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TEAE: Did I flag it right?

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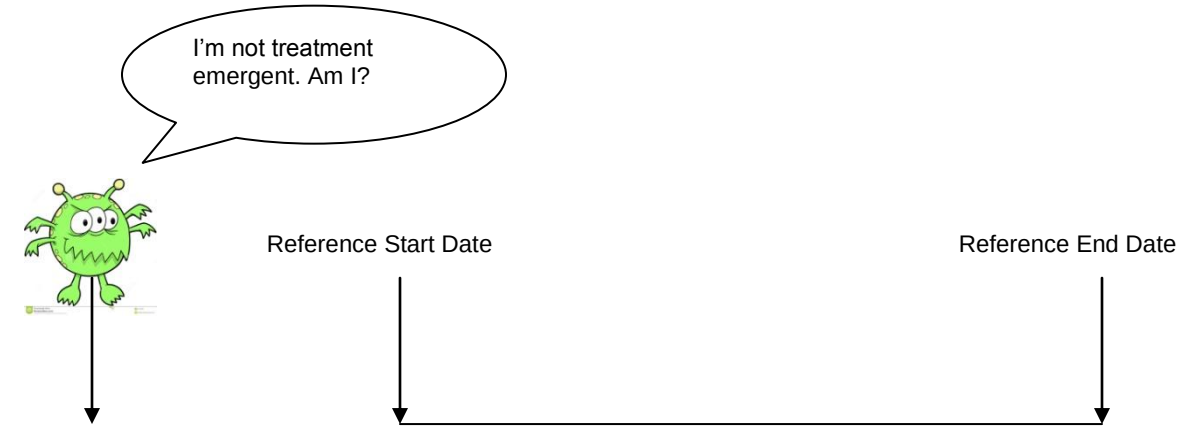
ABSTRACT

As per ICH guidelines for statistical principles for clinical trials (E9) a treatment-emergent adverse event is defined as an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. However there are extensions to the definition of a TEAE that varies from study to study and that we need to remember while deriving this flag. In this paper, we examine the various factors that would contribute in defining a treatment-emergent adverse event.

INTRODUCTION



At a minimum, everyone starts with the AE start date and compares it with the reference start date or treatment start date. Most of us would also consider the reference end date or treatment end date for comparison. We would then flag an AE as TEAE if AE start date is on, or after treatment start date and on or before treatment end date. In this case, we just assumed that a severity level change is captured as a separate AE in the AE dataset with an AE start date as the date severity changed.

SCENARIO 1:

Considering washout period

An important factor that needs to be considered while deriving the TEAE flag is the washout period. A washoutperiod in a clinical study is the period allowed for the administered drug to be eliminated from the body. Any AE that occurs during the period while traces of administered drug remains in the subject's body may be considered as TEAE. For this reason, a washout period in days is also added to the treatment end date in the algorithm for deriving TEAE. Different dugs may have different washout periods and hence should be carefully set after discussion with the investigators and statisticians.

SCENARIO 2:

Handling TEAE flag in cross over studies

When we have cross-over studies, where subjects undergo different treatments, deriving treatment Emergent flag and tying them to the right treatment during which the AE occurred can be tricky. There are usually 2 approaches that we can take to deal with this situation:

1. Use TRTA to show from which drug/period the AE is emergent.

USUBJID	TRTA	AETERM	TRTEMFL	APERIOD	AESTDT	AEENDT
XYZ-123-001-001	DRUG A	HEADACHE	Y	1	2013-04-04	2013-04-05
XYZ-123-001-001	DRUG A	NAUSEA	Y	1	2013-05-23	2013-05-25
XYZ-123-001-001	DRUG B	ITCHING	Y	2	2013-06-07	2013-06-13

2. Create multiple treatment-emergent flag variables (TRTEMxFL) within a single ADAE dataset.

USUBJID	AETERM	TRTEM1FL	TRTEM2FL	AESTDT	AEENDT
XYZ-123-001-001	HEADACHE	Y		2013-04--04	2013-04--05
XYZ-123-001-001	NAUSEA	Y		2013-05--23	2013-05--25
XYZ-123-001-001	ITCHING		Y	2013-06--07	2013-06--13

SCENARIO 3:

Severity change is captured differently in different studies

Figure 1.

Subject Subject	AESPID AESPID	AETERM AETERM	AEST_DT1_RAW AEST_DT1_RAW	AEEN_DT_RAW AEEN_DT_RAW	AETOXGR AETOXGR	AEST_DT2 AEST_DT2
260031001	1	Edema - both feet	18 Aug 2011		2	.
260031001	2	Flu-like illness	03 Sep 2011	05 Sep 2011	2	.
260031001	3	Flu-like illness	08 Sep 2011		3	.
260031001	4	Urinary frequency	24 Aug 2011	28 Aug 2011	1	.
260031001	5	Diarrhea	07 Sep 2011	12 Sep 2011	2	.
260031001	6	Stomatitis	08 Sep 2011		3	.
260031001	7	Rash maculo-papular	09 Sep 2011	12 Sep 2011	3	.
260031001	8	Febrile neutropenia	18 Sep 2011		3	.
260031001	9	worsening ovarian cancer	18 Sep 2011	06 Oct 2011	3	.
260031001	9	worsening ovarian cancer	18 Sep 2011	06 Oct 2011	5	05OCT2011:00:00:00.000
260031001	10	dehydration	13 Sep 2011		2	.
260031001	11	fatigue	08 Sep 2011		3	.
260031001	12	Mucositis	08 Sep 2011		3	.
260031001	13	oral candida	13 Sep 2011		2	.
260031001	14	dysgeusia	10 Sep 2011		2	.
260031001	15	dry mouth	10 Sep 2011		1	.
260031001	16	anorexia	18 Sep 2011		2	.
260031001	17	vomiting	09 Sep 2011	09 Sep 2011	1	.
260031001	18	AST increase	13 Sep 2011		2	.
260031001	19	ALT increase	13 Sep 2011		2	.

