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How to define Treatment Emergent Adverse Event (TEAE) in crossover clinical trials?

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ABSTRACT

Treatment Emergent Adverse Event, TEAE, defines as “an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state” according to the E9 guideline. In crossover clinical trials, TEAE can be more complicated due to several factors such as occurrence in washout period, severity change and partial dates. In this paper, we present these AE scenarios and give suggest solutions. General considerations as well as a conservative method for handling such scenarios are also discussed.

INTRODUCTION

Special care needs to be taken when identifying TEAE in crossover clinical studies since we need to determine which treatment really triggers that TEAE. Things can be more complicated if we happened to have issues like: AE happens in a washout period; AE occurs in a treatment period but displays severity changes in follow-up treatment(s); only partial dates are collected for an AE, etc.. This paper will give examples and suggest solutions for these scenarios. To simplify our discussion, we assume all the examples presented below are ongoing AEs.

SCENARIO 1.

AEs with completed start dates that emerge in washout periods in crossover clinical trials

A subject may receive multiple treatments in crossover studies. To ensure that the first administered drug is completely cleared from the body, a washout period is often added prior to the subsequent treatments. If AEs emerge during the washout period, a high possibility exists that these events are triggered by the earlier drug remaining in the body. These AEs are normally considered as TEAEs (Figure 1), which, as recommended by the CDISC, are flagged in both SDTM.SUPPAE and ADAE. Furthermore, to specify the involved treatments, two procedures may generally be referred (Table 1 and Table 2). In either case, one should include TRTxxA/APxxSDT/APxxEDT in ADAE as references so the accuracy and reliability of TEAE treatments can be clearly identified.

Table 1. Use TRTA to identify treatments in crossover studies (TEAEs emerging from washout periods are highlighted):

SDTM.AE				SUPPAE
USUBJID	AESEQ	AETERM	AESTDTC	AETRTEM
ABC-123-001-001	1	fever	2016-05-13	Y
ABC-123-001-001	2	headache	2016-05-18	Y
ABC-123-001-001	3	bone Pain	2016-08-01	Y

ADaM.ADAE		
TRTA	ASTDT	TRTEMFL
Drug A	13MAY2016	Y
Drug B	18MAY2016	Y
Drug C	01AUG2016	Y

ADaM.ADAE								
TRT01A	TRT02A	TRT03A	AP01SDT	AP01EDT	AP02SDT	AP02EDT	AP03SDT	AP03EDT
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016

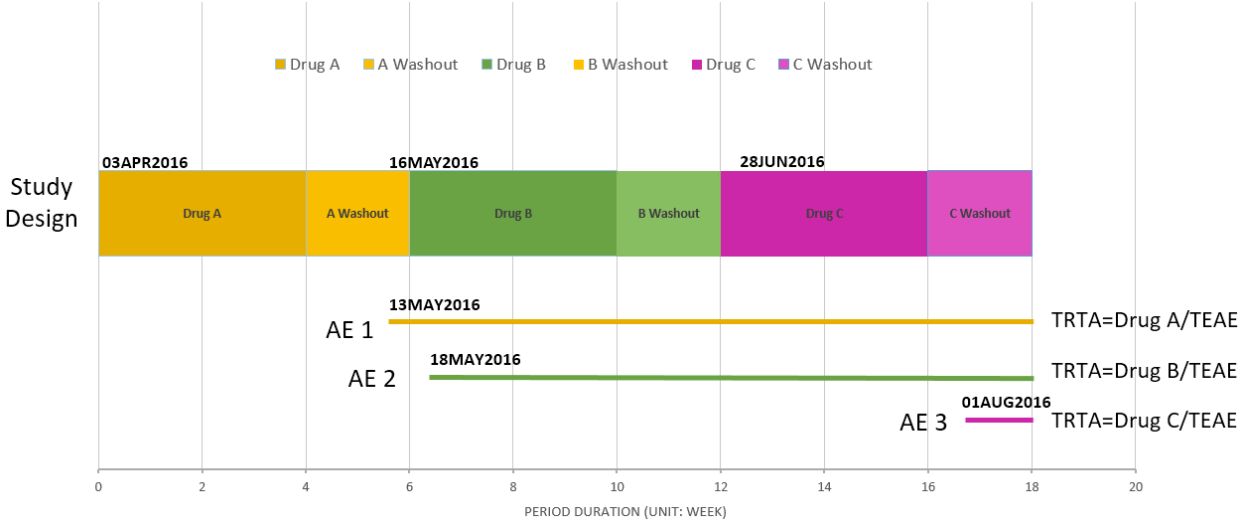
Table 2. Use TRTEMxFL to identify treatments in crossover studies (TEAEs emerging from washout periods are highlighted):

