Developing a Detection and Reporting System for Adverse Events

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Elements of Reporting Detection System

- Written definition of adverse events
- Checklist of expected adverse events
- Evaluation of unexpected adverse events
- Judging intensity and relatedness
- Adverse event data collection form
- Internal and external communication
- Internal tracking
- Training
Written Definition of Adverse Events

- Define AEs so that study staff can identify them
- Explicitly state definitions of:
  - Expectedness
  - Intensity
  - Relatedness
  - Serious AE (CFR 312.32)
Checklist of Expected AEs

- Perform literature review to identify adverse events in similar studies for the same or similar study products

- Will be indicated in investigator brochures and patient inserts
  - Type of study
  - Number of subjects
  - Adverse events
  - Intensity
  - Relatedness
  - Duration
  - Serious adverse events
Examples of Expected Adverse Events

- **Tamiflu**: Nausea and vomiting are frequently reported AEs and therefore expected.

- **Augmentin**: Diarrhea, vomiting, nausea, skin rashes.
Checklist of expected AEs (continued)

- Create checklist that can be used during patient visits

- Researchers will mark yes/no for each expected AE at each visit. If marked yes, more information should be gathered.

- Similar checklists can be created for unexpected AEs
Sample Checklist

Checklist of Expected Adverse Events
Center Number: __________
Participant Number: __________
Visit Number: __________
Date: __/__/____

<table>
<thead>
<tr>
<th>Number</th>
<th>Event</th>
<th>Yes</th>
<th>No</th>
<th>If Yes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Onset Date</td>
<td>End Date</td>
</tr>
<tr>
<td>1</td>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Loss of appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Judging Intensity, Seriousness, and Relatedness

- Refer to written definitions of intensity and relatedness

- NIH reference tables (For AEs, several Toxicity tables, including the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE), WHO) have been used to develop DMID toxicity tables. A toxicity table may also be developed specifically for a protocol.
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transient or mild discomfort</td>
<td>Mild to moderate limitation in activity;</td>
<td>Marked limitation in activity; Medical</td>
<td>Extreme limitation in activity; hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some assistance may be needed</td>
<td>intervention / therapy</td>
<td></td>
</tr>
<tr>
<td>Resp. Tract Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transient or mild discomfort</td>
<td>Mild to moderate limitation in activity;</td>
<td>Marked limitation in activity; Cyanose;</td>
<td>Extreme limitation in activity; hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some assistance may be needed</td>
<td>Medical intervention / therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Transient or mild discomfort</td>
<td>Mild to moderate limitation in activity;</td>
<td>Marked limitation in activity; Medical</td>
<td>Extreme limitation in activity; hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some assistance may be needed</td>
<td>intervention / therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Irritation</td>
<td>Localized rash</td>
<td>Diffuse maculopapular Rash</td>
<td>Generalized urticaria</td>
<td>Stevens-Johnson Syndrome or Erythema multiforme</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furunculo/Impetigo</td>
<td>Localized lesion</td>
<td>Diffuse lesions</td>
<td>Generalized lesions</td>
<td>Systemic infections</td>
</tr>
</tbody>
</table>
Adverse Event Data Collection Form

- CRF must collect
  - Description of event
  - Date of onset/resolution
  - Intensity
  - Relatedness
  - Resolution
  - If it is a serious adverse event, a separate SAE form should also be completed and reporting guidelines followed
### Appendix: SAMPLE Adverse Event Form

**Study Name:**

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**ADVERSE EVENT FORM**

1. Study Number: 
2. Center Number: 
3. Participant Number: 
4. Date of Contact: [month] [day] [year]

5. Diagnosis: 

6. Date of AE onset: [month] [day] [year]

7. Related to study product? 
   - 1: yes
   - 2: no

8. Was the AE serious? (Y or N; Y=yes) 
   - 1: yes, complete the Serious Adverse Event Form and notify FHI immediately.

9. Highest severity of AE during the study: 
   - 1: mild
   - 2: moderate
   - 3: severe

10. Was the AE treated? (Y or N; Y=yes) 
   - 1: yes, complete Concomitant Therapy Form.

11. Outcome of AE: 
   - 1: resolved without sequelae
   - 2: resolved with sequelae, specify sequelae
   - 3: AE still present at study completion/discontinuation
   - 4: participant died as a result of this AE
   - 5: unknown because participant could not be located

12. Date of resolution or death: [month] [day] [year]

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**FOR FHI USE ONLY**

Was the AE anticipated? 
- Y: yes
- N: no

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*Serious means:*
- Life threatening or fatal
- Resulted in significant/persistent disability or incapacity
- Resulted in hospitalization or prolongation of hospitalization
- Congenital anomaly in an infant
- Jeopardized participant and required medical/surgical intervention to prevent serious outcome
- Any other event that the investigator considered serious

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Initials of person completing form

Date of form completion

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Section VIII: Appendices
Monitoring and Reporting Adverse Events

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Responsibility of Investigators

- Ensure a qualified physician who is an investigator is responsible for trial-related medical decisions.

- Ensure adequate medical care provided to participant with AEs. Should inform participant when medical care is needed for intercurrent illness.

- Immediate reporting of all SAEs to sponsor.

- Identify SAEs that may not require immediate reporting, and discuss and agree prospectively with DMID.
What happens when an AE is identified?

Assess the AE: intensity, onset, end date, other conditions that may contribute to the event, other symptoms, etc.

Medical doctor at the site should assess the subject to determine relatedness to the study product, if possible

Site staff should complete AE case report form

Establish clear communication and tracking of AEs at site
Internal Communication (continued)

- PI should develop a written system for reporting AEs
- For example, when identified by study staff, establish clear communication pathways
  - Telephone supervisor
  - Email supervisor and principal investigator
  - Update tables summarizing AEs for study
  - Checklist stating when supervisor and PI notified
Internal tracking

- Develop paper/computer tracking system that documents:
  - Subject with AE
  - Description of AE
  - AE case report form identifiers
  - Date study coordinator notified
  - Date PI notified
  - Date NIH notified (when applicable)
  - Consider IRB reporting requirements for AEs: monthly or annual listing
Training

- Definitions
- Identification of AEs
- Examples/case histories
- Internal tracking system
- Importance of tracking AEs to the success of a study
Conclusion

- Identifying and tracking AEs is mandatory
- The more documentation, the better
- Develop checklists that are accessible by all members of team
- Train all team members who interview subjects
- Test your systems before study begins