In the above AE dataset (Figure 1), subject had an AE "Worsening ovarian cancer" that started on 18 Sep 2011 and ended on 06 Oct 2011. However, the severity of this AE worsened on 05 Oct 2011 and is captured in a separate variable. This whole episode of AE is captured in two observations with the same AESPID, one observation for the actual AE and another for the same AE with changed severity. Now, if the treatment start date for this subject is, let's say 05 Oct 2011, this AE would not be considered as TEAE by just looking at the AE start date and End date. This dataset has to be re-conditioned in order to bring the date of severity change into the AE start date. The following snapshot of the same dataset after re-conditioning shows the AE start date as the date when severity changed from 3 to 5.

FIGURE 2.

SUBJIDN Subject Identifier for the Study, N	AESPID Sponsor-Define Identifier	AETERM Reported Term for the Adverse Event	AETOXGR Standard Toxicity Grade	AESTDTC Start Date/Time of Adverse Event	AEENDTC End Date/Time of Adverse Event
260031001	1	EDEMA - BOTH FEET	2	2011-08-18	
260031001	2	FLU-LIKE ILLNESS	2	2011-09-03	2011-09-05
260031001	3	FLU-LIKE ILLNESS	3	2011-09-08	
260031001	4	URINARY FREQUENCY	1	2011-08-24	2011-08-28
260031001	5	DIARRHEA	2	2011-09-07	2011-09-12
260031001	6	STOMATITIS	3	2011-09-08	
260031001	7	RASH MACULO-PAPULAR	3	2011-09-09	2011-09-12
260031001	8	FEBRILE NEUTROPENIA	3	2011-09-18	
260031001	9	WORSENING OVARIAN CANCER	3	2011-09-18	
260031001	9	WORSENING OVARIAN CANCER	5	2011-10-05	2011-10-06
260031001	10	DEHYDRATION	2	2011-09-13	
260031001	11	FATIGUE	3	2011-09-08	
260031001	12	MUCOSITIS	3	2011-09-08	
260031001	13	ORAL CANDIDA	2	2011-09-13	
260031001	14	DYSGEUSIA	2	2011-09-10	
260031001	15	DRY MOUTH	1	2011-09-10	
260031001	16	ANOREXIA	2	2011-09-18	
260031001	17	VOMITING	1	2011-09-09	2011-09-09
260031001	18	AST INCREASE	2	2011-09-13	
260031001	19	ALT INCREASE	2	2011-09-13	

This dataset can now be used with the TEAE algorithm and the second observation will now be considered as TEAE. Now, if this episode of AE was captured as just one observation with severity change capture in a separate variable, then we would have split the observation into 2 in order to create the same dataset as above.

SCENARIO 4:

Severity changed for good

Now that we have seen the above scenario, consider a similar situation with the severity level getting better. Yes! Anything can come in the raw dataset! In this case, our perfectly re-conditioned dataset and TEAE algorithm will flag the second observation as TEAE where it shouldn't be considered as TEAE as the severity improved. Additional programming logic needs to be deployed to check the severity level change for the same episode of AE and should flag only if the severity worsened and not when improved.

SCENARIO 5:

Partial / missing AE dates

Partial/missing AE start dates and end dates can be really challenging in determining whether an Adverse Event is Treatment Emergent or not. In most cases, we end up imputing these partial/missing dates and derive our TEAE flag based on imputed dates. And usually for AEs, we tend to consider the conservative approach. However, it is also good to check the extent to which we have missing/partial dates in the dataset. For instance, if more than 25% of the AE start/end dates are missing/partial and we go with the conservative approach, then we might end up considering many AEs as TEAEs, which affects the study results negatively. So, it's a good practice to check the percentage of partial/missing dates in your AE domain. And if this percentage is beyond acceptable range, may be you should discuss with the statistics team for alternative approaches apart from conservative approach. This may include querying the sites for approximate dates and other possibilities. Missing AE end date can also be interpreted as AE continuing. Another important check that should be performed, especially if you are imputing start and end dates is to ensure that the end date should not be before the start date.

Consider the following scenario:

Partial AE Start date: --MAR2014

Partial AE End date: -----2014

Now, if we impute the partial dates based on the first day, first month approach, we will end up getting the following imputed dates:

Imputed AE Start date: 01MAR2014

Imputed AE End date: 01JAN2014

Apparently, the imputed AE End date is before the imputed AE Start date. This is a potential problem in our analyses. One way to ensure that this doesn't happen is to use first day, first month approach for the start dates and last day, last month approach for end dates. So with our previous example, the new imputed dates would be:

Imputed AE Start date: 01MAR2014

Imputed AE End date: 31DEC2014

CONCLUSION

Derivation of TEAE flag seems to be very straight forward and simple in most cases. However, it can get complicated based on ones study as well as on the raw data. It is always recommended that whenever we program for treatment emergent adverse events we should keep all the above mentioned scenarios in mind. Derivation of TEAE flag should not be limited to the definition and data, but other factors like study design, explanation in SAP, derivation rules for partial dates should be kept in consideration.

REFERENCES

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

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