Discussion on Adverse Event SDTM – Event Class

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October 30, 2017

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Agenda

01 Overview of General Observations Class

02 Example from EVENTS class

Overview of General Observations Class

General Observations class : Subject-level observations captured during the study
Classified as Interventions, Events, or Findings

INTERVENTION CLASS :-

- **Concomitant Medications (CM)**
- **Exposure as Collected (EC)**
- **Exposure (EX)**
- **Substance Use (SU)**
- **Procedures (PR)**

(1) Data of investigational treatment as specified by the study protocol
(2) Therapeutic and other treatments coincident with the study assessment period (e.g., concomitant medications)
(3) Self-administered by the subject (such as use of alcohol, tobacco, or caffeine).

EVENT CLASS:-

- **Adverse Events (AE)**
- **Clinical Events (CE)**
- **Disposition (DS)**
- **Protocol Deviations (DV)**
- **Healthcare Encounters (HO)**
- **Medical History (MH)**

(1) Planned protocol milestones : randomization , study completion, occurrences, conditions
(2) Occurrences of unplanned events (Adverse Events)
(3) Incidences prior to trial (Medical History)

Overview of General Observations Class(Contd…)

FINDINGS CLASS :- (1) Observations storing results of Tests based on planned/unplanned evaluations (e.g. laboratory tests, ECG testing, and questions listed on questionnaires)

- Drug Accountability (DA)
- Death Details (DD)
- ECG Test Results (EG)
- Inclusion/Exclusion Criterion Not Met (IE)
- Immunogenicity Specimen Assessments (IS)
- Laboratory Test Results (LB)
- Microbiology Specimen (MB)
- Microscopic Findings (MI)
- Morphology (MO)
- Microbiology Susceptibility Test (MS)
- PK Concentrations (PC)
- PK Parameters (PP)
- Physical Examination (PE)
- Questionnaires (QS)
- Reproductive System Findings (RP)
- Disease Response (RS)
- Subject Characteristics (SC)
- Subject Status (SS)
- Tumor Identification (TU)
- Tumor Results (TR)
- Vital Signs (VS)

Adverse Event SDTM

- Adverse Event :- any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment" (ICH E2A)
- Scope of adverse event collection (pre-treatment events related to trial conduct, post treatment AEs, not collecting events that are assessed as efficacy endpoints) can be decided In consultation with regulatory authorities.
- May be captured either as free text or via a pre-specified list of terms.
- The events included in the AE dataset should be consistent with the protocol requirements.

Example

Subject XYZ-001-003 had rash from 10Oct2017 to 12Oct2017 which was related to the study treatment and it was severe

Information of Interest

1. Subject: XYZ-001-003
2. Untoward medical condition : Rash
3. Start date: 10Oct2017
4. End date:12Oct2017
5. Related to study medication
6. Gradually became Severe

AE SDTM METADATA

ae.xpt, Adverse Events — Events. Version 3.2. One record per adverse event per subject, Tabulation

