Paper SI05

ADAE Design for Multiple Phase Trial

Deepak S Grewal, Merck & Co., Inc., North Wales, PA, USA

ABSTRACT

It is important to develop an ADaM dataset that directly supports the analyses planned in the protocol and follows ADaM standards. The typical ADAE design, if applied in trials with multiple phases, will not be sufficient. A single adverse event can occur in a later phase but be related to previous treatment phase or its toxicity grade changes across phases and the structure must account for handling an adverse event in multiple phases. In addition, the ADAE should be designed such that, with a simple subset, the correct AE records for every phase can be obtained. This paper presents a proposed design within the guidelines of CDISC ADaM Occurrence Data Structure (OCCDS) that can support safety reporting across different phases. The design involves having multiple records for single adverse event, for every phase in which it needs to be accounted, that is easy to understand and use.

INTRODUCTION

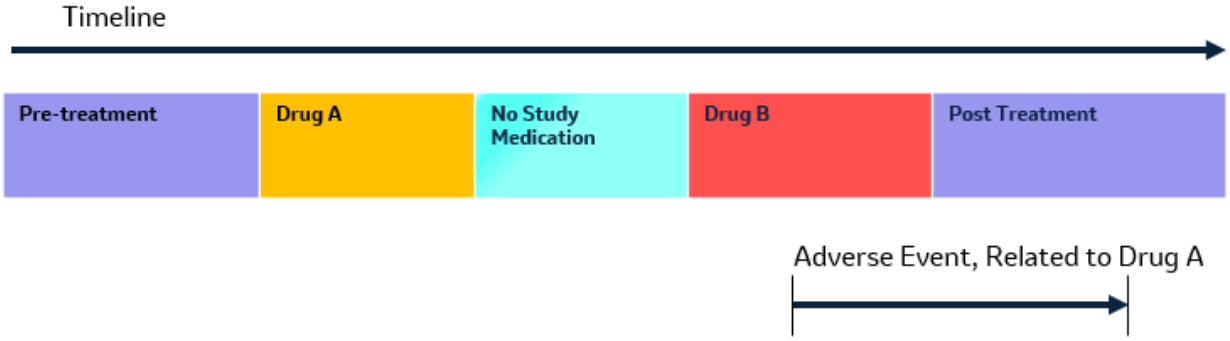
Trial designs and safety analysis special scenario instances for multiple phase trials are getting more complicated. It is important that safety reporting is aligned with clinical know-how of the investigational product, adverse event reporting specifications and makes use of CDISC standards to implement the safety analysis plan for the study. For this paper we will discuss two scenarios that we will handle using ADAE design under CDISC guidance, relation of AE to investigational product and changing of toxicity grade over different periods.

RELATIONSHIP TO IP

Let's consider a case where an AE is marked as related to a drug from previous treatment period. In this example case subject went through treatment period for Drug A and Drug B

USUBJID	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TRT01A	TRT02A
ABC-001	2022-01-13	2022-01-25	2022-02-10	2022-02-22	Drug A	Drug B

AE started during treatment period 2 – Drug B; however, it is related to Drug A from treatment period 1. As noted in figure below.



Below table shows value from AE and SUPPAE data.

SM1, SM2- Study Medication Information

REL1, REL2- Relationship to SM1, SM2 respectively

AEREL- Overall Relationship to any Study Medication

USUBJID	AEDECOD	AESTDTC	AENDTC	SM1	REL1	SM2	REL2	AEREL
ABC-001	Pyrexia	2022-02-14	2022-02-25	Drug A	RELATED	Drug B	NOT RELATED	RELATED

Programmer should work with Clinical and Statistics to understand safety reporting guidance to know how this AE should be summarized. For the above AE let's say the decision is to be counted for Drug B as it happened when the subject was on Drug B and also to be counted under Drug A because it is related to Drug A

To correctly summarize this event, we use TRTA, APERIOD and AREL variables.

TRTA- Actual Treatment

APERIOD- Analysis Period

AREL- Analysis Causality

and create extra record for a same AE to account single AE in both periods. Usually, number of records in ADAE should match SDTM AE but this approach is allowed as per the following text from CDISC ADAM OCCDS (v 1.1). The topic (e.g., an adverse event, concomitant medication) spans several treatment periods and needs to be counted

in each. Based on the analysis need, a separate row might be required for each treatment period spanned and analyzed.

For the first record:

1) Assign APERIOD and TRTA based upon AE start date, which results in Drug B.
2) Since the AE is not related to TRTA (Drug B), create a new variable AREL (Analysis Causality) and set it as "Not Related".

For the second record:

1) Since REL1= "RELATED", set TRTA and APERIOD to TRT01A (Drug A) and AREL as "Related
2) Output as a new record

Also derive Treatment Emergent flag to pick AEs for an individual period or overall.

