$28^{0/7}$ weeks.
GA: gestational age; U/S: ultrasound examination; LMP: last menstrual period; IUI: intrauterine insemination; ET: embryo transfer, FH: fundal height;
* If LMP and U/S do not correlate, default to U/S GA assessment
** For singleton pregnancies only. Unreliable if obesity, or uterine anomalies.
*** Depending on gestational age at Screening Visit/ Visit 1 and depending on the local standard of care, this will be applicable for inclusion in the study.

10.7.2. Methods Of Gestational Age Assessment

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

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

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

10.8. Appendix 8: Definitions of maternal, fetal and neonatal adverse events of special interest as per GAIA

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

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

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

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 30
Maternal Adverse Events of Special Interest	
Maternal Death	Table 31
Hypertensive Disorders of Pregnancy	Table 32
Antenatal bleeding	Table 33
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Fetal Growth restriction	Table 35
Gestational Diabetes Mellitus	Table 36
Non-reassuring fetal status	Table 37
Pathways to Preterm Birth	Table 38
Standard definitions for events of interest not defined as such in GAIA (Chorioamnionitis, Oligohydramnios, Polyhydramnios, Intrahepatic Cholestasis of Pregnancy (ICP), Acute Fatty Liver of Pregnancy, Maternal Sepsis)	Table 39
Neonatal Adverse Events of Special Interest	
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Neonatal encephalopathy	Table 42
Congenital Microcephaly	Table 43
Congenital Anomalies	Table 44
Neonatal Death	Table 45
Neonatal Infections	Table 46
Respiratory Distress in the Neonate	Table 47
Preterm Birth	Table 48
Failure to thrive	Table 49
Standard definitions for adverse events of special interest not defined as such in GAIA (large for gestational age, macrosomia)	Table 50

Table 30 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 • Prenatal ultrasound examination documenting lack of fetal cardiac activity or movement before the onset of labor. OR • Auscultation for fetal heart tones (using electronic devices or non-electronic devices) documenting lack of fetal heartbeat. AND • Maternal report of lack of fetal movement for 24 h or more. OR • Maternal physical examination confirming lack of fetal movement. OR • Radiology findings consistent with intrauterine fetal death. AND • Attended delivery followed by fetal physical examination afterbirth consistent with antepartum death, by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, or pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, mid-wife, nurse practitioner, a physician's assistant or other qualified trained practitioner). OR • Fetal/placental pathology report consistent with antepartum death. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1 or 2 in GA assessment algorithm).
2	Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined physical examination after delivery. AND • Maternal report of lack of fetal movement for 24 h or more. OR • Maternal physical examination confirming lack of fetal movement. OR • Auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND • Attended delivery followed by physical examination after birth consistent with antepartum death, by specialist or qualified trained practitioner appropriate to the health care setting. OR • Fetal/placental pathology report consistent with antepartum death. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm).

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

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

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

Table 31 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: • Ultrasound examination • Fetal heart tones • Positive serum or urine human chorionic gonadotropin pregnancy test • Delivery of a neonate or other products of conception (abortus, stillborn) AND Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy AND Documentation of Cause of death as: • Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications • Indirect: non obstetric complications • 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: • LMP date • 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: • Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications • Indirect: non-obstetric complications • Death during pregnancy, childbirth and the puerperium: other or coincidental • Unspecified: unknown or undetermined
3	Absence of Level 1 or 2 criteria for establishing diagnosis of pregnancy and: • Unsure LMP • 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: • Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric com-plications, unanticipated complications • Indirect: non-obstetric complications • Death during pregnancy, childbirth and the puerperium: other or coincidental • Unspecified: unknown or undetermined.

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

Table 32 Hypertensive disorders of pregnancy (Gestational hypertension, Pre-eclampsia, Pre-eclampsia with severe features including eclampsia)

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

In Ev = Insufficient Evidence

Hypertensive Disorders of Pregnancy Continued	
Preeclampsia with severe features *NOTE :can be diagnosed in the presence or absence of proteinuria*. Vascular: Severely elevated blood pressures, with systolic blood pressure≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only minutes (to facilitate timely anti-hypertensive treatment) Neurologic: Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen/paracetamol) Eclampsia Development of visual changes (including photopsia, scotomata, cortical blindness) Hematologic: New onset thrombocytopenia, with platelet count <100,000/L Gastrointestinal: New onset of nausea, vomiting, epigastric pain Transaminitis (AST and ALT elevated to twice the upper limit of normal) Liver capsular hemorrhage or liver rupture Renal: Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease) Oliguria (urine output <500 mL/24 h) Respiratory: Pulmonary edema (confirmed on clinical exam or imaging)	
Level	**Description**
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND At least one of the criteria for severe disease:
1	At least one of the following: • Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110mmHg, which is confirmed after only minutes OR • Development of severe, persistent headache OR • Development of visual changes OR • Eclampsia* OR • New onset thrombocytopenia (platelets <100,000/L) OR • New onset unremitting epigastric pain OR • AST and ALT elevated to twice upper limit of normal OR • Evidence of liver capsular hematoma or liver rupture (diagnosed on clinical exam or with imaging) OR • Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease) or oliguria (<500 cc/24 h) OR • Pulmonary edema (confirmed on imaging with chest X-ray, or on clinical exam)
2	New onset nausea and vomiting
In Ev	Blood pressure cannot be measured

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

In Ev = Insufficient Evidence

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

Table 33 Antenatal Bleeding

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

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

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

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

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Morbidly adherent placenta	
Level	**Description**
1	**There are two definitions of equal specificity.** 1. Second- or third-trimester ultrasound or MRI evidence of placenta previa, AND One of the following ultrasound features: • Greyscale: loss of the retroplacental sonolucent zone, irregular retroplacental sonolucent zone, thinning or disruption of the hyperechoic serosa–bladder interface, presence of focal exophytic masses invading the urinary bladder, abnormal placental lacunae • Color Doppler: diffuse or focal lacunar flow, vascular lakes with turbulent flow (peak systolic velocity over 15 cm/s), hypervascularity of serosa–bladder interface, markedly dilated vessels over peripheral 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.** 1. Ultrasound evidence of placenta previa, AND hypervascularity at the site of the uteroplacental interface, diagnosed at laparotomy. OR 2. Difficulty with placental separation after delivery of the infant, at either a vaginal or cesarean delivery with resultant hemorrhage due to partial separation.

