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Adverse Events Module

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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 Sussa and Schuster [18].

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

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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
      - Report other adverse events that exceed the specified frequency threshold (e.g., >5%) within any arm

*Required by ClinicalTrials.gov

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Basic Information Needed

Time Frame		
Additional Description		
	Arm Title* Arm Description	Arm Title* 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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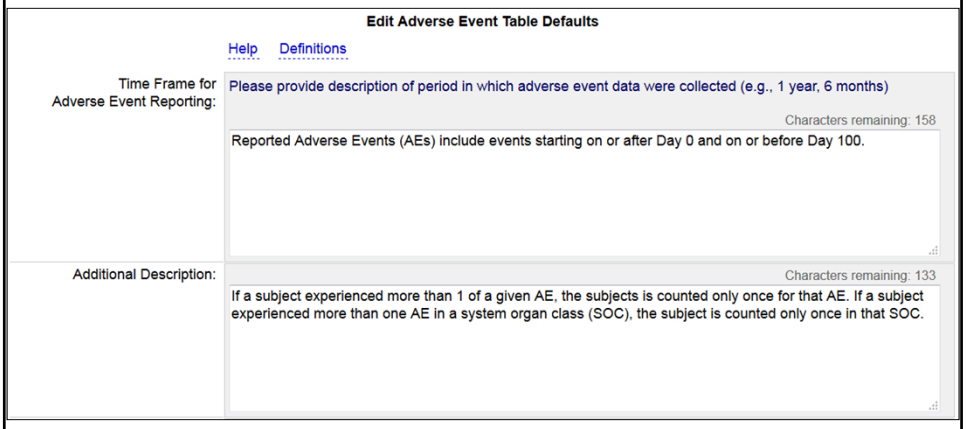
PRS: Edit Adverse Event Table Defaults



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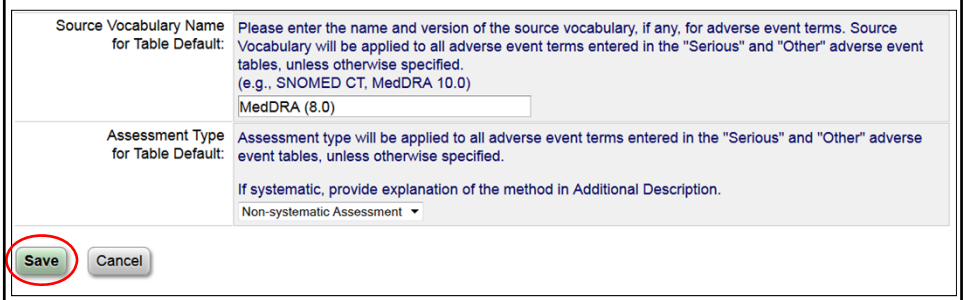
PRS: Edit Adverse Event Table Defaults (cont'd)



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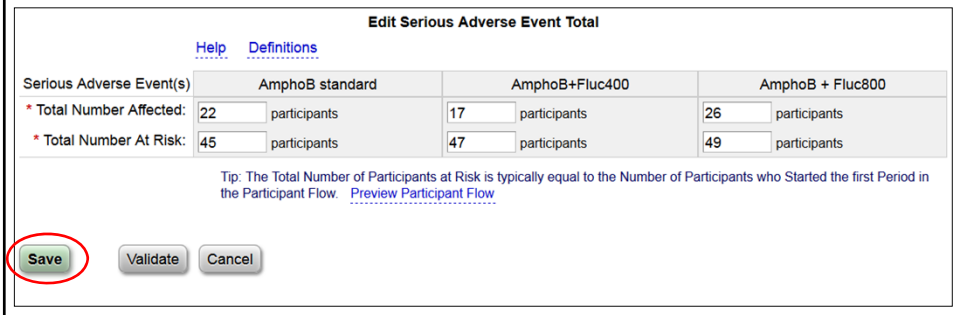
PRS: Edit Serious Adverse Event Total



Edit Serious Adverse Event Total

Help Definitions

Serious Adverse Event(s)	AmphoB standard	AmphoB+Fluc400	AmphoB + Fluc800
* Total Number Affected:	22 participants	17 participants	26 participants
* Total Number At Risk:	45 participants	47 participants	49 participants

Tip: The Total Number of Participants at Risk is typically equal to the Number of Participants who Started the first Period in the Participant Flow. Preview Participant Flow