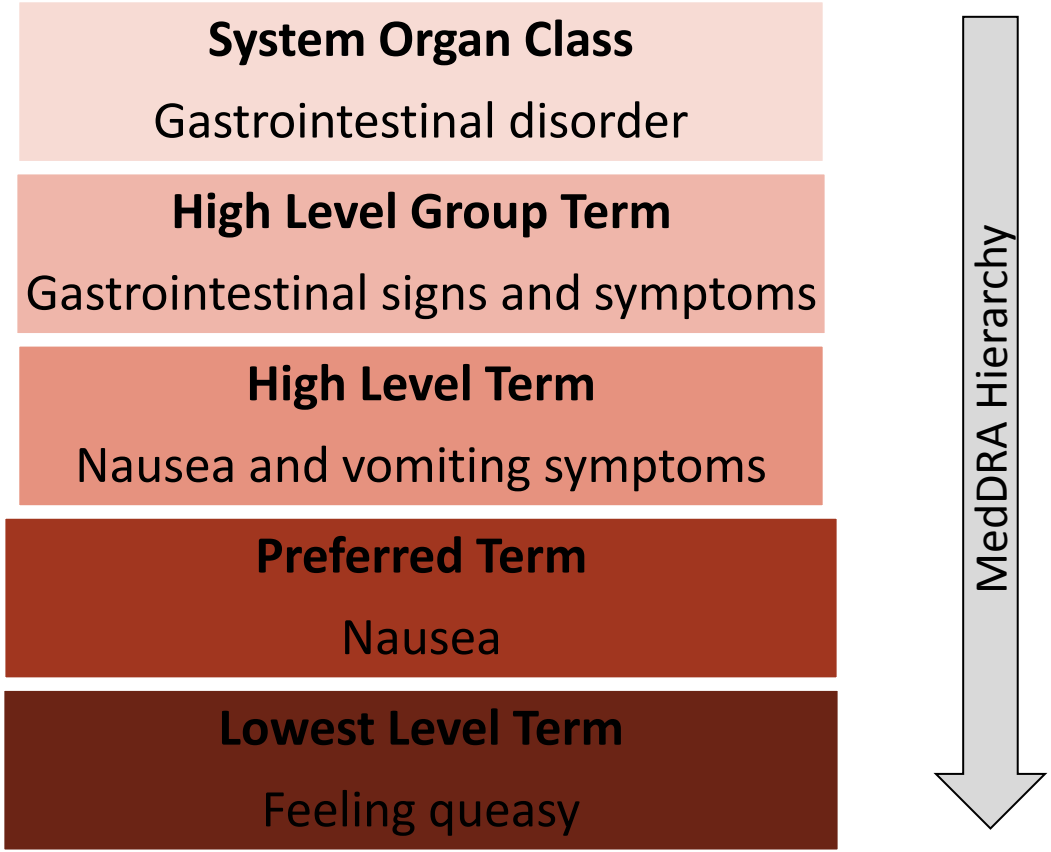
Variable Name	Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	AE	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req
AESEQ	Sequence Number	Num		Identifier	Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.	Req
AEGRPID	Group ID	Char			Used to tie together a block of related records in a single domain for a subject.	Perm
AEREFID	Reference ID	Char			Internal or external identifier such as a serial number on an SAE reporting form.	Perm
AESPID	Sponsor-Defined Identifier	Char			Sponsor-defined identifier. It may be pre-printed on the CRF as an explicit line identifier or defined in the sponsor's operational database. Example: Line number on an Adverse Events page.	Perm
AETERM	Reported Term for the Adverse Event	Char			Verbatim name of the event.	Req
AEMODIFY	Modified Reported Term	Char		Synonym Qualifier	If AETERM is modified to facilitate coding, then AEMODIFY will contain the modified text.	Perm
AELLT	Lowest Level Term	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the Lowest Level Term.	Exp
AELLTCD	Lowest Level Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the Lowest Level Term.	Exp

Patient Identified : unique identifier
In this example USUBJID= XYZ-001-003
Required variable : Can not have a null value

verbatim term collected for the event.
In this example AETERM=Rash
Topic variable
Required variable : Can not have a null value

Why do we need to modify the Verbatim Term?

MedDRA Structure



AE SDTM METADATA (contd...)

Variable Name			Controlled Terms		CDISC Notes	Core
AEDECOD	Dictio			n r	Dictionary-derived text description of AETERM or AEMODIFY. Equivalent to the Preferred Term (PT in MedDRA). The sponsor is expected to provide the dictionary name and version used to map the terms utilizing the define.xml external codelist attributes.	Req
AEPTCD	Preferred Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the Preferred Term.	Exp
AEHLT	Hi				Dictionary-derived text description of the High Level Term for the primary System Organ Class.	Exp
AEHLTCD	Hi			Qualifier	Dictionary-derived code for the High Level Term for the primary System Organ Class.	Exp
AEHLGT	High Level Group Term	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the High Level Group Term for the primary System Organ Class.	Exp
AEHLGTCD	High Level Group Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the High Level Group Term for the primary System Organ Class.	Exp
AECAT	Category for Adverse Event	Char	*	Grouping Qualifier	Used to define a category of related records. Example: BLEEDING, NEUROPSYCHIATRIC.	Perm
AESCAT	Subcategory for A Event		*		tegorization of adverse event. Example: NEUROLOGIC.	Perm
AEPRESP	Pre-Specified A Event				Y" indicates that this adverse event was pre-specified on the CRF. ull for spontaneously reported events (i.e., those collected as free-text verbatim terms)	Perm
AEBODSYS	Body System or Organ Class	Char	*	Record Qualifier	Dictionary derived. Body system or organ class used by the sponsor from the coding dictionary (e.g., MedDRA). When using a multi-axial dictionary such as MedDRA, this should contain the SOC used for the sponsor's analyses and summary tables which may not necessarily be the primary SOC.	Exp
AEBDSYCD	Body System or Organ Class Code	Num	MedDRA	Variable Qualifier	Dictionary derived. Code for the body system or organ class used by the sponsor. When using a multi-axial dictionary such as MedDRA, this should contain the SOC used for the sponsor's analyses and summary tables, which may not necessarily be the primary SOC.	Exp
AESOC	Primary System Organ Class	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the primary System Organ Class. Will be the same as AEBODSYS if the primary SOC was used for analysis.	Exp
AESOCCD	Prima Class	um	MedDRA	Variable Qualifier	Dictionary-derived code for the primary System Organ Class. Will be the same as AEBDSYCD if the primary SOC was used for analysis.	Exp
AELOC	Locati	ar	(LOC)	Record Qualifier	Describes anatomical location relevant for the event (e.g., ARM for skin rash).	Perm
AESEV	Severity/Intensity	Char	(AESEV)	Record Qualifier	The severity or intensity of the event. Examples: MILD, MODERATE, SEVERE.	Perm
AESER	Serious Event	Char	(NY)	Record Qualifier	Is this a serious event?	Exp