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

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

Table 34 Postpartum hemorrhage

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

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

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

Reference: Kerr R, Eckert LO, Winikoff B, et al. Postpartum haemorrhage: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6102-6109.
[1] Can be found in Kerr (*op cit*), Table 1.

Table 35 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).

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

*Level 1 evidence of pregnancy dating as defined by the Preterm Birth Working Group of the Brighton Collaboration. Level 1 pregnancy dating depends on a confirmatory ultrasound performed ≤13 $^{6/7}$ weeks gestation
In Ev = Insufficient Evidence
Reference: Easter SR, Eckert LO, Boghossian N, et al. Fetal growth restriction: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35: 6546-6554.

Table 36 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 (Section 10.7) 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 (Section 10.7) 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

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
	Diagnosis of gestational diabetes based on fasting plasma glucose of 5.1-6.9 mmol/l (92-125 mg/dL) using venous or capillary blood samples.
In Ev	Blood glucose cannot be measured OR Elevated postprandial blood glucose level without confirmatory fasting venous blood or capillary glucose level OR Use of Hemoglobin A1c alone for the diagnosis of GDM without a diagnostic oral glucose tolerance test (OGTT) or elevated fasting plasma glucose level. OR Clinical and laboratory findings such as glucosuria, fundal height greater than dates, obesity, prior history of GDM or family history for the diagnosis of gestational diabetes mellitus without a diagnostic test.

In Ev = Insufficient Evidence

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

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

[1] Major criteria (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).

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

Table 37 Non-reassuring fetal status

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

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

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

Table 38 Pathways to preterm birth

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

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

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
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 (fern) on microscopy of amniotic fluid OR Ultrasound with oligohydramnios (AFI <5 or MVP <2)

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Preterm rupture of membranes	
Level	**Description**
	AND Documented membrane rupture by a diagnostic test (one of the below options): Positive intra-amniotic dye-injection method Positive result on amniotic fluid alpha-fetoprotein test kit Amniotic fluid pH measurement (nitrazine paper test) Amniotic fluid placental alpha macroglobulin-1 protein assay (PAMG-1) test (AmniSure test) Amniotic fluid insulin-like growth factor binding protein (IGFBP-1) test (Actim PROM test)
2	Clinical history of rupture of membranes AND Visible leakage of fluid on vaginal speculum examination AND Visible arborization (ferning) on microscopy of amniotic fluid OR Documented membrane rupture by a diagnostic test (one of those listed above) OR Ultrasound with oligohydramnios (AFI <5 or MVP <2)
3	Clinical history of rupture of membranes AND Visible leakage of presumed amniotic fluid; this may be on vaginal speculum examination (pooling in vagina), on inspection of the perineum (wet perineum due to leakage of fluid from the vagina), or fluid soaked cloth/clothes/sanitary pad.
Preterm labor	
Level	Description
All	Patient is determined to be have delivered preterm (at less than 37 gestation-completed weeks (less than 259 days)).
1	On presentation, >4 documented uterine contractions per hour as determined by a tocodynometer AND Documented change in length or dilation of cervix by physical examination or transvaginal ultrasound over a two hour period, with clinical criteria for documenting cervical change by exam including: 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
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

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Preterm rupture of membranes	
Level	**Description**
	Delivering provider reports from recall that he or she decided that the patient needed to undergo induction of labor or cesarean delivery
3	From recall, patient confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND Patient reports from recall that the healthcare provider indicated that she needed to undergo induction of labor or cesarean delivery

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

Table 39 Standard Definitions for Maternal Adverse Events of Special Interest not defined as events in GAIA

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

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

References:
[1] Geenes V. 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 40 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

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Small for Gestational Age (continued)	
Level	**Description**
3b	Weight below 10th percentile for gestational age AND The following used in assessment of weight: Infant weighed within the first 48 hours of life Newborn weight assessed by measuring the difference between an adult holding the infant and the adult being weighed alone on any scale AND The following assessment of gestational age: Uncertain LMP with fundal height OR Uncertain LMP with newborn physical assessment OR Uncertain LMP with birthweight
4	Baby noted to be small, but no actual weight Baby with GA assessed only by infant examination Diagnosis extracted from billing codes or chart, with no documentation of actual birth weight or GA

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

Table 41 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

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
	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 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 42 Neonatal encephalopathy

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

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

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

Table 43 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*
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*

Postnatally Diagnosed Microcephaly (continued)	
Level	**Description**
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
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

Prenatally Diagnosed Microcephaly (continued)	
Level	**Description**
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 M, Munoz FM, Sell E, et al. Congenital microcephaly: Case definition & guidelines for data collection, analysis, and presentation of safety data after maternal immunisation. Vaccine. 35; 6472 – 6482.

Table 44 Major Congenital anomalies

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

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

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
	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:

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

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

Table 45 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

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
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)

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
	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 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 46 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 Recognised virus identified using a validated assay from an upper respiratory sample OR Recognised pathogen identified using a validated method and from a normally sterile site AND 3 or more criteria below: Temperature ≥37.5 ◦C or <35.5 ◦C Tachypnea or Nasal flaring or Chest in-drawing or Grunting Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% Apneas Increased respiratory secretions or Increased suctioning requirements Cough or wheeze or crepitations Increased CRP or procalcitonin
2	New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND 4 or more criteria below: Temperature ≥37.5 ◦C or <35.5 ◦C Tachypnea or Nasal flaring or Chest in-drawing or Grunting

	Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% Apneas Increased respiratory secretions or Increased suctioning requirements Cough or wheeze or crepitations Increased CRP or procalcitonin
3	2 or more criteria below: Difficulty in breathing/Tachypnea Severe chest in-drawing Nasal flaring Grunting Wheezing Stridor Fever

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

Table 47 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

Level	Description
	No medical record documentation, but reporting through either a non-medical observer (e.g. mother, father, community worker) or via standard census mechanisms (e.g. Demographic and Health Surveillance System) OR Collection of information from medical record review or billing codes.
3	No need for a level 3 per working group.
4	Not enough information to ascertain case of respiratory distress.
5	Not a case of respiratory distress in the neonate.

