Adverse Event Reporting in IND Studies

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Disclosure

• No financial relationships to disclose.
Outline

- Definition of adverse events
- Assessment
- Reporting requirements
- Examples
Adverse Event

• Any unfavourable or unintended sign, symptom or disease that appears after a medical treatment regardless of attribution
  – Worsening of baseline condition
• Relationship to treatment
• Concurrent medication
• Co-morbidity
Attribution

• Decision of PI
  – Unrelated
  – Unlikely
  – Possible
  – Probable
  – Definite
Severity of Adverse Events

- NCI-CTC – dictionary of common toxicity criteria
- Events graded from 1-5
- Common Toxicity Criteria for Adverse Events (CTCAE v 4)
• Death
• Life threatening
• Inpatient hospitalization or prolongation hospitalization
• Persistent or significant incapacity
OR
• Congenital abnormality or birth defect
Expected versus Unexpected

• Any adverse event that is not listed in the current labeling
  – Package insert
  – Investigator’s brochure

• Issues with Phase 1 studies of new biologicals
Reporting Adverse Events

• Define reporting requirements in protocol
• Need to carefully consider definition in protocol
  – Avoid over-reporting
  – Ensure capture important events
• AEs captured on case report forms
  – Onset date – relation to intervention
  – Severity
  – Attribution
  – Interventions
  – Resolution

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ADVERSE EVENT RECORD

Study Name/H #: __________/________ CAGT ID: ____________
Patient’s Initials: ____________ Medical Record Number: __________

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>SAE</th>
<th>DLT</th>
<th>Date Dose Given</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Apex/Nadir</th>
<th>Action Taken</th>
<th>Outcome</th>
<th>Study Drug Relationship</th>
<th>Disease Relationship</th>
<th>Other Tx. Relationship</th>
<th>Specify Other Tx.</th>
</tr>
</thead>
<tbody>
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<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Relationship</th>
<th>Disease</th>
<th>Relationship</th>
<th>Other Tx.</th>
<th>Relationship</th>
<th>Specify Other Tx.</th>
<th>Grade</th>
<th>SAE Related Event</th>
<th>Dose Limiting Toxicity</th>
<th>Action Taken</th>
<th>Outcome</th>
<th>Relationship</th>
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<td></td>
<td></td>
<td>1=Mild</td>
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<td>1=Recovered</td>
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<td></td>
<td>2= Moderate</td>
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<td>2=Dose reduced</td>
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<td></td>
<td>3=Severe</td>
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<td>3=Regimen interrupted</td>
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<td>4=Lethal</td>
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<td></td>
<td></td>
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<td>4=Therapy discontinued</td>
</tr>
</tbody>
</table>

* Serious Adverse Event is one which results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in a persistent or significant disability/incapacity or is a congenital anomaly/ birth defect, events which, in the investigator’s opinion, suggest a significant hazard, or contraindication that is considered serious.

Form Completed By: __________________________ Date __/__/____ Date Entered __/__/____
Investigator Signature ___________________________ Date __/__/____
PI Signature ___________________________ Date __/__/____

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When to Report

• Expedited versus routine

• Who to report to?
  – IRB
  – FDA
  – RAC/IBC if gene transfer
  – Other if support eg GCRC, NIH
What to Report

• Study drug administration
• Adverse event
• Treatment
• Attribution
• Interpretation and significance
Current NIH Requirements for Reporting Safety Information

• Principal Investigators to report ASAP, but within 15 calendar days after sponsor receipt of information - serious adverse events that are:
  – Non-fatal, non-life threatening
  – Unexpected
  – Possibly associated with use of the gene transfer product

*NIH Guidelines, New Appendix M-I-C-4-b*
• Principal Investigators to report **ASAP, but within 7 calendar days** after sponsor receipt of information – serious adverse events that are:
  – Fatal, Life threatening
  – Unexpected
  – Possibly associated with use of the gene transfer product

_NIH Guidelines, New Appendix M-I-C-4-b_
• Serious adverse events in which a causal relationship between the product and the event can be ruled out should be reported at the time of submission of the annual report.
Current NIH Requirements for Reporting Safety Information