SDTM.AE				SUPPAE
USUBJID	AESEQ	AETERM	AESTDTC	AETRTEM
ABC-123-001-001	1	fever	2016-05-13	Y
ABC-123-001-001	2	headache	2016-05-18	Y
ABC-123-001-001	3	bone pain	2016-08-01	Y

ADaM.ADAE			
ASTDT	TRTEM1FL	TRTEM2FL	TRTEM3FL
13MAY2016	Y		
18MAY2016		Y	
01AUG2016			Y

ADaM.ADAE								
TRT01A	TRT02A	TRT03A	AP01SDT	AP01EDT	AP02SDT	AP02EDT	AP03SDT	AP03EDT
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016

Figure 1. AEs emerging from washout periods are identified as TEAEs



In this scenario, we are focused on washout-occurring AEs. In addition, we consider only the ideal cases in which there is no severity change and partial date issues, so that the derivation of TEAE flags and corresponding treatments can be straightforwardly identified. This is by no means the only possible scenarios, which are delineated in detail below.

SCENARIO 2

AEs with severity changes in crossover clinical trials

In this scenario, programming team needs to work closely with data management team because of non-uniformity in data collection for AEs with severity changes. In some cases, only AEs with increasing (but not decreasing) severity are entered in the database, which enables straightforward flagging TEAE in programming. In some other cases, AEs with different severity (that is, either increasing or decreasing) are all entered, in which the initial dates of severity changes are presented as AE start dates. In handling such data, particular attention needs to be paid to check if a post-treatment AE has occurred before. If yes, then comparison between current and previous severity needs to be made in order to determine whether it is TEAE or not. In the examples below (Table 3 and Figure 2), we show a case in which an AE first occurred in Drug A period and then subsided in the Drug B period. By definition, it is not considered a TEAE for Drug B. On the other hand, the symptom “headache” emerged in both Drug B and C and then intensified in the period of Drug C, so it should be flagged as TEAE for both treatments.

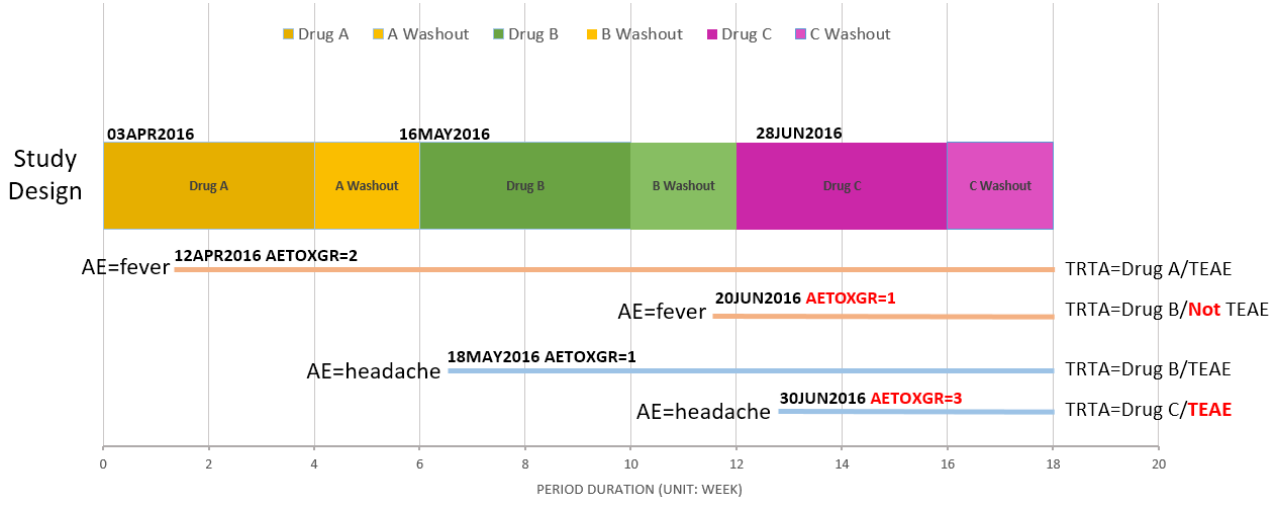
Table 3. Compare severity of the same AEs to eliminate TEAE flag for those with lessened symptoms after the exposure (highlighted in yellow):