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

Table 48 Preterm Birth

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

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

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

Table 49 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
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 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 50 Standard Definitions for Neonatal Adverse Events of Special 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).

10.9 Appendix 9: Protocol Amendment/Administrative change history

The Protocol Amendment/Administrative change Summary of Changes Table for the current amendment/administrative change is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY

Document	Date of Issue
Amendment 3	30-SEP-2020
Amendment 2	19-MAY-2020
Amendment 1	27-JAN-2020
Administrative Change 1	08-OCT-2019
Original Protocol	09-JUL-2019

Amendments/Administrative changes summary of changes table:

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
Amend-ment 1	**27-JAN-2020**	Globally	Number of maternal subjects has been increased from ~150 (i.e., ~50 per group) to ~300 (i.e, ~100 per group). Number of infant subjects has been increased from ~150 (i.e., ~50 per group) to ~300 (i.e, ~100 per group). Number of infant subjects in each blood sampling subcohort has been increased from ~ 16 per timepoint per study group to ~ 33 per timepoint per study group.	To provide additional safety and immune response data in support of subsequent studies
		Section 1.3, Table 2, Intervals between study visits – Maternal subjects	The minimum interval between Visit 1 and Visit 3 is 25 rather than 28 days.	To facilitate availability of immune response data at Visit 3.
		Section 1.3, Table 4, Intervals between study visits – Infant Subjects	Language has been added to clarify that If consent is not obtained within the allowed interval, but the parent(s) /LAR(s) still wish the infant to participate, consent may be obtained at any time until the Day 43 visit. Refer to the SPM for additional details.	To minimize infant subject attrition and enhance protocol compliance.

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
		Section 4.1, Data collection	Reference to eDiary collection of maternal medically attended RTI data has been removed.	The eDiary captures occurrences of maternal medically attended AEs but does not specifically query for occurrences of maternal medically attended RTIs.
		Section 4.2.5	The second paragraph, indicating that after all safety data up to 6 months post delivery/birth are available for all subjects and statistical analyses by group are performed by GSK Biologicals, the study can no longer be considered observer-blinded, has been removed.	The schedule of analyses has changed and this analysis will no longer be performed. Refer to Section 9.5.1 for details of the current schedule of analyses.
		Section 4.4, End of study definition	A paragraph equating End of Study with completion of assays needed to evaluate primary and secondary objectives has been removed.	The paragraph is incorrect.
		Section 5.1.1, Inclusion criteria, maternal subjects	"before performing any study specific procedures" has been replaced with "before any study specific procedures are performed."	Original language implies incorrectly that subjects perform these procedures.
		Section 5.2.1, Exclusion criteria, maternal subjects	" "Within 6 months before vaccination" has been removed from the following phrase: "Known or suspected impairment of the immune system or autoimmune disorder within 6 months before vaccination (based on medical history Prior receipt of an RSV vaccine" replaces "Previous participation in a clinical trial of an RSV vaccine""	Presence of an autoimmune disorder or impairment of the immune system at screening is exclusionary, regardless of when the disorder/impairment first occurred. Revision better captures the intent of the exclusion criterion, since subjects who take part in clinical trials

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
			From the phrase "Planned administration of any vaccine within 29 days before study vaccine administration (Day -28 to Day 1) and through Day 43 post- delivery….." Day 43 has been removed; and "administration" has been added to "planned administration" ("planned administration / administration"). Consanguinity has been defined as second degree cousin or closer.	of RSV vaccines may receive a placebo or other control preparation. Revision permits administration of MMR vaccine immediately post-delivery and clarifies that exclusions pertain to both "planned administration' and 'administration' of vaccines during the specified interval. To improve clarity.
		Section 6.1, Study interventions administered	Formulation information for sodium chloride has been updated Manufacturer has been updated, for both products, to "GSK Biologicals."	Formulation updated based on implementation of the IDMP ISO requirements To make clear that "manufacturer" should indicate the site where the vaccine/product is released.
		Section 6.4, Study intervention compliance	Language modified to reflect the fact that the person administering the intervention may be unblinded. "And in the eCRF" was removed from the phrase "intervention number administered, and the administration date and time will be recorded in the source documents and in the eCRF."	To ensure compliance while simplifying implementation at study sites. All of these parameters are recorded in the source document. Some but not all of them are also recorded in the eCRF. Administration time is not captured in the eCRF.
		Section 7.1.1	Language adjusted to indicate that re-screening is allowed only for clinically significant Grade 1 hematological /	For consistency with maternal subject exclusion criteria

