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# Adverse Events Module

**Rebecca J. Williams, Pharm.D., MPH**
Assistant Director, ClinicalTrials.gov
National Library of Medicine

http://ClinicalTrials.gov

## Outline

- Overview of Adverse Events (AE) module
- PRS data elements
- ClinicalTrials.gov review criteria
- Examples

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## Purpose

- The Adverse Events module is designed to summarize data regarding the serious and other (not including serious) adverse events that were collected during the study.
  - The module is not used for “real time” (“spontaneous”) adverse event reporting while the study is ongoing
  - The module includes summary data at the end of the study

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## FDAAA* Provision

“A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial.”

[Sec. 282(j)(3)(I)(iii)(I)]

*Food and Drug Administration Amendments Act of 2007

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# FDAAA Provision (cont'd)

"A table of anticipated and unanticipated adverse events **that are not included in the [Serious Adverse Events] table**…that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial."

[Sec. 282(j)(3)(I)(iii)(II)]

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# Journal Article Format

**Primary safety assessment of the number of patients with severe, life-threatening, or fatal treatment-related toxicities.**

| Variable | AmB ($n$ = 47) | AmB+Fluc400 ($n$ = 48) | AmB+Fluc800 ($n$ = 45) |
|---|---|---|---|
| Related to either study drug | | | |
| Overall | | | |
| Patients with event | 19 (40.4) | 18 (37.5) | 14 (31.1) |
| 90% CI, %[a] | 28.3–53.5 | 25.8–50.4 | 19.9–44.3 |
| $P$[b] | | .573 | .794 |
| By severity[c] | | | |
| Severe | 13 (27.6) | 13 (27.1) | 9 (20.0) |
| Life-threatening | 6 (12.8) | 5 (10.4) | 5 (11.1) |
| Fatal | 0 | 0 | 0 |
| By relatedness[c] | | | |
| Probably related | 16 (34.0) | 16 (33.3) | 12 (26.7) |
| Definitely related | 3 (6.4) | 2 (4.2) | 2 (4.4) |
| Related to fluconazole | | | |
| Overall | | | |
| Patients with event | 0 | 0 | 2 (4.4) |
| 90% CI, %[a] | 0.0–6.2 | 0.0–6.1 | 0.8–13.3 |
| $P$[b] | | >.99 | .098 |
| By severity[c] | | | |
| Severe | 0 | 0 | 1 (2.2) |
| Life-threatening | 0 | 0 | 1 (2.2) |
| Fatal | 0 | 0 | 0 |
| By relatedness[c] | | | |
| Probably | 0 | 0 | 2 (4.4) |
| Definitely | 0 | 0 | 0 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. AmB, amphotericin B deoxycholate; AmB+Fluc400, amphotericin B deoxycholate plus fluconazole administered at a dosage of 400 mg; AmB+Fluc800, amphotericin B deoxycholate plus fluconazole administered at a dosage of 800 mg; CI, confidence interval.

[a] CI based on exact binomial methods.

[b] Descriptive $P$ value based on a 1-sided exact unconditional test for each combination therapy arm that compared the combination therapy arm with the standard arm using procedures described in Suissa and Schuster [18].

[c] If a patient experienced >1 event, the patient is counted only once for the most severe or most-related event.



Pappas PG, Chetchotisakd P, Larsen RA et al. Clin Infect Dis. 2009

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# ClinicalTrials.gov Format

| | |
|---|---|
| **Time Frame** | Reported Adverse Events (AEs) include events starting on or after Day 0 and on or before Day 100. |
| **Additional Description** | If a subject experienced more than 1 of a given AE, the subjects is counted only once for that AE. If a subject experienced more than one AE in a system organ class (SOC), the subject is counted only once in that SOC. |

**Reporting Groups**

| | Description |
|---|---|
| **AmphoB Standard** | Amphotericin B 0.7 mg/kg for 14 day followed by fluconazole 400 mg daily for 8 weeks. For subjects in the standard therapy arm whose Amphotericin B dose is continued beyond 14 days, fluconazole initiation will be delayed. |
| **AmphoB+Fluc400** | Amphotericin B 0.7 mg/kg and the randomized dose of fluconazole at 400 mg/day for the first 14 days, then the randomized dose of fluconazole at 400 mg/day respectively for an additional 8 weeks. |
| **AmphoB + Fluc800** | Amphotericin B 0.7 mg/kg and the randomized dose of fluconazole at 800 mg/day for the first 14 days, then the randomized dose of fluconazole at 800 mg/day respectively for an additional 8 weeks. |