Save Validate Cancel

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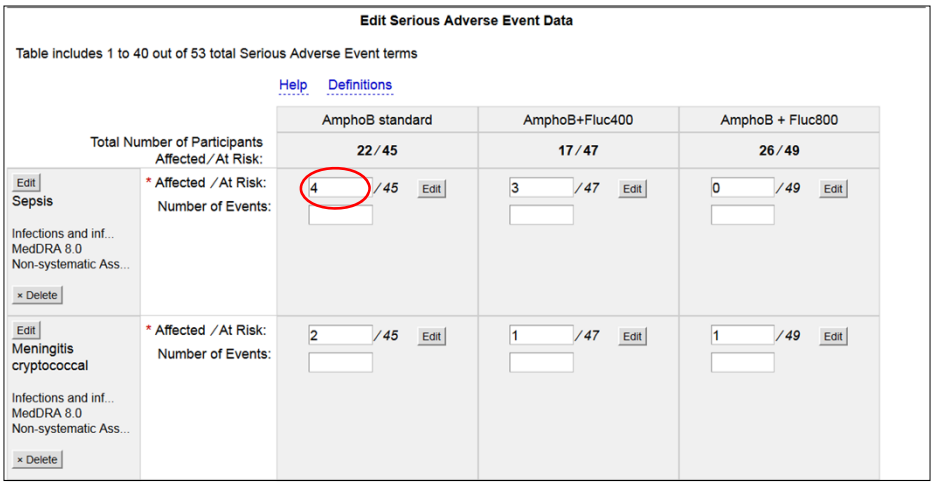
PRS: Edit Serious Adverse Event Data



Edit Serious Adverse Event Data

Table includes 1 to 40 out of 53 total Serious Adverse Event terms

Help Definitions

		AmphoB standard	AmphoB+Fluc400	AmphoB + Fluc800
Total Number of Participants Affected/At Risk:		22/45	17/47	26/49
Edit Sepsis Infections and inf... MedDRA 8.0 Non-systematic Ass... × Delete	* Affected /At Risk: Number of Events:	4 /45 Edit	3 /47 Edit	0 /49 Edit
Edit Meningitis cryptococcal Infections and inf... MedDRA 8.0 Non-systematic Ass... × Delete	* Affected /At Risk: Number of Events:	2 /45 Edit	1 /47 Edit	1 /49 Edit

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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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PRS Review

Adverse Events

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.
Source Vocabulary Name	MedDRA (8.0)
Assessment Type	Non-systematic Assessment

Arm/Group Title	AmphoB Standard	AmphoB+Fluc400	AmphoB + Fluc800
Arm/Group Description	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.	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.	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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PRS Review (cont'd)

Serious Adverse Events

	AmphoB Standard Affected / at Risk (%)	AmphoB+Fluc400 Affected / at Risk (%)	AmphoB + Fluc800 Affected / at Risk (%)
Total	22/45 (48.89%)	17/47 (36.17%)	26/49 (53.06%)
Infections ... Sepsis [*A]	4/45 (8.89%)	3/47 (6.38%)	0/49 (0%)
Infections ... Meningitis cryptococcal [*A]	2/45 (4.44%)	1/47 (2.13%)	1/49 (2.04%)
Infections ... Pneumocystis jiroveci pneumonia [*B]	1/45 (2.22%)	2/47 (4.26%)	1/49 (2.04%)
Infections ... Sinusitis [*B]	0/45 (0%)	0/47 (0%)	2/49 (4.08%)
Infections ... AIDS related complication [*B]	0/45 (0%)	0/47 (0%)	1/49 (2.04%)

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Review (cont'd)

Recruitment Details	Subjects were screened and enrolled at 10 sites in the US and 5 sites in Thailand.
Pre-Assignment Details	

Arm/Group Title	AmphoB Standard	AmphoB+Fluc400	AmphoB + Fluc800	Total (Not public)
Arm/Group Description	Amphotericin B 0.7 mg/kg for 14 day...	Amphotericin B 0.7 mg/kg and the ra...	Amphotericin B 0.7 mg/kg and the ra...	
Period Title: **Overall Study**				
Started	47 [1]	48 [2]	48 [3]	143
Completed	36	33	31	100
Not Completed	11	15	17	43

[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**

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Example – Corrected

Overall Study

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

Time Frame	
Additional Description	Adverse events were not collected in this study

Serious Adverse Events

	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, 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

Measured Values

	α–Strain Vaccine
Number of Participants Analyzed	130
Number of Participants Reporting Serious Adverse Events [*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	1/135 (0.74%)
Vascular disorders	
Hypertension	1/135 (0.74%)
General disorders	
Pyrexia	4/135 (2.96%)
Renal and urinary disorders	
Urinary tract infection	2/135 (1.48%)
Vesicoureteric reflux ….	….

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Additional Information

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

FDAAA-related information (see Submit Studies):
http://clinicaltrials.gov/manage-recs/fdaaa

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

Questions?
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