Preferred term using coding dictionary
Required Variable: Can not be missing

This is what we discussed in MedDRA

From coding dictionary associated with the adverse event by the sponsor

AE Severity

AE SDTM METADATA (contd…)

AE start and End date

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
AESTDTC	Start Date/Time of Adverse Event	Char	ISO 8601	Timing		Exp
AEENDTC	End Date/Time of Adverse Event	Char	ISO 8601	Timing		Exp
AESTDY	Study Day of Start of Adverse Event	Num		Timing	Study day of start of adverse event relative to the sponsor-defined RFSTDTC.	Perm
AEENDY	Study Day of End of Adverse Event	Num		Timing	Study day of end of event relative to the sponsor-defined RFSTDTC.	Perm
AEDUR	Duration of Adverse Event	Char	ISO 8601	Timing	Collected duration and unit of an adverse event. Used only if collected on the CRF and not derived from start and end date/times. Example: P1DT2H (for 1 day, 2 hours).	Perm
AEENRF	End Relative to Reference Period	Char	(STENRF)	Timing	Describes the end of the event relative to the sponsor-defined reference period. The sponsor-defined reference period is a continuous period of time defined by a discrete starting point (RFSTDTC) and a discrete ending point (RFENDTC) of the trial.	Perm
AEENRTPT	End Relative to Reference Time Point	Char	(STENRF)	Timing	Identifies the end of the event as being before or after the reference time point defined by variable AEENTPT.	Perm
AEENTPT	End Reference Time Point	Char		Timing	Description of date/time in ISO 8601 character format of the reference point referred to by AEENRTPT. Examples: "2003-12-25" or "VISIT 2".	Perm

** Indicates variable may be subject to controlled terminology, (Parenthesis indicates CDISC/NCI codelist code value)*

AE SDTM METADATA (contd...)