SDTM.AE						SUPPAE
USUBJID	AESEQ	AETERM	AESTDTC	AESEV	AETOXGR	AETRTEM
ABC-123-001-001	1	Fever	2016-04-12	Moderate	2	Y
ABC-123-001-001	2	Fever	2016-06-20	Mild	1	
ABC-123-001-002	1	Headache	2016-05-18	Mild	1	Y
ABC-123-001-002	2	Headache	2016-06-30	Severe	3	Y

ADaM.ADAE		
TRTA	ASTDT	TRTEMFL
Drug A	12APR2016	Y
Drug B	20JUN2016	
Drug B	18MAY2016	Y
Drug C	30JUN2016	Y

ADaM.ADAE								
TRT01A	TRT02A	TRT03A	AP01SDT	AP01EDT	AP02SDT	AP02EDT	AP03SDT	AP03EDT
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016

Figure 2. Identify TRTA for the same AEs occurring in multiple treatments with severity changes



Partial date issue is another challenge for proper TEAE determination, especially for crossover clinical trials. Scenario 3 will cover a simple (single treatment) and scenario 4 will illustrate a more complex (crossover) case.

SCENARIO 3.

AEs with partial start dates in single treatment clinical trials

Although different sponsors are normally employed for AE imputation in different studies, a conservative method exists as follows:

- If the day is unknown, then:
    - If the month and year match month and year of treatment exposure start dates, then impute the day the same as the exposure start date; otherwise, assign the first day of the month
- If the month is unknown, then:
    - If the year matches the year of treatment exposure start dates, then impute the month and day the same as the exposure start date; otherwise, assign 'January'
- If the year is unknown, then the date will not be imputed.

CDISC Guideline specifies that ASTDT/ASTDTF can be included in ADAE to keep the imputed date/location (Table 4). We can use ASTDT to compare with the treatment start date to see whether the AE is treatment emergent or not. On the other hand, for AEs with completely missing dates, we do not normally impute but instead label them as TEAE so to be conservative. It is thus highly recommended to discuss with your biostatistician before making such decisions.

Table 4. Use conservative method to identify TEAEs (highlighted in yellow) in single treatment clinical trials:

SDTM.AE			SDTM.SUPPAE
USUBJID	AETERM	AESTDTC	AETRTEM
ABC-123-001-001	Fever	2016	Y
ABC-123-001-001	Headache	2016-02	Y
ABC-123-001-001	Bone Pain	2016-03	Y
ABC-123-001-001	Back Pain		Y

ADaM.ADAE			
TRTSDT	ASTDT	ASTDTF	TRTEMFL
14FEB2016	14FEB2016	M	Y
14FEB2016	14FEB2016	D	Y
14FEB2016	01MAR2016	D	Y
14FEB2016			Y

SCENARIO 4.

AEs with partial dates in crossover clinical trials

The imputation method discussed in *Scenario 3* can also be applied here. At the same time, more attention needs to be paid in considering multiple treatments. Take the subject who had fever on 2016-05 as an example (Table 5 and Figure 3). Here, if we only consider Drug A, then "2016-05" is not the same month as Drug A exposure start date (2016-04-03), so the imputed AE start date is 2016-05-01. By contrast, if we consider Drug B, the month of AE is the same as exposure month (2016-05-16), so the imputed AE start date would be "2016-05-16". As a result, two records with different ASTDT are generated on the ADaM level.