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# ClinicalTrials.gov Format (cont'd)

Serious Adverse Events

| | AmphoB Standard | AmphoB+Fluc400 | AmphoB + Fluc800 |
|---|---|---|---|
| **Total, serious adverse events** | | | |
| # participants affected / at risk | 22/45 (48.89%) | 17/47 (36.17%) | 26/49 (53.06%) |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia [*2] | | | |
| # participants affected / at risk | 1/45 (2.22%) | 0/47 (0.00%) | 2/49 (4.08%) |
| Anaemia [*2] | | | |
| # participants affected / at risk | 2/45 (4.44%) | 0/47 (0.00%) | 0/49 (0.00%) |
| Thrombocytopenia [*2] | | | |
| # participants affected / at risk | 0/45 (0.00%) | 0/47 (0.00%) | 1/49 (2.04%) |
| **Cardiac disorders** | | | |
| Cardiac failure congestive [*2] | | | |
| # participants affected / at risk | 0/45 (0.00%) | 0/47 (0.00%) | 1/49 (2.04%) |
| Cardio-respiratory arrest [*2] | | | |
| # participants affected / at risk | 0/45 (0.00%) | 0/47 (0.00%) | 1/49 (2.04%) |

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# ClinicalTrials.gov Format (cont'd)

**Frequency Threshold**

| Threshold above which other adverse events are reported | 5% |
|---|---|

**Other Adverse Events**

| | AmphoB Standard | AmphoB+Fluc400 | AmphoB + Fluc800 |
|---|---|---|---|
| Total, other (not including serious) adverse events | | | |
| # participants affected / at risk | 44/45 | 47/47 | 49/49 |
| Blood and lymphatic system disorders | | | |
| Anaemia * 1 | | | |
| # participants affected / at risk | 21/45 (46.67%) | 27/47 (57.45%) | 24/49 (48.98%) |
| Thrombocytopenia * 1 | | | |
| # participants affected / at risk | 2/45 (4.44%) | 4/47 (8.51%) | 4/49 (8.16%) |
| Neutropenia * 1 | | | |
| # participants affected / at risk | 2/45 (4.44%) | 1/47 (2.13%) | 3/49 (6.12%) |

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# Data Elements Overall Adverse Event Module

- Time Frame
- Additional Description (about adverse event data collection)
- Source Vocabulary Name (e.g., MedDRA 8.0)
- Assessment Type
  - Systematic or Non-Systematic

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## Data Elements
## Serious Adverse Event (SAE) Table

- Arm/Group*
  - Title
  - Description
- Total Number Affected by any SAE*
- Total Number at Risk for SAE*

*Required by ClinicalTrials.gov

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## Data Elements SAE Table (cont'd)

- Adverse Event Term*
  - Adverse Event Term Additional Description
  - Organ System*
    - Select from list
  - Number of Affected Participants (# with SAE)*
  - Number of Events (SAEs)
  - *If different from overall, per SAE term*
    - Number of Participants at Risk
    - Source Vocabulary Name
    - Assessment Type

*Required by ClinicalTrials.gov

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## Data Elements
## Other Adverse Events Table

- Same data elements as SAE table plus:
  - Frequency Threshold for Reporting Other (Not Including Serious) Adverse Events*
    - Threshold must be less than or equal to 5 percent

*Required by ClinicalTrials.gov

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## Basic Information Needed

| | | |
|---|---|---|
| Time Frame | | |
| Additional Description | | |
| | **Arm Title*** | **Arm Title*** |
| | **Arm Description*** | **Arm Description*** |
| | | |
| Total # Participants with any AE* | | |
| Total # Participants at Risk* | | |
| | | |
| Adverse Event Term* | # with event/# at risk | # with event/# at risk |
| - Organ System (select from list)* | | |
| | | |

