Adverse Event Reporting in IND Studies

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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

Attribution

- 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 3)
- http://ctep.cancer.gov/reporting/ctc v30.htm

Serious Adverse Event

- 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

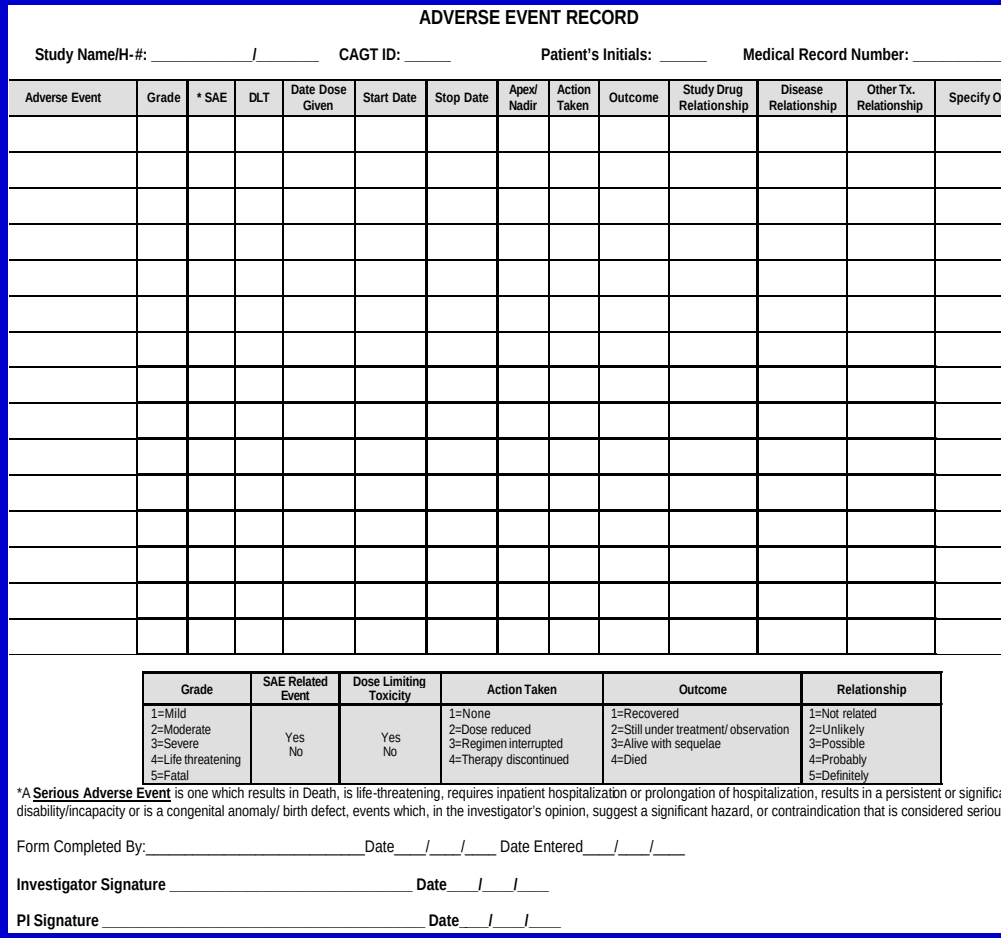
Reporting Adverse Events

- Define reporting requirements in protocol
- Need to carefully consider definition in protocol
  - –Avoid over-reporting
  - –Ensure capture important events

Documentation

AEs captured on case report forms

- Onset date – relation to intervention
- Severity
- Attribution
- Interventions
- Resolution



ADVERSE EVENT RECORD

Study Name/H-#: _____/_____ CAGT ID: _____ Patient's Initials: _____ Medical Record Number: _____

Adverse Event	Grade	* SAE	DLT	Date Dose Given	Start Date	Stop Date	Apex/ Nadir	Action Taken	Outcome	Study Drug Relationship	Disease Relationship	Other Tx. Relationship	Specify O

Grade	SAE Related Event	Dose Limiting Toxicity	Action Taken	Outcome	Relationship
1=Mild 2=Moderate 3=Severe 4=Life threatening 5=Fatal	Yes No	Yes No	1=None 2=Dose reduced 3=Regimen interrupted 4=Therapy discontinued	1=Recovered 2=Still under treatment/ observation 3=Alive with sequelae 4=Died	1=Not related 2=Unlikely 3=Possible 4=Probably 5=Definitely

*A **Serious Adverse Event** is one which results in Death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in a persistent or significa 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 seriou

Form Completed By:_____Date___/___/___ Date Entered___/___/___

Investigator Signature _____ **Date**___/___/___

PI Signature _____ **Date**___/___/___

When to Report

- Expedited versus routine

- Who to report to?
  - IRB
  - FDA
  - RAC/IBC if gene transfer
  - Other if support eg GCRC

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

Current NIH Requirements for Reporting Safety Information

- 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

FDA and OBA

- 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

Resources from the NIH Office of Biotechnology Web Page

- Genetic Modification Clinical Research Information System (GeMCRIS)
  - A public database of human gene transfer trials registered with the National Institutes of Health

CRIS - Home - Netscape

Edit View Go Bookmarks Tools Window Help

GeMCRIS

Genetic Modification Clinical Research Information System
Version 1.8

Home | Search | User Help

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wser Requirements

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.