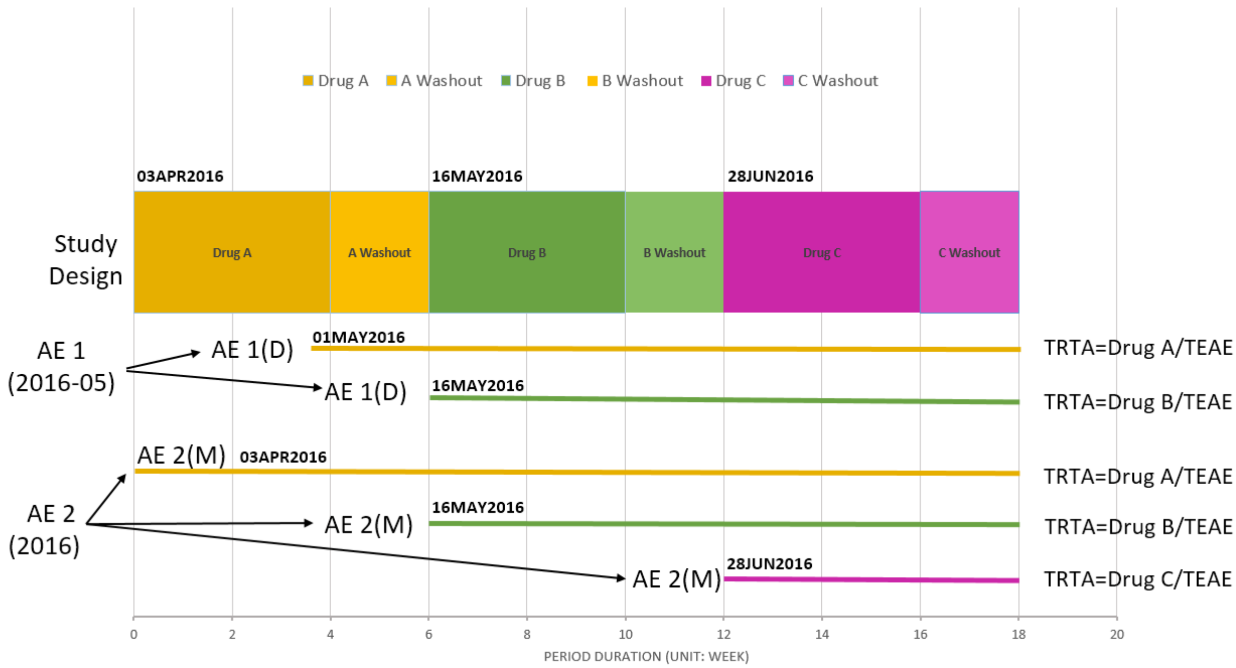
Table 5. One-to-multiple records mapping from SDTM.AE to ADAE may occur after imputation:

SDTM.AE			SDTM.SUPPAE
USUBJID	AETERM	AESTDTC	AETRTEM
ABC-123-001-001	Fever	2016-05	Y
ABC-123-001-001	Headache	2016	Y

ADaM.ADAE			
TRTA	ASTDT	ASTDTF	TRTEMFL
Drug A	01MAY2016	D	Y
Drug B	16MAY2016	D	Y
Drug A	03APR2016	M	Y
Drug B	16MAY2016	M	Y
Drug C	28JUN2016	M	Y

ADaM.ADAE								
TRT01A	TRT02A	TRT03A	AP01SDT	AP01EDT	AP02SDT	AP02EDT	AP03SDT	AP03EDT
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016
Drug A	Drug B	Drug C	03APR2016	15MAY2016	16MAY2016	27JUN2016	28JUN2016	09AUG2016

Figure 3. Identify TRTA for the partial dated AEs in crossover study



CONCLUSION

Derivation of TEAE flags can be complicated by AEs with severity changes and (or) partial date in crossover clinical trials. This paper describes both simple and complex scenarios and offers conservative solutions to avoid missing any possible TEAEs. These, however, should not be applied indiscriminately to other cases considering the specific study design, SAP explanation and other factors employed in your studies. As good practice, it is highly recommended to get the data management team involved and to get partial date frequently refreshed. If such practice cannot be satisfactorily met, discussions with biostatistics/clinical operations about the imputation method may then be necessary before assigning TEAE flags.

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