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
AEACN	Action Taken with Study Treatment	Char	(ACN)	Record Qualifier	Describes changes to the study treatment as a result of the event. AEACN is specifically for the relationship to study treatment. AEACNOTH is for actions unrelated to dose adjustments of study treatment. Examples of AEACN values include ICH E2B values: DRUG WITHDRAWN, DOSE REDUCED, DOSE INCREASED, DOSE NOT CHANGED, UNKNOWN or NOT APPLICABLE.	Exp
AEACNOTH	Other Action			Record Qualifier	Describes other actions taken as a result of the event that are unrelated to dose adjustments of study treatment. Usually reported as free text. Example: "TREATMENT UNBLINDED. PRIMARY CARE PHYSICIAN NOTIFIED."	Perm
AEREL	Causality	Char	*	Record Qualifier	Records the investigator's opinion as to the causality of the event to the treatment. ICH E2A and E2B examples include NOT RELATED, UNLIKELY RELATED, POSSIBLY RELATED, RELATED. Controlled Terminology may be defined in the future. Check with regulatory authority for population of this variable.	Exp
AERELNST	Relationship to Non-Study Treatment	Char		Record Qualifier	Records the investigator's opinion as to whether the event may have been due to a treatment other than study drug. May be reported as free text. Example: "MORE LIKELY RELATED TO ASPIRIN USE.".	Perm
AEPATT	Pattern of Adverse Event	Char	*	Record Qualifier	Used to indicate the pattern of the event over time. Examples: INTERMITTENT, CONTINUOUS, SINGLE EVENT.	Perm
AEOUT	Outcome of Adverse Event	Char	(OUT)	Record Qualifier	Description of the outcome of an event.	Perm
AESCAN	Involves Cancer	Char	(NY)	Record Qualifier	Was the serious event associated with the development of cancer?	Perm
AESCONG	Congenital Anomaly or Birth Defect	Char	(NY)	Record Qualifier	Was the serious event associated with congenital anomaly or birth defect?	Perm
AESDISAB	Persist or Signif Disability/Incapacity	Char	(NY)	Record Qualifier	Did the serious event result in persistent or significant disability/incapacity?	Perm
AESDTH	Results in Death	Char	(NY)	Record Qualifier	Did the serious event result in death?	Perm
AESHOSP	Requires or Prolongs Hospitalization	Char	(NY)	Record Qualifier	Did the serious event require or prolong hospitalization?	Perm
AESLIFE	Is Life Threatening	Char	(NY)	Record Qualifier	Was the serious event life threatening?	Perm
AESOD	Occ		(NY)	Record Qualifier	Did the serious event occur with an overdose?	Perm
AESMIE AECONTRT	Other M y Important Conc nt or Additional Trtmnt Given	Char Char	(NY) (NY)	Record Record Qualifier	Do additional categories for seriousness apply? Was another treatment given because of the occurrence of the event?	Perm Perm
AETOXGR	Standard Toxicity Grade	Char	*	Record Qualifier	Toxicity grade according to a standard toxicity scale such as Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Sponsor should specify name of the scale and version used in the metadata (see Assumption 6d). If value is from a numeric scale, represent only the number (e.g., "2" and not "Grade 2").	Perm

AE Related to Study medication

Final Toxicity Grade

NCI COMMON TERMINOLOGY CRITERIA for AE

- The NCI Common Terminology Criteria for Adverse Events : Descriptive terminology for Adverse Event (AE) reporting.
- Grade refers to the severity of the AE.
- A grading (severity) scale is provided for each AE term.
- The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
  - Grade 4 : Life-threatening consequences; urgent intervention indicated.
  - Grade 5 : Death related to AE. (AETOXGR can have values from Grade1 to Grade 4, Death due to AE is not reported in AETOXGR, it will be captured in DISPOSITION SDTM with Reason for Death as Adverse Event)

URL for the guidance document: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

SNAPSHOT of GRADES from NCI CTC AE guideline

Blood and lymphatic system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					

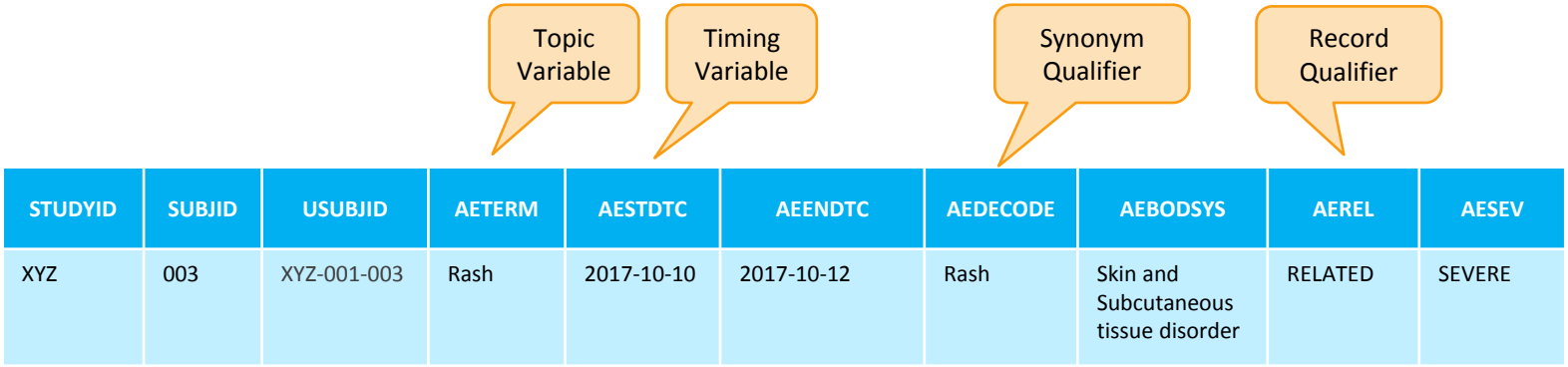
Example

Subject XYZ-001-003 had rash from 10Oct2017 to 12Oct2017 which was related to the study treatment and it was severe