Related Information

- About The RAC
- NIH Guidelines
- Documents (With Quarterly Reports)

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:

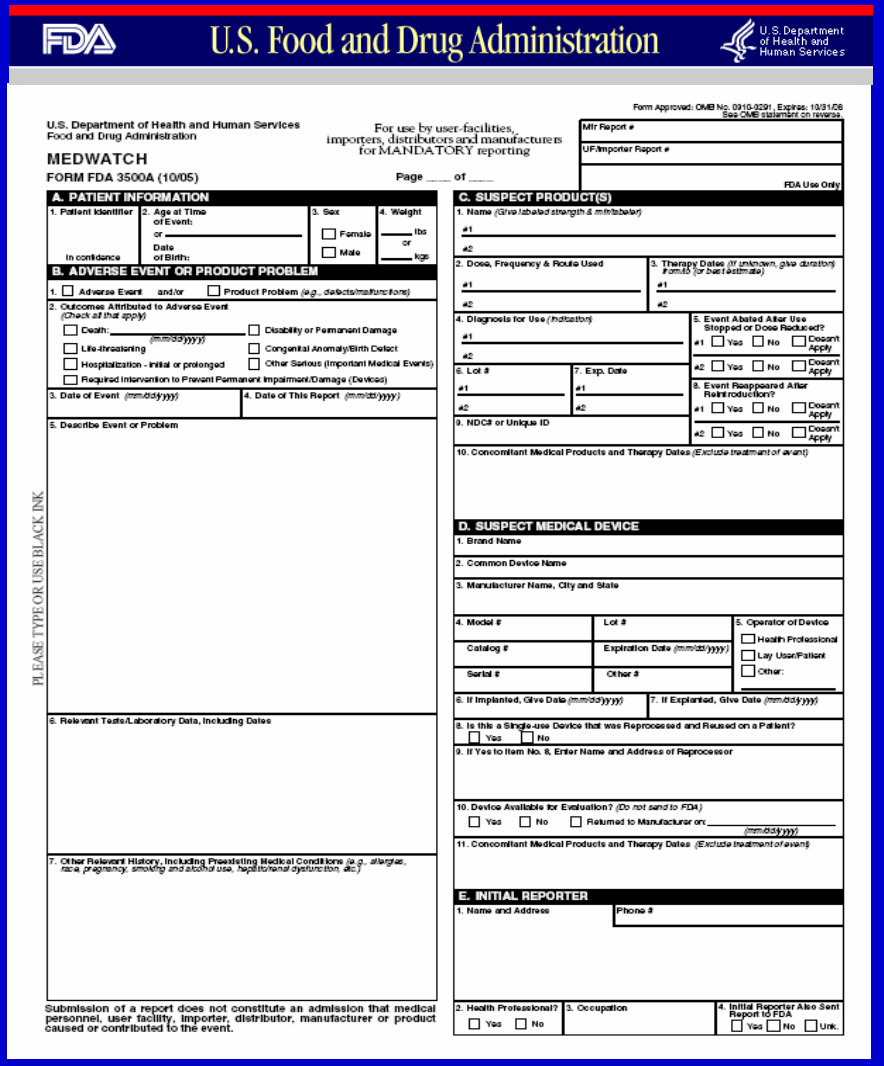
Connect to:

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/



FDA U.S. Food and Drug Administration — U.S. Department of Health and Human Services

Form Approved: OMB No. 0910-0291; Expires: 10/31/08
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH
FORM FDA 3500A (10/05)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr Report #
UF/Importer Report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier / In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex: ☐ Female ☐ Male
4. Weight: ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   ☐ Death: ____ (mm/dd/yyyy)
   ☐ Life-threatening
   ☐ Hospitalization - initial or prolonged
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
   ☐ Disability or Permanent Damage
   ☐ Congenital Anomaly/Birth Defect
   ☐ Other Serious (Important Medical Events)
3. Date of Event (mm/dd/yyyy)
4. Date of This Report (mm/dd/yyyy)
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & manufacturer) #1 / #2
2. Dose, Frequency & Route Used #1 / #2
3. Therapy Dates (If unknown, give duration) #1 / #2
4. Diagnosis for Use (Indication) #1 / #2
5. Event Abated After Use Stopped or Dose Reduced? #1 ☐ Yes ☐ No ☐ Doesn't Apply; #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # #1 / #2
7. Exp. Date #1 / #2
8. Event Reappeared After Reintroduction? #1 ☐ Yes ☐ No ☐ Doesn't Apply; #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# or Unique ID
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mm/dd/yyyy) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. INITIAL REPORTER

1. Name and Address / Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

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. He is 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. Thirty 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

Scenario 3

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