Safety Reporting

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IND Sponsor Clinical Safety Office

IMPAACT 2000 Training Meeting
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Objectives

• How to report events in IMPAACT 2000

• Overall safety oversight plan
One Possible Approach to AEs: Keys Steps for Evaluation & Reporting

1: Is parent’s report confirmed by concurrent clin. exam?
   - YES: Continue
   - NO: Stop [Sect 7.12.1]

2: What is the Reporting Window for this event in this child? [Table 5]
   - Day 0 – 28?
   - Day 29 – 56?
   - Day 57+ AND Before Oct 31?
     [NO NEW Events, only Grade >3 AE or SAE that is probably or definitely related to Pre-RSV Season Study Visit procedures]
   - Day 57+ AND November 1 through March 31st?
     [Protocol Specified Events]
Basic Evaluation Steps for AEs

3: Does Event meet SAE or Expedited Criteria?
   - Yes: See SAE/Expeditied Rules [Sect. 7.3] & Review Stopping Triggers [Sect. 7.7]
   - No: Continue

4: Is event on the Solicited AE List [App. 4]?, AND Does event meet “Defined” criteria [App. 4]?
   - YES to BOTH: See Solicited AE Rules [Section 7.15.1]
   - No: Report as Unsolicited AE
Adverse Events (Day 0 \(\rightarrow\) 28)

- May be Solicited or Unsolicited
- Record on CRF in FSTRF & Grade as follows:
  - **Fever:** grade per table 4, Sect. 7.15.2
    - Temp = 100.0 to 100.3°F \(\rightarrow\) Grade 0 on the signs and symptoms form in FSTRF, regardless of modality [e.g. rectal or temporal]
  - **Solicited AE:** grade per Table 3, Sect. 7.15.1
  - **All other AEs:** grade per DAIDS AE Grading Table*

*Version 1.0 - December 2004 (Clarification dated August 2009).

In the event that this table is updated following protocol implementation, events will continue to be evaluated per this version of the DAIDS AE Grading Table. The DAIDS AE Grading Table is available on the RSC website at [http://rsc.tech-res.com/safetyandpharmacovigilance](http://rsc.tech-res.com/safetyandpharmacovigilance)
## AE Reporting Rules

### Study Day/Phase + Calendar Date => Reporting Procedure

<table>
<thead>
<tr>
<th>Study Phase at the time of event onset</th>
<th>Calendar Date</th>
<th>AEs to record on CRFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 0 to Day 28 Visit (Acute Phase)</td>
<td>ANY</td>
<td>• All SAEs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• All solicited AEs that meet Appendix 4 criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• All unsolicited AEs (Grades 1 to 4), with the exception of the following conditions if not treated with prescription medication or OTC medications with antipyretic properties: diaper rashes, teething pain, and spitting up.</td>
</tr>
</tbody>
</table>

Note: SAEs and LRIs must be reported via DAIDS Adverse Experience Reporting System (DAERS; see Section Error! Reference source not found.).
## AE Reporting Rules

### Study Day/Phase + Calendar Date => Reporting Procedure

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</table>
| Day 29 to Day 56 Visit (Post-Acute Phase) | ANY           | • All SAEs  
• LRI that meet Appendix 4 criteria  
Note: SAEs and LRIs must be reported via DAERS (see Section Error! Reference source not found.). |
# AE Reporting Rules

**Study Day/Phase + Calendar Date => Reporting Procedure**

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Day 57 and until RSV Season Surveillance Period</td>
<td>Up to October 31(^{st}) in year of inoculation</td>
<td>NONE except Grade ≥3 AE or SAE that are probably or definitely related to Pre-RSV Season Study Visit procedures. Note: During this period, there will be no vaccine shedding; therefore, no new events will be related to the study product.</td>
</tr>
</tbody>
</table>
# AE Reporting Rules

Study Day/Phase + Calendar Date => Reporting Procedure

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</table>
| RSV Season Surveillance Period        | November 1st to March 31st following inoculation | - Fever, URI, and otitis media that meet SAE definitions  
- Medically attended:  
  - fever  
  - URI  
  - LRI  
  - otitis media  

Note: these events do not need to meet the Appendix 4 criteria. SAEs and LRIs must be reported via DAERS (see Section Error! Reference source not found.).
**AE Reporting Rules**

**Study Day/Phase + Calendar Date => Reporting Procedure**

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</tr>
</thead>
<tbody>
<tr>
<td>Post-RSV Season</td>
<td>April 1\textsuperscript{st}-April 30\textsuperscript{th} in the year after the inoculation</td>
<td>NONE except Grade $\geq$3 AE or SAE that are probably or definitely related to Post-RSV Season Study Visit procedures.</td>
</tr>
</tbody>
</table>
Timeline for Filing Reports

- Report via DAERS no later than 3 reporting days after site awareness of the event
- Grading generally per DAIDS
- Also report per local IRB requirements
Reporting a Pausing Rule Event (Day 0\(\rightarrow\) 56)

Pausing Rule

- An SAE that cannot be attributed to an etiology or cannot be attributed to a cause unrelated to the study product, OR
- An LRI per Appendix 4, OR
- A fever of Grade 4 during Days 0 to 28, OR
- Any Grade 3 or above solicited AE (other than fever) during Days 0 to 28

If any of these events occur, the site will report the event (as outlined in Sections 7.2 and 7.3) AND will notify the team of the event (including a description of the event) via email at impaact.team2000@fstrf.org within 24 hours of site notification.

The protocol team will notify all sites to suspend enrollment and immunization.
Steps After Pause Reported

- The protocol team will notify all sites to suspend enrollment and immunization.
- The site reporting the event will complete the event assessment including the collection of viral samples.
- Respiratory viral samples collected from the child up to that point will be shipped to the Johns Hopkins University laboratory as soon as possible (see MOP).
- Study accrual will remain suspended while the SDAC checks treatment assignment and virology studies are started.
- The DSMB will be informed of the event by the Protocol Chair and will receive all pertinent data.
- Follow-up visits for children already inoculated will continue as outlined in Appendix 2.
Unanticipated Problems (UPs)

- Unexpected ... nature, severity, or frequency in relation to
  - The research procedures per protocol and informed consent or other study documents; and
  - The population; and
- Possibly, probably, or definitely related to participation in the research; and
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

UPs must be reported to the local IRB per their requirements. Non-Serious AEs that are UPs must also be reported to the sponsor Clinical Safety Office (CSO). Submit the local IRB UP report form to the CSO at the following address no later than 7 calendar days of the site investigator awareness of the event.

RCHSPB Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspfsafety@mail.nih.gov

Report all UPs to local IRBs per requirements.
Report UPs that are not SAEs to the Sponsor Clinical Safety Office (CSO) no later than 7 calendar days of site awareness of the event.
General Safety Oversight

• Protocol Safety Review Team (PSRT) will review aggregate data Q2 weeks during active immunization phases (+ 56 days after last kid immunized, so may be till ~ Dec 9th)

• Monthly Otherwise.

• Data and Safety Monitoring Board (DSMB)
  – Review Q ~6 months
  – Review data if stopping rule triggered or as requested by the DSMB
Questions