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
			biochemistry values that are expected to be transitory	
		Section 8.1.3, Immunological Read-outs, Table 15	Priority rank of RSV-B NAb (neutralizing antibody) assays has been corrected from "3" to "2." Priority rank of Respiratory Syncytial Virus PreF3 Ab.IgG (concentration) has been changed from "2" to "3."	Reflects the fact that a single aliquot will be prepared and used for both RSV-A and RSV-B Nab testing.
		Section 8.2.1.2.1, Physical Examination, Maternal subjects	Language describing vaginal examinations has been modified.	Modified to improve clarity.
		Section 8.2.2.2, Physical Examination, Infant subjects	Protocol-required elements of physical examinations for infant subjects have been simplified	Simplified to improve consistency with standard of care.
		Section 8.2.3.3.3, Overview of IDMC reviews	Section has been adjusted to describe 5 planned IDMC data reviews.	Updated for consistency with additional enrolment and revised sequence of analyses.
		Section 8.4.3.1, when to conduct a maternal MA-RTI assessment visit	Language to account for instances where 'medical attendance' occurs in the context of a scheduled per-protocol study visit has been added	Additions made to facilitate collection of MA-RTI data.
		Section 9.2.1 and 9.2.2, Sample size determinations for safety and immune response	Data based on a sample size of 100 maternal subjects per group have been added.	Reflects increase in overall enrolment from ~ 150 to ~ 300 maternal subjects.
		Section 9.3, Populations for analyses	Descriptions of maternal and infant subject populations for analyses have been presented separately. Descriptions of infant subject populations for analyses have been corrected.	Adjusted to clarify differences in maternal / infant subject populations for analysis and corrected to remove inappropriate references to "post-vaccination" status in infant subjects, who are not, themselves, vaccinated.
		Section 9.5.1, Sequence of Analyses	A total of 4 rather than 5 analyses will be performed.	Updated for consistency with the increase in

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
			For the first 3 analyses, cutoff dates, number of subjects to be considered and parameters to be evaluated have been updated.	enrolment from ~ 150 to ~ 300 maternal and infant subjects.
		Section 9.5.2, Statistical considerations for interim analysis	The original reference to "final data" was incorrect and has been replaced.	To more accurately reflect the sequence of analyses described in Section 9.5.1.
Admin-istrative Change 1	**08-OCT-2019**	Facesheet	List of contributing authors has been updated	Persons serving as oversight data manager and study development lead have changed
		Section 4.4, End of Study Definition	Typographical error corrected. "V3-NB" should be "V2-NB"	The Primary Completion Date (PCD) occurs on completion of the Day 43 post-delivery visit in Epoch 002. V2-NB, rather than V3-NB, is the correct label for the infant subject's Day 43 post-delivery visit.
		Section 6.3.5, Emergency Unblinding	The fax number for North America and Puerto Rico has been removed.	The emergency unblinding helpdesk fax number for North America and Puerto Rico was decommissioned.
		Section 10.6.2, Glossary of Terms, definition provided for pregnancy related adverse events of interest	The specific list of pregnancy related adverse events of interest provided in the Glossary of Terms is inconsistent with the list of pregnancy related adverse events of interest presented in the body of the protocol (in Table 5).	To avoid confusion, the specific list of pregnancy related adverse events of interest provided in the Glossary of terms has been replaced with a cross-reference to Table 5.
		Section 10.8, Appendix 8, Definitions of maternal, fetal and neonatal events of interest as per GAIA, Table 36, Gestational diabetes mellitus (pregnancy induced hyperglycemia)	Cross References to the Gestational Age Assessment Tables were corrected.	References to Appendix C were replaced with references to Section 10.7.
		Section 10.8, Appendix 8, Definitions of maternal, fetal and neonatal events of interest as per GAIA, Table 49, Failure to Thrive	For the definitions of diagnostic certainty levels 2a and 3a: The criterion pertaining to weight for	The phrase "through at least 2 centile spaces on growth chart" has

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
			age deceleration has been clarified.	been modified to read "two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time" to improve clarity.

Detailed description of Protocol Amendment 2:

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

Facesheet:

Contributing authors (Cont.)	• PPD, PPD, PPD and PPD, Study Delivery Leads

Section 1.2, Schema

This is a multi-center, randomized, observer-blinded, placebo-controlled study. ***Up to*** ~~A~~***approximately*** 300 healthy maternal subjects 18 to 40 years of age (inclusive, at the time of informed consent) will be assigned to one of 3 study groups, and will receive a single intramuscular injection between 28 $^{0/7}$ to 33 $^{6/7}$ weeks of gestation (inclusive) as follows:

- RSVPreF3, 60 µg (N ***up to*** ~ 100),
- RSVPreF3, 120 µg (N ***up to*** ~ 100), or
- Saline placebo (N ***up to*** ~ 100).

Section 1.3, Schedules of Activities (SoA)

- Maternal subject Visits ***2 (day 8)***, 3 (day 31), 4 (Day 61), 7 (Day 121 post delivery) and 8 (Day 181 post delivery) and infant subject Visits ~~3-NB (day 121 post-delivery/birth), 4-NB (day 181 post-delivery/birth) and~~ ***1-NB through 5-NB (birth*** to 12 months after birth) may be conducted through a home visit ~~if allowed by local law and if the site has appropriate infrastructure and logistics to complete all study procedures~~ ***by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).*** ~~Blood samples collected during a home visit must be centrifuged within 2 hours after collection.~~
- Respiratory tract illness (RTI) assessment visits ***and event-driven safety visits*** may take place at the investigator's clinical facility or another medical facility, or via a home visit by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).

- ***The visit location must have appropriate infrastructure and logistics to support completion of all study procedures. Blood samples must be centrifuged within 1 hour after collection if used to assess biochemistry, or within 2 hours of collection if used to assess hematology or immune response.***
- **Contact** may be via telephone, SMS, email or other means ***(including videotelephony or telemedicine)***, depending on local best practice. If the study site is the subject's primary healthcare facility, contact with study personnel may also be made in the context of a visit for routine or event-driven care.

Refer to Section 8 for information about special circumstances (e.g., the Covid 19 pandemic) and their impact on study activities.