- Roles and Responsibilities
  - PI is responsible for reporting safety information
  - PI may delegate to another party, such as a corporate sponsor, the role, but not the responsibility, of reporting safety information to NIH
IRB Reporting

• Per local IRB policies
• Also need to report to IBC if gene transfer studies
Genetic Modification Clinical Research Information System (GeMCRIS)

- A public database of human gene transfer trials registered with the National Institutes of Health
Welcome to the NIH Genetic Modification Clinical Research Information System (GeMCRIS). GeMCRIS is a comprehensive information resource and analytical tool for scientists, research participants, institutional oversight committees, sponsors, federal officials, and others with an interest in human gene transfer research. GeMCRIS allows users to access an array of information about human gene transfer trials registered with the NIH, including medical conditions under study, institutions where trials are being conducted, investigators carrying out these trials, gene products being used, route of gene product delivery, and summaries of study protocols.

To facilitate access to this information, GeMCRIS offers a number of preformatted reports. You can also create your own query tailored to your particular information needs. To get started, use the "Search" menu item above, or click the "Frequently Asked Questions" link on the left to learn more about using the system.

We are seeking comments on GeMCRIS's utility and ease of use. Please take a moment to respond to the questions on the form provided through the "Feedback" link on this page. Your input is critical to ensuring that the system meets the needs of all its diverse users.
Key Features of GeMCRIS:

- On-line adverse event reporting to NIH
  - One format for NIH and FDA
- Security measures to protect trade secret and patient confidential information
- On-line search capability
- Implementation of controlled medical vocabularies
- Controlled scientific vocabulary developed specifically for gene transfer research
GeMCRIS: Key Information

- Protocol title
- Study phase
- Clinical indication(s)
- Investigator(s)
- Clinical trial site(s)
- Scientific abstract
- Non-technical abstract

- Investigational strategy
- Vector
- Transgene
- Route of administration
Accessing GeMCRIS:

Connect to:

http://www.gemcris.od.nih.gov/
Reporting to FDA

- May use GEMCRIS form
- May use IRB form
- FDA MedWatch forms
  - Form 3500A for 361 HCT/Ps

http://www.fda.gov/medwatch/
Follow-Up Reporting

- When additional information becomes available
- Change in grade or attribution
- On request
Scenario 1

Patient A is enrolled on an IND study of ex vivo expanded cord blood.

- 30 minutes after infusion he developed fevers, chills and hypotension.
- Started on antibiotics and requires transfer to ICU for inotropes.
- Blood cultures from the patient and cord grow Staph Aureus.
Is this an SAE?

- Inotrope usage so grade 4
- Life threatening
- Transfer to ICU so prolonged hospitalization
Who does the attending physician on the floor report to?
Scenario 1

- Attending reports to
  - Principal investigator/IND sponsor
  - Processing facility

- PI/IND sponsor reports to
  - IRB
  - FDA
  - Processing facility
Scenario 2

Patient B has multiply relapsed cancer and also has a history of frequent migraine.

• He is enrolled on an IND study of genetically modified T cells.
• 30 minutes post infusion he develops a headache that requires Morphine before it resolves.
• He is discharged after the routine 4 hour monitoring period.
Is this an SAE?

- Grade 3 as required narcotics
- Did not extend outpatient clinic stay and did not require admission
- Attribution
  - Past history of migraine
  - Closely related to infusion? Exacerbated by DMSO
How does the PI report?
How does the PI report?

• Grade 3 not related event with annual report
• Grade 3 unexpected possibly related to gene transfer product
  – IRB and IBC
  – RAC
  – FDA
Patient C has multiply relapsed leukemia with refractory disease and is enrolled on an IND study of a genetically modified tumor vaccine. She has no adverse effects from the vaccine but also no clinical response. Two weeks later she is placed on hospice care and three weeks later she dies of leukemia.
How does the PI report?
Scenario 3

- Expected event but as death on gene transfer study PI/IND sponsor reports to
  - IRB and IBC
  - FDA
  - RAC