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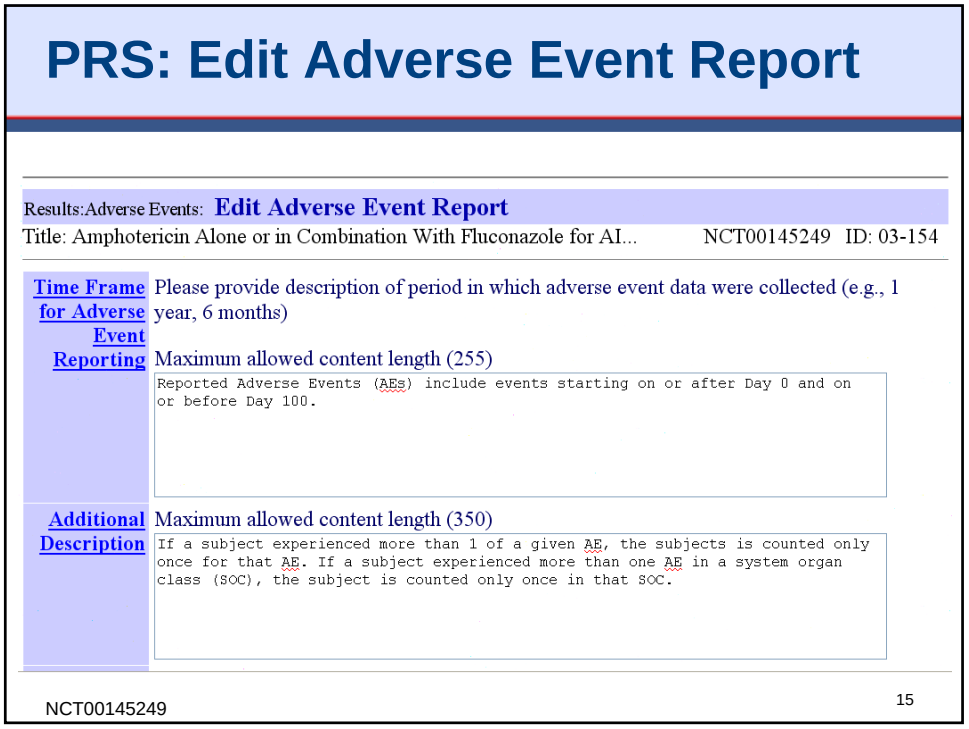
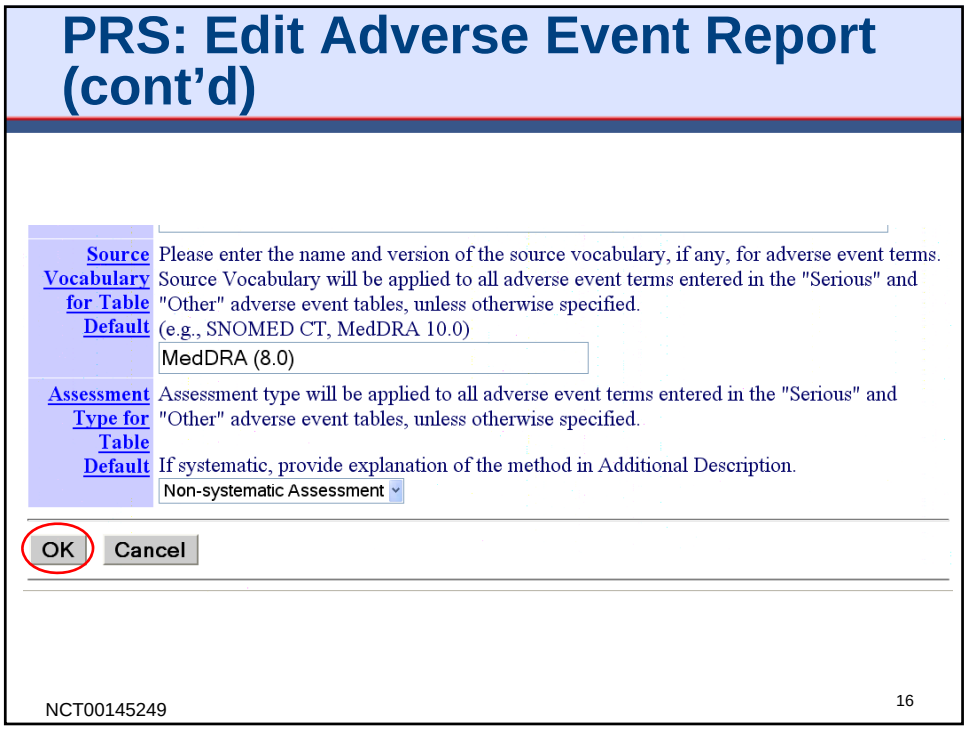
# PRS: Edit Adverse Event Report