Table 1

Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28 0/7 - 33 6/7**	~~**29 0/7 - 34 6/7**~~	~~**32 0/7 - 37 6**~~	~~**36 0/7 - Delivery**~~								
Blood sample (hematology / biochemistry, ~ 5.5 ml)	●	●	●								●		Table 11 If screening sample ≤ 15 days before V1, then V1 sample not required. During an event-driven safety visit, additional samples are per investigator's discretion and standard of care and ~~may~~ ***to*** be tested locally.
Pregnancy-related AESIs		●	●	●	●	●	●			●	●	●	Section***s 8.3.3.2,*** 10.3.8
Suspected, probable and confirmed cases of		●	●	●	●	●	●	●	●	●	●	●	***Section 8.3.2.1***

Visit / Contact	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Monthly contacts**	**Safety Visit**	**MA-RTI Visit**	For monthly contacts: Table 2 & Section 8.4.2. After delivery, maternal & infant monthly contacts coincide.
Gestational Age (GA)		**28** **0/7** **-** **33** **6/7**	~~**29** **0/7** **- 34** **6/7**~~	~~**32** **0/7** **- 37** **6**~~	~~**36** **0/7** **- Delivery**~~								
COVID-19 infection													
MAEs		●	●	●	●	●	●	●	●	●	●		***Sections 8 and 10.3.9.3***

Table 2: Intervals between study visits – maternal subjects

Interval	Optimal interval	Allowed interval	Additional Information
V1 → V2	7 days	7 – ~~9~~ ***14*** days	
V1 → V3	30 days	~~25~~ ***20*** – ~~34~~ ***45*** days	
V1 → V4	60 days	~~58~~ ***50*** ~~64~~ ***75*** days	
V5 (delivery)	0 days	~~0~~ ***1 day before to*** 3 days ***post delivery***	Collect maternal blood sample at any point from ~~start of labor~~ ***the day before*** up to delivery. If blood is not collected during delivery, collect maternal blood sample no later than 3 days after delivery. **A cord blood sample should be collected at the time of each delivery. If cord blood cannot be collected at delivery**, a blood sample should be collected from the infant subject as soon as possible and no later than 3 days after birth.
V5 → V6	42 days	40 – ~~46~~ ***60*** days	
V5 → V7	120 days	~~116~~ ***110*** – ~~130~~ ***140*** days	Visit may coincide with infant subject's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule)
V5 → V8	180 days	165 – ~~195~~ ***200*** days	

Table 3: Schedule of activities for infants

Visit / Contact		*To coincide with maternal visits 6, 7, 8*				*Event-Driven*			
	V1-NB	**V2-NB**	**V3-NB**	**V4-NB**	**Monthly contacts**	**RTI Visit**	***C1-NB***	**V5-NB**	NB=Newborn *Monthly Contacts* coincide with maternal monthly contacts. *RTI Visit:* Sections 8.4.3 and 8.4.4.
Demographic data and lifestyle characteristics	●	●	●	●			●	●	Section ~~8.2.1.1.1~~ ***8.2.2.1***, Record at Visit 1-NB and if changes in lifestyle characteristics thereafter
Weight, length, head circumference, physical examination	●	●	●	●				●	Section ~~8.2.2~~ ***8.2.2.2***
Suspected, probable and confirmed cases of COVID-19 infection	●	●	●	●	●	●	●	●	
MAEs	●	●	●	●	●		●	●	Section***s 8 and*** 10.3.9.3

Table 4: Intervals between study visits – infant subjects

Interval	Optimal interval	Allowed interval	Additional Information
Birth → V1-NB	0 days	0 - 3 days ***(for blood sample collection)***	If no cord blood was obtained, a blood sample should be collected at this visit. If consent is not obtained within the allowed interval, but the parent(s) /LAR(s) still wish the infant to participate, consent may be obtained at any time until the Day 43 visit. Refer to the SPM for additional details.
Birth → V2-NB	4***2*** days	***28*** – ***60*** ~~40 – 46~~ days	
Birth → V3-NB	120 days	***110*** -***140*** ~~116 – 130~~ days	Visit may coincide with infant subject's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule
Birth → V4-NB	180 days	165 – ~~195~~ ***200*** days	
Birth → C1-NB	270 days	256 – 286 days	
Birth → V5-NB	365 days	~~350~~ 3***3***0 – ~~380~~ ***400*** days	

Figure 1: Overall design – maternal subjects

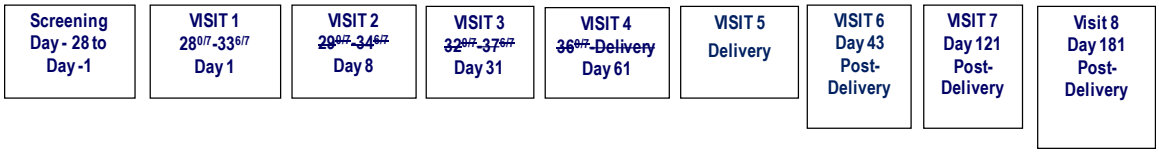

Table 6: Study groups, subcohorts, interventions, epochs and blinding foreseen in the study

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	**Approximate Number of maternal subjects**	**Age of maternal subject at enrolment (Min/Max)**	**Intervention name**	**Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)**	**Approximate Number of infant subjects**	**Study groups for randomization (Allocation 1:1:1:1:1:1:1:1:1)**	**Epoch 001 Maternal subjects Only (Screening)**	**Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind)**	**Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)**
RSV MAT 60	***Up to*** 100	18 – 40 years	RSVPreF3_60	BS1_60	***Up to*** 33	RSVMAT60_BS1	•	•	•
				BS2_60	***Up to*** 33	RSVMAT60_BS2		•	
				BS3_60	***Up to*** 33	RSVMAT60_BS3		•	
RSV MAT 120	***Up to*** 100	18 – 40 years	RSVPreF3_120	BS1_120	***Up to*** 33	RSVMAT120_BS1	•	•	•
				BS2_120	***Up to*** 33	RSVMAT120_BS2		•	
				BS3_120	***Up to*** 33	RSVMAT120_BS3		•	
Control	***Up to*** 100	18 – 40 years	Control	BS1_C	***Up to*** 33	Control_BS1	•	•	•

Section 4.4: End of study definition

~~End of Study (EoS) must be achieved no later than 8 months after the last infant subjectlast visit (LSLV; Visit 5-NB).~~

End of study (EoS) ~~cannot be achieved ***before*** occurs with~~ the last (infant) subject last visit (LSLV; Visit 5-NB).