Information of Interest

1. Subject: XYZ-001-003	USUBJID
2. Untoward medical condition : Rash	AETERM
3. Start date: 10Oct2017	AESTDTC
4. End date:12Oct2017	AEENDTC
5. Related to study medication	AEREL
6. Gradually became Severe	AESEV

AE Data Snapshot



STUDYID	SUBJID	USUBJID	AETERM	AESTDTC	AEENDTC	AEDECODE	AEBODSYS	AEREL	AESEV
XYZ	003	XYZ-001-003	Rash	2017-10-10	2017-10-12	Rash	Skin and Subcutaneous tissue disorder	RELATED	SEVERE

EXAMPLE 2

This is an example of data from an AE CRF that collects AE terms as free text. The first study drug was administered to the subject on October 13, 2006 at 12:00. Three AEs were reported. AEs were coded using MedDRA, and the sponsor's procedures include the possibility of modifying the reported term to aid in coding.

Verbatim Term

Modified Term for Reporting purpose

Decoded as per MedDRA Dictionary

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESTDTC	AEENDTC	AEMODIFY	AEDECOD
1	ABC123	AE	123101	1	POUNDING HEADACHE	2005-10-12	2005-10-12	HEADACHE	Headache
2	ABC123	AE	123101	2	BACK PAIN FOR 6 HOURS	2005-10-13T13:05	2005-10-13T19:00	BACK PAIN	Back pain
3	ABC123	AE	123101	3	PULMONARY EMBOLISM	2005-10-21			Pulmonary embolism

Row	AEBODSYS	AESEV	AESER	AEACN	AEREL
1 (cont)	Nervous system disorders	SEVERE	N	NOT APPLICABLE	DEFINITELY NOT RELATED
2 (cont)	Musculoskeletal and connective tissue disorders	MODERATE	N	DOSE REDUCED	PROBABLY RELATED
3 (cont)	Vascular disorders	MODERATE	Y	DOSE REDUCED	PROBABLY NOT RELATED

Row	AEOUT	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDY	AEENDY	AEENRF
1 (cont)	RECOVERED/RESOLVED							-1	-1	
2 (cont)	RECOVERED/RESOLVED							1	1	
3 (cont)	RECOVERING/RESOLVING				Y	Y		9		AFTER

EXAMPLE 2

This is an example of data from an AE CRF that collects AE terms as free text. The first study drug was administered to the subject on October 13, 2006 at 12:00. Three AEs were reported. AEs were coded using MedDRA, and the sponsor's procedures include the possibility of modifying the reported term to aid in coding.

The CRF is structured so that seriousness category variables (e.g., AESDTH, AESHOSP) are checked only when AESER is answered "Y."

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESTDTC	AEENDTC	AEMODIFY	AEDECOD
1	ABC123	AE	123101	1	POUNDING HEADACHE	2005-10-12	2005-10-12	HEADACHE	Headache
2	ABC123	AE	123101	2	BACK PAIN FOR 6 HOURS	2005-10-13T13:05	2005-10-13T	BACK PAIN	Back pain
3	ABC123	AE	123101	3	PULMONARY EMBOLISM	2005-10-21			Pulmonary embolism

Row	AEBODSYS	AESEV	AESER	AEACN	AEREL
1 (cont)	Nervous system disorders	SEVERE	N	NOT APPLICABLE	DEFINITELY NOT RELATED
2 (cont)	Musculoskeletal and connective tissue disorders	MODERATE	N	DOSE REDUCED	PROBABLY RELATED
3 (cont)	Vascular disorders	MODERATE	Y	DOSE REDUCED	PROBABLY NOT RELATED

Row	AEOUT	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDY	AEENDY	AEENRF
1 (cont)	RECOVERED/RESOLVED							-1	-1	
2 (cont)	RECOVERED/RESOLVED							1	1	
3 (cont)	RECOVERING/RESOLVING				Y	Y		9		AFTER

AE STRUCTURE

- The structure of the AE domain is one record per adverse event per subject.
- You may submit one record that covers an adverse event from start to finish
  - A patient may have multiple AE records with changes in severity, causality, seriousness and outcome
  - These records can be “Collapsed” into a single AE record showing highest level of severity, causality etc.

OR

- You may submit a new record when severity, causality, or seriousness changes or worsens.
  - One record per adverse event per subject per changing severity, causality etc
  - Individual record in above case, Indicates that each record is considered to represent a different event.

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