# PRS: Edit Adverse Event Report (cont'd)



# PRS: Edit Serious Adverse Event Total

Results:Adverse Event Overview: **Edit Serious Adverse Event Total**

Title: Amphotericin Alone or in Combination With Fluconazole for AI... NCT00145249 ID: 03-154

Please enter the number of participants affected and at risk as integers.

| Serious Adverse Event(s) | AmphoB standard *Amphotericin B 0.7 mg/kg for 1...* | | AmphoB+Fluc400 *Amphotericin B 0.7 mg/kg and t...* | | AmphoB + Fluc800 *Amphotericin B 0.7 mg/kg and t...* | |
|---|---|---|---|---|---|---|
| Maximum for any Serious Adverse Event | 4 *(Calculated)* | | 3 *(Calculated)* | | 3 *(Calculated)* | |
| Sum for all Serious Adverse Events | 30 *(Calculated)* | | 21 *(Calculated)* | | 38 *(Calculated)* | |
| | # Affected * | # at Risk * | # Affected * | # at Risk * | # Affected * | # at Risk * |
| Total | 22 | 45 | 17 | 47 | 26 | 49 |

OK Cancel

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# PRS: Edit Serious Adverse Event Subset Data

Results:Adverse Event Overview:Adverse Event Subset: **Edit Serious Adverse Event Subset Data**

Title: Amphotericin Alone or in Com ... ID: 03-154

Please enter the number of participar ...

| Serious Adverse Event(s) | AmphoB standard *Amphotericin B 0.7 mg/kg for 1...* | |
|---|---|---|
| | # Affected * | # at Risk * |
| Total | 22 | 45 |
| | # Affected * | # Events | # at Risk [blank =Total] |
| Sepsis *Non-systematic Assessment* | 4 | NOTE : Missing # of events | [45] |
| Meningitis cryptococcal *Non-systematic Assessment* | 2 | NOTE : Missing # of events | [45] |

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## General Review Criteria

- Abbreviations are expanded first time used
- No spelling errors exist
- Arms/Groups
  - Informative Titles (“Arm/Group,” “Period,” “Milestone”)
  - Arm/Group Descriptions are descriptive; contain information about the interventions administered (e.g., dosage, dosage form, frequency of administration) or groups evaluated
- Information is consistent with other sections of record (or discrepancies explained)
- No written results or conclusions

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## Specific Review Criteria

- Time Frame
  - If provided, is specific and understandable
- Additional Description
  - If provided, content is relevant to data element
- Number of Participants at Risk
  - Matches number STARTED or other row (Milestone) in Participant Flow module (or discrepancy is explained in Additional Description)

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# Review

**Reporting Groups**

| | Description |
|---|---|
| **AmphoB Standard** | Amphotericin B 0.7 mg/kg for 14 day followed by fluconazole 400 mg daily for 8 weeks. For subjects in the standard therapy arm whose Amphotericin B dose is continued beyond 14 days, fluconazole initiation will be delayed. |
| **AmphoB+Fluc400** | Amphotericin B 0.7 mg/kg and the randomized dose of fluconazole at 400 mg/day for the first 14 days, then the randomized dose of fluconazole at 400 mg/day respectively for an additional 8 weeks. |
| **AmphoB + Fluc800** | Amphotericin B 0.7 mg/kg and the randomized dose of fluconazole at 800 mg/day for the first 14 days, then the randomized dose of fluconazole at 800 mg/day respectively for an additional 8 weeks. |

| | |
|---|---|
| **Time Frame** | Reported Adverse Events (AEs) include events starting on or after Day 0 and on or before Day 100. |
| **Additional Description** | If a subject experienced more than 1 of a given AE, the subjects is counted only once for that AE. If a subject experienced more than one AE in a system organ class (SOC), the subject is counted only once in that SOC. |

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# Review (cont'd)

**Serious Adverse Events**

| | AmphoB Standard | AmphoB+Fluc400 | AmphoB + Fluc800 |
|---|---|---|---|
| **Total # participants affected/at risk** | **22/45 (48.89%)** | **17/47 (36.17%)** | **26/49 (53.06%)** |
| **Infections and infestations** | | | |
| **Sepsis** * A | | | |
| **# participants affected/at risk** | 4/45 (8.89%) | 3/47 (6.38%) | 0/49 (0%) |
| **Meningitis cryptococcal** * A | | | |
| **# participants affected/at risk** | 2/45 (4.44%) | 1/47 (2.13%) | 1/49 (2.04%) |