Section 5.2.1.2: Prior / Concomitant therapy

- ***Prior receipt of a COVID-19 vaccine.***

Table 9: Study interventions administered

Since the table was re-formatted, the prior and current versions are given in full.

Current version:

Study intervention name:	**RSVPreF3_60**		**RSVPreF3_120**		**Placebo**
Study intervention formulation:	RSVPreF 3 (60 µg)	Sodium chloride (NaCl) ***(0.9%);*** Water for injections q.s**,** 0.5 mL	RSVPreF 3 (120 µg)	Sodium chloride (NaCl) ***(0.9%);*** Water for injections q.s**,** 0.5 mL	Sodium chloride (NaCl) ***(0.9%);*** Water for injections q.s**,** 0.5 mL
Presentation:	***Powder for suspension for injection, vial***	***Solution for injection; vial***	***Powder for suspension for injection, vial***	***Solution for injection; vial***	***Solution for injection; vial***
Route of administration:	***Intramuscular use***		***Intramuscular use***		***Intramuscular use***
Administration site:					
• **Location** • **Laterality ***	Deltoid Non-Dominant		Deltoid Non-Dominant		Deltoid Non-Dominant
Number of doses to be administered:	1		1		1
Volume to be administered:	0.5 ml		0.5 ml		0.5 ml
Packaging, labelling and TM:	Refer to the SPM		Refer to the SPM		Refer to the SPM
Manufacturer:	GSK Biologicals		GSK Biologicals		GSK Biologicals

Prior version:

~~**Study Intervention Name:**~~	~~RSVPreF3_60~~	~~RSVPreF3_120~~	~~Control~~
~~**Vaccine/product name ***~~	~~RSVPreF3 mid dose~~	~~RSVPreF3 high dose~~	~~-~~
	~~NaCl~~	~~NaCl~~	~~NaCl~~
~~**Presentation**~~	~~Vial~~	~~Vial~~	~~Vial~~
~~**Vaccine/product: formulation**~~	~~RSVPreF3 (60µg) Sodium Chloride (NaCl) water for injection q.s. 0.5 mL~~	~~RSVPreF3(120µg) Sodium Chloride (NaCl) water for injection q.s. 0.5 mL~~	~~Sodium Chloride (NaCl) water for injection q.s. 0.5 mL~~
~~**Route of Administration**~~	~~IM injection~~	~~IM injection~~	~~IM injection~~
~~**Administration site:**~~ ~~**Location**~~ ~~**Laterality ****~~	~~Deltoid~~ ~~Non-dominant~~	~~Deltoid~~ ~~Non-dominant~~	~~Deltoid~~ ~~Non-dominant~~
~~**Number of doses to be administered:**~~	~~1~~	~~1~~	~~1~~
~~**Volume to be administered**~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~
~~**Packaging and Labelling**~~	~~Refer to the SPM~~	~~Refer to the SPM~~	~~Refer to the SPM~~
~~**Manufacturer**~~	~~RSVPreF3 antigen: GSK Biologicals~~	~~RSVPreF3 antigen: GSK Biologicals~~	~~-~~
	~~NaCl: GSK Biologicals~~	~~NaCl: GSK Biologicals~~	~~NaCl: GSK Biologicals~~

Section 6.3.2, Randomization to study intervention

Up to ~~Aapproximately~~ 300 eligible pregnant women will be randomly assigned to 3 study (intervention) groups in a 1:1:1 ratio and at the same time, their (as yet unborn) infants will be randomly assigned to 3 blood sampling subcohorts (also in a 1:1:1 ratio). This yields ***up to*** ~~approximately~~ 100 pregnant women per group and ***up to*** ~~approximately~~ 33 infants per blood sampling subcohort within each group…

Figures 3 and 4:

The following footnote was added to each figure.

****Numbers are approximate and represent maximum subject enrolment.***

Table 11: Biological samples – maternal subjects

Maternal Sample type	Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information
Whole Blood	Hematology, Biochemistry	~5.5	ml	Screening	As needed to achieve ***up to*** ~~***approximately***~~ 300 eligible subjects at Visit 1.
Urine	Protein, Glucose	Dipstick	NA	Screening	As needed to achieve ***up to*** ~~approximately~~ 300 eligible subjects at Visit 1.

Table 12: Biological samples – infant subjects

Infant Sample type	Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information	
Blood	Immune response	~2.5	ml	Visit 1-NB (Within 3 days after birth	ONLY if cord blood cannot be collected.	Volume must be reduced if weight ≤ 2.5 kg. [Trial-related blood loss for infant subjects should be ≤ 1 % at each timepoint. Total blood volume is estimated at 80 to 90 ml/kg body weight, and venipuncture should not exceed ~ 1.6 ml for a 2kg baby or 2.0 ml for a 2.5 kg baby.] Refer to the Laboratory Manual for additional information.
		~2.5*	ml	Visit 2-NB (Day 43)		
		~2.5*	ml	Visit 3-NB (Month 4)		
		~2.5*	ml	Visit 4-NB (Month 6)		
		~ 2.5 ~5.0	ml	Minimum TOTAL, assuming body weight > ***2.5*** kg and cord blood (Table 11) collected Minimum TOTAL, assuming body weight > ***2.5*** kg and cord blood NOT collected		

Table 15: Immunological read-outs

Blood sampling timepoint		No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint			
Maternal subjects				
V1 (Day 1)	pre vaccination	***up to*** ~~***approximately***~~ ≃300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V3 (Day 31)	post vaccination	***up to*** ~~***approximately***~~ ≃300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V5 (Delivery) (venous blood and cord blood)*	delivery	***up to*** ~~***approximately***~~ ≃300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V6 (Day 43 post-Delivery	post delivery	***up to*** ~~***approximately***~~ ≃300	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
Infant subjects				
V1-NB (Birth)*	birth (only if cord blood cannot be collected)	Event-driven	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V2-NB (Day 43)	post birth 1	***up to*** ~~***approximately***~~ ≃100	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V3-NB (Day 121)	post birth 2	***up to*** ~~***approximately***~~ ≃100	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2
V4-NB (Day 181)	post birth 3	***up to*** ~~***approximately***~~ ≃100	RSV-A NAb (neutralizing antibody)	1
			Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)	3
			RSV-B NAb (neutralizing antibody)	2

Section 8: Study assessments and procedures

Readers are reminded that study visits /***contacts***, assessments and procedures *do not* replace local standards of care, and that any adverse event / potential adverse event identified during a study visit***/contact*** or procedure should be treated according to local medical practice or by referral to an appropriate health care provider.

