Clarification Memorandum # 1 for:

IMPAACT 2021
Randomized Phase I/II Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Children 6 to 24 Months of Age

Version 3.0, dated 28 April 2022

DAIDS Study ID 38530
IND # 018943 Held By DAIDS

Clarification Memorandum Date: 18 January 2023

Summary of Clarifications

This Clarification Memorandum (CM) updates the Protocol Team roster, clarifies the type of data included in Data and Safety Monitoring Board (DSMB) post-accrual season study reviews, and clarifies the listing of solicited adverse events (AEs) to note that wheezing may include a diagnosis of bronchiolitis.

Implementation

Single Institutional Review Board (sIRB) approval of this CM is not required by the study sponsor prior to implementation. However, the CM will be submitted to the sIRB (Advarra) centrally by the IMPAACT Operations Center for their information. In addition, sites may submit this CM to other site regulatory entities for their information or, if required by the regulatory entities, for their approval prior to implementation.

The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants.

This CM should be maintained in each site's essential documents file for IMPAACT 2021. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT 2021 protocol.

The modifications included in this CM are listed below in order of appearance within a specified clarification in the protocol and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in bold; deletions are indicated by strike-through.

1. Protocol Roster Update

To reflect current Protocol Team membership, Jared Kneebone, Sam Yi, and Marcus Bolton are removed from the roster and Azizza Davis, John Binkowski, Carly Hoffmann, and Michelle Haber are added:

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2. Clarification of Data Included in DSMB Post-Accrual Season Study Reviews

a) *Section 1.4, Rationale, Evaluation of Study Products subsection, Page 32*:

Table 1: Post-Accrual Season Study Review Criteria

	Yes	No
1. Is there a statistically significant ($p<0.05$) difference in the percentage with immune response (**e.g.,** ≥4-fold rise in serum ~~RSV-neutralizing antibodies~~ **IgG antibody to RSV F protein**) to the candidate vaccines such that one or two products can be identified to be immunologically superior to the remaining product or products, with the absence of a safety signal among the higher performing product(s)?		
If yes, the DSMB may recommend that the study close to accrual		
If no, the DSMB will consider the following questions for each specific product:		
2. Is the upper limit of the 95% confidence interval for the percentage of participants exhibiting **immune response (e.g.,** ~~a~~ ≥4-fold rise in serum ~~RSV-neutralizing antibodies~~ **IgG antibody to RSV F protein)** at the Day 56 Visit less than 70%?		
3. Have more than two participants receiving the specific product experienced LRI of ≥ Grade 2 in the 28 days following study product administration for which vaccine virus was isolated without other potential explanation? 4. Were there two or more participants who experienced vaccine-associated Grade 4 events of similar type (as listed below) after study product administration with presence of vaccine virus without other potential explanation? Otitis media within 28 days of study product administration Pharyngitis within 28 days of study product administration		

b) *Section 9.4.3, Rationale, Monitoring by the NIAID Data and Safety Monitoring Board, Page 76, fourth paragraph*:

The DSMB might consider halting enrollment to a vaccine arm:

1. For clear differences in immunogenicity: if there **is** a statistically significant difference in the percentage with immune response (**e.g.,** ≥4-fold rise in serum ~~RSV-neutralizing antibodies~~ **IgG antibody to RSV F protein**) to the candidate vaccines such that one or two products can be identified to be immunologically superior to the remaining product or products, with the absence of a safety signal among the higher performing product(s)
2. For inadequate immunogenicity: the upper limit of a 95% CI around the response rate (**e.g.,** ≥4-fold rise in ~~RSV-neutralizing antibody titer~~ **serum IgG antibody to RSV F protein**) for a vaccine arm is less than 70%. [With a sample size of 10 (15, 20, 25, 30, 38), this would occur if the observed response rate was <30% (<40%, <45%, <48%, <50%, <53%)]
3. for safety concerns (also considering vaccine virus shedding and adventitious data):

a. if >2 participants receiving the specific product experience LRIs of ≥Grade 2 in the 28 days following study product administration for which vaccine virus is isolated without other potential explanation
b. if there are ≥2 participants with vaccine-associated Grade 4 events of similar type (otitis media or pharyngitis within 28 days of study product administration) with presence of vaccine virus without other potential explanation.

3. Inclusion of Bronchiolitis in Listing of Solicited AEs

a) *Section 7.2, Safety-Related Data Collection, Adverse Events subsection, Page 60, 2nd paragraph*:

[…]For this study, the solicited AEs are defined in Appendix III and include the following:

1. Fever
2. Upper respiratory illness (URI)
   a. Rhinorrhea
   b. Pharyngitis,
   c. Cough without LRI, or
   d. Hoarseness.
3. Otitis Media
4. Lower respiratory illness (LRI)
   a. Wheezing **(may include bronchiolitis)**,
   b. Pneumonia,
   c. Laryngotracheobronchitis (croup),
   d. Rhonchi, or
   e. Rales.

b) *Appendix III: Definitions of Solicited Adverse Events, Page 91:*

Event	Defined
Fever	Temporal temperatures ≥100.0°F unconfirmed by rectal temp -or- Rectal temperature of ≥100.4°F.
Acute Otitis Media[1]	Loss of tympanic membrane landmarks, accompanied by erythema and loss of mobility. May or may not be associated with fever or other respiratory symptoms. Confirmed with tympanometry if possible.
Upper Respiratory Tract Illness (URI)	
Rhinorrhea	Two or more consecutive days of clear or purulent discharge from the nares. Note: Not associated with crying, change of room temperature, or eating and drinking.
Pharyngitis[1]	Pharyngeal erythema accompanied by exudate or pharyngeal erythema with enlarged tender lymph nodes. Note: May be associated with sore throat, or painful or difficult swallowing.
Cough without LRI	Two or more consecutive days of 3 or more episodes of cough during a 15-minute timed observation period, or cough awakens child from sleep. Note: Not associated with eating, drinking or choking.
Hoarseness	An unnaturally deep or rough quality of voice.
Lower Respiratory Tract Illness (LRI)	
Wheezing[2,3] **(may include bronchiolitis[5])**	Sustained, high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.

Pneumonia[1,2,3]	Rales and crackles, originating in the lower respiratory tract, usually accompanied by tachypnea, which do not clear with cough. May be confirmed by x-ray showing areas of consolidation.
Laryngotracheobronchitis (croup) [1,2,4]	Barking cough, hoarseness, and inspiratory stridor
Rhonchi[2,3]	Coarse breath sounds which are not transmitted noises from the upper airway and do not clear with cough.
Rales[2,3]	Abnormal lung sound heard through a stethoscope. Rales may be sibilant (whistling), dry (crackling) or wet (more sloshy) depending on the amount and density of fluid refluxing back and forth in the air passages.

1 Diagnosis must be made by a medical professional

2 Must be sustained over 20 minutes.

3 Clinical assessment must be made by a medical professional and confirmed by a second medical professional, if possible.

4 It is not necessary for medical professional(s) to witness inspiratory stridor as long as parent or guardian report is consistent with stridor and a medical professional judges the symptoms in total to be consistent with croup.

5 Bronchiolitis should be recorded as a solicited AE whether wheezing is detected or not.

NOTE: Solicited AEs will only be entered into eCRFs according to guidance outlined in Section 7.2