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# Review (cont'd)

**Overall Study**

| | AmphoB Standard | AmphoB+Fluc400 | AmphoB + Fluc800 |
|---|---|---|---|
| **STARTED** | 47 [1] | 48 [2] | 48 [3] |
| **COMPLETED** | 36 | 33 | 31 |
| **Not Completed** | **11** | **15** | **17** |

[1] 47 subjects randomized; 45 subjects treated

[2] 48 subjects randomized; 47 subjects treated-2 subjects randomized to AmphoB rec'd AmphoB+Fluc400

[3] 48 subjects randomized; 49 treated-3 subjects randomized to AmphoB+Fluc400 rec'd AmphoB+Fluc800

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# Example – Error

**Overall Study**

| | AllergyRid at Once | AllergyRid Spread |
|---|---|---|
| **STARTED** | 182 | 183 |
| **COMPLETED** | 175 | 176 |
| **Not Completed** | 7 | 7 |

| |
|---|
| **Time Frame** |
| **Additional Description** |

**Serious Adverse Events**

| | AllergyRid at Once | AllergyRid Spread |
|---|---|---|
| **Total # participants affected/at risk** | 0/0 | 0/0 |

**Other Adverse Events**

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

| | AllergyRid at Once | AllergyRid Spread |
|---|---|---|
| **Total # participants affected/at risk** | 0/0 | 0/0 |

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# Example – Corrected

**Reporting Groups**

| | Description |
|---|---|
| **AllergyRid at Once** | Participants will be administered 5 sprays in each nostril daily. The sprays will be all at one time. |
| **AllergyRid Spread** | Participants will be administered 5 sprays in each nostril daily. The sprays will be distributed over eight hours (i.e., Two sprays in the morning, one in the afternoon, two sprays in the evening). |

| | |
|---|---|
| **Time Frame** | |
| **Additional Description** | Adverse Events were not collected for this study. |

**Serious Adverse Events**

| | AllergyRid at Once | AllergyRid Spread |
|---|---|---|
| **Total # participants affected/at risk** | 0/0 | 0/0 |

**Other Adverse Events**
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

| | AllergyRid at Once | AllergyRid Spread |
|---|---|---|
| **Total # participants affected/at risk** | 0/0 | 0/0 |

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# Example – Error

**1. Primary Outcome Measure:**

| | |
|---|---|
| **Measure Title** | **Number of Participants Reporting Serious Adverse Events (SAE)** |
| **Measure Description** | An SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above. |
| **Time Frame** | Months 138, 150, 162, 174, and 186 after Day 0 |
| **Safety Issue?** | Yes |

**Population Description** -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

**Reporting Groups**

| | Description |
|---|---|
| **α-Strain Vaccine** | Participants are administered 2 doses of α-Strain Vaccine. The first on Day 0 and the second during Month 12. |

**Measured Values**

| | α-Strain Vaccine |
|---|---|
| **Number of Participants Analyzed** | 130 |
| **Number of Participants Reporting Serious Adverse Events (SAE)** *[units: participants]* | 4 |

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# Example – Error

| Time Frame |
| --- |
| Additional Description |

Serious Adverse Events

| | α-Strain Vaccine |
| --- | --- |
| Total # participants affected/at risk | 6/135 (4.44%) |
| Cardiac disorders | |
| Acute Myocardial Infarction †A | |
| # participants affected/at risk | 1/135 (0.74%) |
| Vascular disorders | |
| Hypertension †A | |
| # participants affected/at risk | 1/135 (0.74%) |
| General disorders | |
| Pyrexia †A | |
| # participants affected/at risk | 4/135 (2.96%) |
| Renal and urinary disorders | |
| Urinary tract infection †A | |
| # participants affected/at risk | 2/135 (1.48%) |
| Vesicoureteric reflux †A | |
| # participants affected/at risk | 1/135 (0.74%) |

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# Additional Information

General ClinicalTrials.gov information:
http://prsinfo.clinicaltrials.gov

FDAAA-related information:
http://prsinfo.clinicaltrials.gov/fdaaa.html

Office of Extramural Research:
http://grants.nih.gov/Clinicaltrials_fdaaa/

Questions?
register@clinicaltrials.gov