Safety Reporting

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Objectives

• Reporting Adverse Events for IMPAACT 2013
  • Reporting time periods for AEs
  • Solicited vs unsolicited AEs
    • Definitions of solicited AEs
      • Which solicited AEs require expedited reporting
    • Grading of solicited AEs
    • Rules for recording solicited AEs
  • Events that required expedited reporting

• General Safety Oversight of study

• Pausing and Stopping Rules
Surveillance for Adverse Events

• All events that occur during IMPAACT 2013 protocol-specified AE reporting periods (see protocol Table 2), following inoculation with study product, is considered an AE and should be evaluated as a potential expedited AE (per DAIDS).
Recording and Reporting Time Periods for AEs

**Period of Enrollment**
- **Apr 1**
- **Oct 14**

**Inoculation**
- **D 0-28**
  - Acute Phase
  - Reporting time period
  - All SAEs
    - Solicited AEs
    - Unsolicited AEs
  - CRF Recording Requirements
    - DAERS

- **D 29-56**
  - Post-Acute Phase
  - Reporting time period
  - All SAEs
  - CRF Recording Requirements
    - DAERS

- **D 56-Oct 31**
  - Pre-RSV Season
  - Reporting time period
  - Only SAEs and AEs ≥ Gr 3 related to procedures performed during Pre-RSV Season Study Visit
  - CRF Reporting Requirements
    - DAERS

- **Nov 1-Mar 31**
  - RSV Season
  - Reporting time period
  - All SAEs
    - Fever, LRI, URI, and/or OM that are medically attended
  - CRF Reporting Requirements
    - DAERS

- **Apr 1-Apr 30**
  - Post-RSV Season
  - Reporting time period
  - Only SAEs and AEs ≥ Gr 3 related to procedures performed during Post-RSV Season Study Visit
  - CRF Reporting Requirements
    - DAERS

**Throughout study**
- Unresolved AE with onset date during Day 0 to midnight on 28th day after inoculation
- Unresolved SAE with onset date prior to midnight on 56th day following inoculation
- Unresolved SAE with onset date during RSV Surveillance Period or related to the Pre- or Post-RSV Season Study Visit
### Time Periods for Recording AEs

Table 3: AE CRF Recording Requirements; Section 7.2

<table>
<thead>
<tr>
<th>Study Phase at time of AE onset</th>
<th>AEs to record on CRFs</th>
</tr>
</thead>
</table>
| **Day 0 to 12 MN of 28\(^{th}\) day after inoculation (Acute Phase)** | • All SAEs  
• All solicited AEs that meet Appendix IV criteria  
• All unsolicited AEs (Grades 1 to 4), except diaper rashes, teething pain, and spitting up that are not Rx’d with prescription or OTC meds |
| **12:01 am on 29\(^{th}\) day post inoculation to 12 MN of 56\(^{th}\) day following inoculation (Post-Acute Phase)** | • All SAEs |
| **>Day 56 day following inoculation up to Oct 31 in year of inoculation** | • Grade ≥3 AEs or SAEs with onset after Day 56 and prior to RSV Surveillance Period related to Pre-RSV Season Study Visit procedures |
| **Nov 1 – Mar 31 (RSV Season Surveillance Period)** | • Fever, LRI, URI, and/or otitis media that are medically attended  
• All SAEs |
| **Apr 1-30 (Post-RSV Season)** | ONLY Grade ≥3 AE or SAE deemed related to Post-RSV Season Study Visit procedures |
| **Throughout study** | Unresolved AE with onset date during Day 0 to midnight on 28\(^{th}\) day after inoculation  
Unresolved SAE with onset date prior to midnight on 56\(^{th}\) day following inoculation  
Unresolved SAE with onset date during RSV Surveillance Period or related to the Pre- or Post-RSV Season Study Visit |
Adverse Events: Solicited vs Unsolicited AEs

• In IMPAACT 2013, AEs are categorized by whether they are:
  • **Solicited (see App IV)**
    • solicited AE = AE that occurs during the period of time that RSV vaccine virus replicates after inoculation and is a sign or symptoms that meets definitions in Appendix IV
      • occurs within the 1st 28 days after inoculation = ACUTE PHASE
    • protocol-specific grading tables (Tables 3 and 4) used to determine severity
      or
  • **Unsolicited**
    • due to other causes at any time during the study
    • Use DAIDS AE Grading Table used to determine severity
Adverse Events:

Definitions of Solicited AEs occurring from Day 0 to midnight on 28th day following inoculation. (see Appendix IV; Section 8.1.1)

<table>
<thead>
<tr>
<th>Event</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Temporal temperatures ≥100.0°F unconfirmed by rectal temp or Rectal temperature of ≥100.4°F.</td>
</tr>
<tr>
<td>Acute Otitis Media¹</td>
<td>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.</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>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.</td>
</tr>
<tr>
<td>Pharyngitis¹</td>
<td>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.</td>
</tr>
<tr>
<td>Cough without LRI</td>
<td>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.</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>An unnaturally deep or rough quality of voice.</td>
</tr>
<tr>
<td>Wheezing²,³</td>
<td>Sustained, high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.</td>
</tr>
<tr>
<td>Pneumonia¹,²,³</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>Laryngotracheobronchitis (croup)¹,²,³</td>
<td>Barking cough, hoarseness, and inspiratory stridor.</td>
</tr>
<tr>
<td>Rhonchi²,³</td>
<td>Coarse breath sounds which are not transmitted noises from the upper airway and do not clear with cough.</td>
</tr>
<tr>
<td>Rales²,³</td>
<td>Abnormal lung sound heard through a stethoscope. Rales may be sibilant (whistling), dry (crackling) or wet (more sleshy) depending on the amount and density of fluid refluxing back and forth in the air passages.</td>
</tr>
</tbody>
</table>

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.

