IMPAACT 2000 Investigator’s Meeting
August 29, 2014
Protocol IMPAACT2000: RSV LID Δ M2-2

Adverse Events
Adverse Event

- Any unfavorable and unintended sign, symptom, or disease
- Temporally associated with the use of the study product
- Includes:
  - exacerbation of pre-existing conditions
  - intercurrent illnesses
- Does not necessarily have a causal relationship

Following common events will not be recorded as AEs unless treated with a prescription medication or OTC antipyretic medication:
- diaper rashes
- teething pain
- spitting up

Adverse Events

- Solicited Adverse Events: Solicited AEs
- Unsolicited Adverse Events: AEs
- Serious Adverse Events: SAEs

- Each category has defined grading and reporting requirements
Solicited AEs

- Solicited AEs
  - Predefined
  - Occur after study product administration
  - Maybe expected if study product is insufficiently attenuated
  - Protocol defined definition
    - Protocol Appendix 4
  - Protocol defined grading
    - Fever Grading (Protocol Table 3)
    - Solicited AE Grading (Protocol Table 4)
  - Solicited by site investigator
  - Elicited or volunteered from parents/guardians or subjects
  - Captured on temperature cards

Solicited AEs

- Fever
- Upper respiratory illness (URI)
  - Rhinorrhea
  - Pharyngitis
  - Cough without LRI
  - Hoarseness
- Otitis Media
- Lower respiratory illness (LRI)
  - Wheezing
  - Pneumonia
  - Laryngotracheobronchitis (croup)
  - Rhonchi
  - Rales

# Solicited AE Definitions

<table>
<thead>
<tr>
<th>Event</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Temporal temperatures $\geq 100.0^\circ$F unconfirmed by rectal temp or Rectal temperatures $\geq 100.4^\circ$F.</td>
</tr>
<tr>
<td>Acute Otitis Media</td>
<td>Loss of tympanic 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. Diagnosis must be made by a medical professional</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Two or more consecutive days of clear or purulent discharge from the nares. Not associated with crying, change of room temperature, eating/drinking.</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Two or more consecutive days of pharyngeal erythema accompanied by exudate, and/or enlarged tender lymph nodes. May be associated with sore throat, or painful or difficulty swallowing.</td>
</tr>
<tr>
<td>Cough</td>
<td>Two or more consecutive days of 3 or more episodes of cough during a 15 minute timed observation period. Not associated with eating, drinking or choking.</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>An unnaturally deep or rough quality of voice, noted by research staff, subject, or parent or guardian.</td>
</tr>
</tbody>
</table>

## Protocol Specified AE Definition

<table>
<thead>
<tr>
<th><strong>Lower Respiratory Tract Illness</strong></th>
<th><strong>Definition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wheezeing</strong></td>
<td>Sustained high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Laryngotracheobronchitis</strong></td>
<td>Barking cough, hoarseness, and inspiratory stridor.</td>
</tr>
<tr>
<td><strong>Rhonchi</strong></td>
<td>Course breath sounds which are not transmitted noises from the upper airway and do not clear with cough.</td>
</tr>
<tr>
<td><strong>Rales</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

Must be sustained over 20 minutes.
Diagnosis made by a medical professional and confirmed by a second medical professional, if possible.

## Solicited AE Grading Table

<table>
<thead>
<tr>
<th>Severity</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (0) None</td>
<td>-</td>
</tr>
<tr>
<td>Grade (1) Mild</td>
<td>No medical intervention required; may include over-the-counter medications managed by the subject or caregiver for treatment of symptoms.</td>
</tr>
<tr>
<td>Grade (2) Moderate</td>
<td>Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications.</td>
</tr>
<tr>
<td>Grade (3) Severe</td>
<td>Prolonged medical intervention and/or hospitalization required.</td>
</tr>
<tr>
<td>Grade (4) Life-threatening</td>
<td>Life-threatening illness requiring hospitalization with intensive care.</td>
</tr>
</tbody>
</table>

Temporal Temperature Monitoring

Following temporal thermometer manufacturer’s instructions, take the temporal temperature THREE times and document the highest temperature, indicate “T”.

If >100.0°F

Temporal temperature confirmed by rectal temperature within 20 minutes

Rectal temperature is <100.4°F; document and indicate “R”*  

Rectal temperature is ≥100.4°F; document and indicate “R”*  

Does not meet solicited AE criteria

Fever

Solicited AE

Perform visit as per protocol SOE and complete the appropriate AE CRF

Temporal temperature not confirmed by rectal temperature

Study automatically counts this event as fever; indicate “T”*

*Document in subject study files

## Solicited AE: Fever Grading Table

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<th>Severity</th>
<th>Defined</th>
</tr>
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<tbody>
<tr>
<td>Grade (0)</td>
<td>≥100.0°F but &lt;100.4°F  (≥37.8°C &lt; 38°C)</td>
</tr>
<tr>
<td>Grade (1)</td>
<td>≥100.4°F but ≤101.4°F  (≥38°C but ≤38.6°C)</td>
</tr>
<tr>
<td>Grade (2)</td>
<td>≥101.5°F but ≤102.4°F  (≥38.7°C but ≤39.1°C)</td>
</tr>
<tr>
<td>Grade (3)</td>
<td>≥102.5°F but ≤104.8°F  (≥39.2°C but ≤40.5°C)</td>
</tr>
<tr>
<td>Grade (4)</td>
<td>≥104.9°F  (≥40.6°C)</td>
</tr>
</tbody>
</table>

- Applies to any modality of temperature measurement

Unsolicited AEs

- Unsolicited Adverse Events
  - All other AEs
  - Grade per DAIDS AE grading table

http://rsc.tech-res.com/safetyandpharmacovigilance
Serious Adverse Event

- Whether considered related to the study product or not, meeting one of the following outcomes:
  - Death
  - Life threatening:
  - Hospitalization:
    - at least an overnight stay in the hospital or emergency ward for treatment that would have been inappropriate if administered in the outpatient setting
  - Results in a congenital anomaly or birth defect
  - Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - An important medical event
  - may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

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**Appendix 4: Definition of Solicited AE**