Study Procedures During Special Circumstances

During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For the duration of such special circumstances:

- ***Enrolment of ADDITIONAL maternal subjects may be placed on hold. Decisions on re-starting enrolment to achieve the planned sample size will be made in a manner consistent with guidance from public health and other competent authorities.***
- ***The following measures may be implemented for enrolled participants:***
  - ***If it is not possible to conduct a protocol-specified, scheduled or event-driven visit as described in Section 1.3, the visit may be replaced with a contact conducted by telephone, videotelephony or telemedicine. SMS and email are not allowed.***
  - ***Biological samples may be collected at a different location* other than the study site or the subject's home. Biological samples should not be collected if they cannot be obtained within the visit interval (Table 2, Table 4), processed in a timely manner or appropriately stored until the intended use.***
    - ***Nasal swabs and blood samples for assessment of immune response should only be collected using centrally provided supplies.***
    - ***Hematocrit and dipstick urinalysis may be evaluated locally, using local supplies, if collection using centrally provided supplies is not feasible.***
  - ***If hematocrit is evaluated locally, date, result and normal range should be recorded in the eCRF in the Comment section for the relevant visit.***
  - ***If any other missing data were collected during a visit for standard care in the appropriate interval (Table 2 for maternal subjects; Table 4 for infant subjects), and if the medical records for this visit are accessible to site staff (as allowed by local law), then the data from the medical record may be recorded in the subject's study source document and entered into the eCRF.***
- ***"Medically attended visits" will include actual visits to or from medical personnel and instances where, due to the special circumstances, the subject cannot seek medical advice for symptoms/an illness by visiting a medical facility or arranging for a home visit, and seeks this advice instead via telephone, SMS, email, videotelephony or telemedicine, or other means.***
- ***The eDiary device provided to the maternal subject may be returned to the site by conventional mail after Day 181 post-delivery/birth, if the Day 181 post- delivery / birth visits (Visit 8 / Visit 4-NB) cannot be performed.***

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

The impact of measures taken during special circumstances on the per protocol set for immunogenicity will be determined on a case by case basis.

Section 8.2.3.1: Limitation on number of doses administered per day (first 30 maternal subjects)

…..all (***up to ~~approximately~~*** 300) maternal subjects must be closely observed at the study site for at least 60 minutes…..

Section 8.2.3.3.1: Holding rules assessed by the investigator

The investigator is not permitted to start the administration of the next dose or enrol additional subjects until ***provided with written documentation of the favourable outcome of the safety evaluation, and written authorization to proceed.*** ~~receipt of the favourable outcome of the safety evaluation, documented and provided in writing, authorising the investigator to proceed.~~ Refer to Table 23 for contact information.

The below flow of communication must be followed.

- The central sponsor team ensures that SBIR is blocked, ~~and~~ all sites administering study vaccine/product are informed***, and all country or region- specific regulatory authorities are informed.***
- Where required per local / regional regulation, ***the central sponsor team submits a substantial amendment to the local/regional authority requesting authorization to re-start the study.***
- ***When all required authorizations to re-start the study in a country / region have been provided, ~~T~~t***he central sponsor team ~~notifies~~ ***provides written notification to*** local sponsor contacts~~of this decision~~; local sponsor contacts then ***provide written notification to*** ~~notify~~ study sites.

Section 8.2.3.3.2: Holding rules assessed during IDMC evaluations

If the study is placed on hold, the investigator must suspend enrolment and study vaccine/product administration. As noted in Section 8.3.3.3.1, the investigator is not permitted to start the administration of the next dose or enrol additional subjects until provided with written documentation of the favourable outcome of the IDMC evaluation, and written authorization to proceed.

The below flow of communication must be followed.

- IDMC Chair (or his/her representative) notifies the Clinical Research & Deve~~v~~lopment Lead (CRDL).
- ***The central sponsor team ensures that all country or region- specific regulatory authorities are informed.***
- Where required per local / regional regulation, the ***central sponsor team submits a substantial amendment to the local/regional authority requesting authorization to***

re-start the study, and will not re-start the study until approval of the substantial amendment.

- ***When all required authorizations to re-start the study have been provided,*** the ***CRDL /*** central sponsor team ***provides written notification to*** local sponsor contacts; local sponsor contacts then ***provide written notification to*** study sites.
- ~~The CRDL / central sponsor team notifies local sponsor contacts of this decision; local GSK sponsor contacts then notify study sites.~~

Table 21: Timeframes for collecting and reporting safety (and RTI) information

Footnote only: Pre = pre-vaccination; V=visit; ***C = contact;*** D= Day.

Section 8.3.2.1: COVID-19 Infection

COVID-19 cases identified within the existing framework of the study (e.g., MA-RTI in maternal subjects, suspected RTI assessments in infants) will be captured and reported using standard AE, medically-attended AE or SAE criteria, as outlined in Section 10.3.

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

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

Section 8.3.3.2: Additional Reporting Guidance for the Study Pregnancy

A medical complication that requires an unplanned caesarian section or an emergency induction of vaginal delivery may be reported as an SAE/AESI (as applicable), using the corresponding Expedited AE report form.