TRTEMFL- Treatment Emergent Analysis Flag, this flag is used to flag AEs Overall and any AE from first exposure to last exposure + Y number of days.

TRTEM01FL - Treatment Emergent Period 01 flag, any AE between start of Period 1 study medication and earliest of Last dose of period 1 study medication + Y days and start of second period or marked as related to Period 1 if outside this window. Derivation in SAS code,

If tr01sdt <= astdt <= min (tr01edt +30, tr02sdt) or REL1 = "RELATED" then TRTEM01FL = 'Y'

TRTEM02FL - Treatment Emergent Period 02 flag, any AE between start of Period 2 study medication and earliest of Last dose of period 2 study medication + Y days and start of third treatment period (if any) or marked as related to Period 2 if outside this window. Derivation in SAS code,

If tr02sdt <= astdt <= min (tr02edt +30, tr03sdt) or REL2 = "RELATED" then TRTEM02FL = 'Y'

USUBJID	AEDECOD	ASTDT	AEENDT	SM1	REL1	SM2	REL2	AREL	APERIOD	TRTA	TRTEMFL	TREM01FL	TREM02FL
ABC-001	Pyrexia	2022-02-14	2022-02-15	Drug A	RELATED	Drug B	NOT RELATED	Not Related	Drug B	Drug B	Y		Y
ABC-001	Pyrexia	2022-02-14	2022-02-15	Drug A	RELATED	Drug B	NOT RELATED	Related	Drug A	Drug A	Y	Y	

Note that for the second record ASTDT and AENDT are not changed and even though they are not in treatment period 1, TRTA and APERIOD correspond to Period 1.

For analysis with a simple subset of TRTEM01FL= 'Y' or TRTEM02FL= 'Y', TRTA and APERIOD values account them under correct column for tables. Assuming there was only one Pyrexia event. For All Treatment Emergent AEs table, Pyrexia will get counted under both Drug A and Drug B.

PT	Drug A (N=XX)	Drug B (N=YY)
Pyrexia	1(z%)	1(z%)

For All Drug Related Treatment Emergent AE (where (TRTEM01FL= 'Y' or TRTEM02FL= 'Y') and AREL is 'Related'), this AE will get summarized only under Drug A

PT	Drug A (N=XX)	Drug B (N=YY)
Pyrexia	1(z%)	0

AE TOXICITY GRADE CHANGING ACROSS TREATMENT PERIODS

Adverse Event can change its toxicity grade over time. If toxicity grade worsens or changes over a different period, it is important to know how to summarize such AEs and correctly assign worst toxicity grade to the corresponding treatment period.

In the example below, subject received Study Medication over three treatment periods.

USUBJID	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TR03SDT	TR03EDT
ABC-004	2022-01-13	2022-01-25	2022-02-10	2022-02-22	2022-03-01	2022-03-10

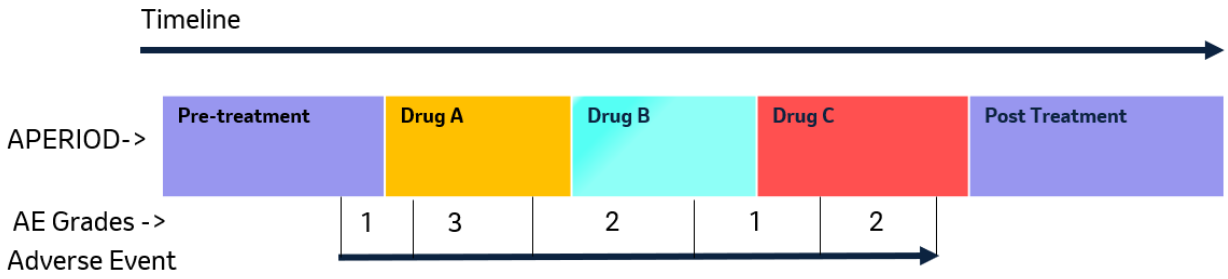
TRT01A	TRT02A	TRT03A
Drug A	Drug B	Drug C

The worst AE record from AE dataset shows this.

USUBJID	AEDECOD	AESTDTC	AENDTC	AETOXGR
ABC-004	Nausea	2022-01-12	2022-03-10	3

Let's assume that Clinical decision to report AEs that change toxicity across different periods by reporting worst toxicity grade for AE in each period only if it worsened during that period or started in that period.

This AE's toxicity grade changes over multiple periods as shown in figure below.



1) AE started before start of treatment
2) AE worsened in period 1 and Period 3, compared to last grade.
3) EPOCH values are based on FADTC, which is a start date for that toxicity.