NOTE: Solicited AEs will only be recorded on CRFs according to criteria defined in Section 7.2

LRI events require Expedited Reporting
Adverse Events (AEs): Grading of Solicited AEs

2 Specific Tables are Used to Grade Solicited AEs

### Table 3: Grading Table for Solicited AEs

<table>
<thead>
<tr>
<th>Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (0) None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Grade (1) Mild</td>
<td>No medical intervention required; may include use of over-the-counter medications managed by the 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>Illness requiring hospitalization with intensive care</td>
</tr>
<tr>
<td>Grade (5) Death</td>
<td>Event resulting in fatal outcome to the participant</td>
</tr>
</tbody>
</table>

### Table 4: Fever Grading

<table>
<thead>
<tr>
<th>Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (0)</td>
<td>≥100.0°F but &lt;100.4°F (≥37.8°C but &lt;38°C)</td>
</tr>
<tr>
<td>Grade (1)</td>
<td>≥100.4°F but ≤101.4°F (≥38°C but &lt;38.6°C)</td>
</tr>
<tr>
<td>Grade (2)</td>
<td>≥101.5°F but ≤102.4°F (≥38.6°C but ≤39.1°C)</td>
</tr>
<tr>
<td>Grade (3)</td>
<td>≥102.5°F but ≤104.8°F (≥39.2°C but ≤40.4°C)</td>
</tr>
<tr>
<td>Grade (4)</td>
<td>≥104.9°F (≥40.5°C)</td>
</tr>
</tbody>
</table>
Adverse Events: Rules for Recording Solicited AEs on CRFs

• Except for fever (see protocol Section 8.1.1), solicited AEs elicited by history but **Unconfirmed by Clinical Assessment**
  • Do **NOT** record on CRFs

• Solicited AEs elicited by history but **no Clinical Exam done**:
  • if description meets “definition” in the column criteria in Appendix IV:
    • record on CRFs as AEs
  • if description fails to meet the “definition” in the column criteria in Appendix IV:
    • record only on the source document and **NOT** on the CRF
Adverse Events: Expedited Reporting Requirements (Section 7.3.2)

- SAEs (as per protocol instructions)
- All Solicited events in LRI category during the periods specified in protocol Table 5 (see also Appendix IV)

<table>
<thead>
<tr>
<th>Lower Respiratory Tract Illness (LRI)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing(^{2,3})</td>
<td>Sustained, high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.</td>
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<tr>
<td>Pneumonia(^{1,2,3})</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>
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</tbody>
</table>

- Timeline for Reporting
  - Report via DAERS no later than 3 reporting days after site awareness of the event
  - For IRB, report as per IRB requirements
General Safety Oversight

- **Protocol Safety Review Team (PSRT)**
  - includes:
    - Protocol Chair or Vice Chair, Data Manager, DAIDS or NICHD Medical Officer, Protocol Statistician
  - will closely monitor participant safety through routine review of safety data reports generated by the SDMC
  - will review data relevant to safety monitoring at least twice per month during the active immunization phases and then at least once a month thereafter
  - will be notified of events that met the protocol pausing or stopping criteria

- **Data and Safety Monitoring Board (DSMB)**
  - will monitor safety through reviews of study data
  - reviews take place at least twice a year or as specified by DSMB
  - review data if stopping criteria is triggered or as requested by the DSMB
Pausing Rules (Section 8.2)

• Protocol will be paused if one of the following AEs occur
  • Day 0 through MN of 28\textsuperscript{th} day following inoculation:
    • LRI per Appendix IV (Solicited AE)
    OR
    • Fever of Grade 4
    OR
    • Grade 3 or above solicited AE (other than fever)
  • Day 0 through MN of 56\textsuperscript{th} day following inoculation:
    • An SAE that cannot be attributed to an etiology or cannot be attributed to a cause unrelated to the study product
Pausing Rules (MOP Section 6.2)

• If a site identifies that **pausing criterion has been met**, site will perform following steps:
  • Notify IMPAACT team (with description) at impaact.team2013@fstrf.org within 24 hours of event ID
  • Determine if local IRB requires reporting for a study pause
  • Report via the DAERS reporting system if required in protocol Table 5
  • Continue to conduct the protocol-specified evaluations on previously enrolled/active participants
  • Ship all respiratory viral samples for the participant who experienced the event that met pausing criteria
• IMPAACT team notifies all sites to suspend enrollment and inoculations
• FSTRF closes accrual
• IMPAACT team notifies sites via email when/if the study enrollment and inoculations may resume
• **It is imperative that sites follow the pausing steps so that the event can be assessed expeditiously and not delay further enrollment**
Stopping Rule Criteria (Section 8.2)

- Enrollment and inoculations will be suspended if:
  - 1 or more participants who received active RSV vaccine develops or experiences:
    - SAE that cannot be attributed to an etiology or cannot be attributed to a cause unrelated to study vaccine
    OR
    - LRI associated with shedding of vaccine virus at the time of LRI (even if another pathogen is identified, unless the RSV is confirmed to be wt RSV)
    OR
    - LRI that is not explained by a diagnosis unrelated to vaccine virus
    OR
    - Grade 4 fever or any Grade 3 or Grade 4 solicited AE other than fever associated with shedding of vaccine virus
    OR
    - Any pattern of research laboratory values or clinical symptoms is observed that is considered a significant safety issue for participants

- DSMB will make recommendations to Protocol Chair
- Sponsor and PSRT will determine if enrollment can resume, or if the study needs to be stopped.