All congenital anomalies (minor and major) are to be reported as serious adverse events (SAEs). To confirm if a medical condition is a congenital anomaly the WHO/CDC/ICBDSR birth defects surveillance manual [WHO/CDC/ICBDSR, 2014], available online, can be reviewed.

Only major congenital anomalies meet the criteria for the GAIA case definition of neonatal AESI. To assess if a congenital anomaly is major and meets the criterion for the AESI reporting the same website can be consulted.

Section 8.4.3.1: For a maternal MA-RTI

Conduct an assessment visit (Section ~~8.5.4~~ ***8.4.4***),

Figure 6: Decision Tree for Site Personnel – Maternal surveillance and assessment (footnotes only)

[1]Details regarding Surveillance are provided in Section ~~8.5.2~~ ***8.4.2*** and the SPM.

[2]Details regarding the RTI assessment visit are provided in Section ~~8.5.4~~ ***8.4.4*** and the SPM.

Section 8.4.3.1: For an infant RTI

Conduct an assessment visit, as described in Section ~~8.5.4~~ ***8.4.4***

Figure 7: Decision Tree for site personnel - infant surveillance and assessment (Footnotes only)

[1]Details regarding Surveillance are provided in Section ~~8.5.2~~ ***8.4.2*** and the SPM.
[2]Cough, runny nose, blocked nose, difficulty in breathing, wheezing are described in Section ~~8.5.1.2~~ ***8.4.3.2***
[3]Details regarding the RTI assessment visit are provided in Section ~~8.5.4~~ ***8.4.4*** and the SPM.
[4] Post-visit follow up is described in Sections ~~8.5.6~~ ***8.4.6*** and in the SPM.

Section 9.2: Sample size determination:

Up to ~~Approximately~~ 300 subjects will be randomised to achieve ***up to*** ~~approximately~~ 270 evaluable subjects for an estimated total of ***up to*** ~~approximately~~ 90 evaluable maternal subjects per study group.

Section 9.5.1.1: First Analysis

By-study-group ***safety and*** immunogenicity analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

Immunogenicity ~~These~~ analyses will include all available test results at…

~~Aggregate (blinded) safety analyses will be performed by the GSK Biologicals biostatistics team.~~ ~~***These***~~***Safety*** analyses will ***be performed by blinded treatment group, with the letters "A," "B," and "C" replacing treatment-specific group identifiers in all results summaries. Steps will be taken to minimize the risk of unblinding (e.g., events that happen in a single group will be masked by adding the same amount of counts to other groups). Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.***

Safety analyses will include all available data for:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

A report summarizing these ***safety and immunogenicity*** results will be prepared but will not be made available to investigators.

Section 9.5.1.3: Third Analysis:

By-study-group safety analyses will include the following data from all ~~300~~ ***vaccinated*** subjects who have reached the Day 43 post-delivery visit:

Section 10.2, Appendix 2: Clinical laboratory tests

All study-required laboratory assessments detailed in Tabld 26 except urinalysis ***should*** ~~will~~ be performed by a central laboratory. ~~The results of any test carried out locally must be entered into the eCRF.~~ ***During special circumstances, hematocrit may be performed locally if it is not possible to collect a blood sample for central analysis using GSK-provided supplies, with results entered into the eCRF (see Section 8).***

Section 11.0: REFERENCES

World Health Organization / Centers for Disease Control/ International Clearinghouse for Birth Defects Surveillance and Research [WHO/CDC/ICBDSR]. Birth defects surveillance: a manual for programme managers. Geneva: World Health Organization; 2014. Chapter 1. Available at¨ https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html. Accessed 8 May 2020.

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Detailed description of Protocol Amendment 3:

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

Table 6 Study groups, subcohorts, interventions, epochs and blinding foreseen in the study

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	*Approximate Number of maternal subjects*	*Age of maternal subject at enrolment (Min/Max)*	*Intervention name*	*Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)*	*Approximate Number of infant subjects*	*Study groups for randomization (Allocation 1:1:1:1:1:1:1:1)*	*Epoch 001 Maternal subjects Only (Screening)*	*Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind) **	*Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)*

**** After the second analysis, the study will not be considered observer blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study***.

4.2.5 Study blinding

Therefore, double blinding is not feasible and the study will be conducted in an observer-blinded manner ***until the second analysis is conducted***, as described in Section 6.3.4. ***After the second analysis, the study will not be considered observer-blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study.***

6.3.4 Blinding and unblinding

Investigators will remain blinded to each subject's assigned study intervention ***until*** ~~throughout~~ the ***second analysis. After*** ~~course of~~ the ***second analysis, the investigator's brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments.*** ~~study.~~

8.0 Study assessments and procedures

Study Procedures During Special Circumstances: ***COVID-19 pandemic***

Study Procedures During Special Circumstance: E-diary failure

- ***In case ERT portal/ alerts are not functioning, contacts will be conducted at least weekly until Visit 8 (maternal subjects) / 4-NB (infant subjects). Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local laws and best practice.***

8.4.2 Surveillance

- ***In the event that ERT portal/ alerts are not functioning, the site should contact subjects at least weekly until Visit 8 (maternal subjects) / 4-NB (infant subjects) to complete surveillance questions and collect information about adverse events. Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local best practice.***

9.5.1.2 Second analysis

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified). ***Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.***

9.5.1.3 Third analysis

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project. (~~to preserve the observer blinding).~~

Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases. In addition, blinded SAE and AESI listings for all subjects will be provided.

10.3.8 Recording and follow-up of AEs, SAEs, AESIs and subsequent pregnancies

The maternal subject should be trained on how and when to complete each field of the Subject Diary. ***In case ERT portal/ alerts are not functioning, contacts will be conducted at least weekly until NB4/V8. Contact may be via telephone, SMS, email or other means (including videotelephony or telemedicine), depending on local laws and best practice.***

11. REFERENCES

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