USUBJID	FASEQ	FAOBJ	FAGRPID	FATESTCD	FATEST	FAORRES	FADTC	FAENDTC	EPOCH
ABC-004	201	Nausea	AE	TOXGR	Toxicity Grade	1	2022-01-12	2022-01-14	Screening
ABC-004	202	Nausea	AE	TOXGR	Toxicity Grade	3	2022-01-15	2022-01-21	Drug A Cycle 1 Day 2
ABC-004	203	Nausea	AE	TOXGR	Toxicity Grade	2	2022-01-22	2022-02-17	Drug A Cycle 2 Day 1
ABC-004	204	Nausea	AE	TOXGR	Toxicity Grade	1	2022-02-18	2022-03-05	Drug B Cycle 1 Day 10
ABC-004	205	Nausea	AE	TOXGR	Toxicity Grade	2	2022-03-06	2022-03-09	Drug C Cycle 2 Day 3

To summarize this correctly, we would need to make use of AOCCzzFL, ATOXGR, APERIOD and TRTA variables
AOCCP1FL- 1st Occurrence of Max AE Wors. in Per. 1
AOCCP2FL- 1st Occurrence of Max AE Wors. in Per. 2
AOCCP3FL- 1st Occurrence of Max AE Wors. in Per. 3
ATOXGR- Analysis Toxicity Grade
ACAT1- Analysis Category 1, to distinguish records from FAAE and AE

Below are ADAE records that come from FAAE.
1) AOCCP1FL and AOCCP3FL captured the worsening of AE by flagging those records. There is no AE worsening in Period 2, hence no records where AOCCP2FL is set to Y.
2) ASTDT, AENDT are same as FADTC and FAENDTC
3) ATOXGR is based upon FAORRES values.

USUBJID	FASEQ	FAOBJ	ACAT1	ATOXGR	FADTC	FAENDTC	ASTDT	AENDT	AOCCP1FL	AOCCP2FL	AOCCP3FL
ABC-004	201	Nausea	SEVERITY DETAILS	1	2022-01-12	2022-01-14	2022-01-12	2022-01-14			
ABC-004	202	Nausea	SEVERITY DETAILS	3	2022-01-15	2022-01-21	2022-01-15	2022-01-21	Y		
ABC-004	203	Nausea	SEVERITY DETAILS	2	2022-01-22	2022-02-17	2022-01-22	2022-02-17			
ABC-004	204	Nausea	SEVERITY DETAILS	1	2022-02-18	2022-03-05	2022-02-18	2022-03-05			
ABC-004	205	Nausea	SEVERITY DETAILS	2	2022-03-06	2022-03-09	2022-03-06	2022-03-09			Y

ADAE records from AE domain.
1) The records ASTDT, AENDT and ATOXGR is based on FA records that have AOCCzzFL flag set to Y, this results in more than one record from a single SDTM AE record.
2) Based upon the AOCCzzFL- TRTA and APERIOD are assigned.

USUBJID	AESEQ	AEDECOD	ACAT1	ATOXGR	AESTDTC	AEENDTC	ASTDT	AENDT	TRTA	APERIOD	TRTEMFL
ABC-004	101	Nausea	ADVERSE EVENTS SUMMARY	3	2022-01-12	2022-03-09	2022-01-15	2022-01-21	Drug A	Drug A	Y
ABC-004	101	Nausea	ADVERSE EVENTS SUMMARY	2	2022-01-12	2022-03-09	2022-03-06	2022-03-09	Drug C	Drug C	Y

For generating a summary, we use records from ADAE where ACAT1 = "ADVERSE EVENTS SUMMARY" and TRTEMFL = 'Y'. This approach has two advantages: -

1) Simple subset and corresponding TRTA and APERIOD values summarize the event under the correct column.
2) AE that started before baseline and its toxicity grade worsening after treatment are correctly summarized in the correct treatment periods.

Assuming there was just one Nausea event during the trial, worst toxicity grade for this event will get counted under Drug A and Drug C, with worst grade 3 and 2 respectively.

	Drug A		Drug B		Drug C	
	n	(%)	n	(%)	n	(%)
Nausea	1	(xx)	0	(0.0)	1	(zz)
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)
Grade 2	0	(0.0)	0	(0.0)	1	(xx)
Grade 3	1	(xx)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)

CONCLUSION

The ADAE design proposed in this paper allows the programmer to implement clinical summarizing rules for a challenging multiphase safety reporting and stay compliant with guidelines of CDISC ADaM Occurrence Data Structure (OCCDS). It also improves traceability between final summary and ADAE dataset by having more than one AE summary record for single AE and using the variables TRTA, APERIOD and TRTEMFL which gives one to one match between summary record and the counts under each column. It also helps trace information within ADAE, between the worst AE records and AE details record through AOCCzzFL variables.

REFERENCES

ADaM Structure for Occurrence Data (OCCDS) Implementation Guide 1.1
https://www.cdisc.org/standards/foundational/adam/adam-structure-occurrence-data-implementation-guide-v1-1

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Deepak S Grewal
Merck & Co., Inc.
North Wales, PA, USA
deepak.grewal@merck.com