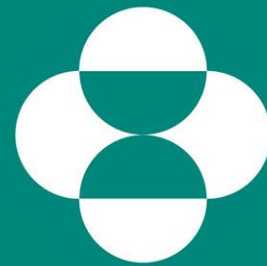


ADAE Design for Multiple Phase Trial

Author: Deepak S. Grewal



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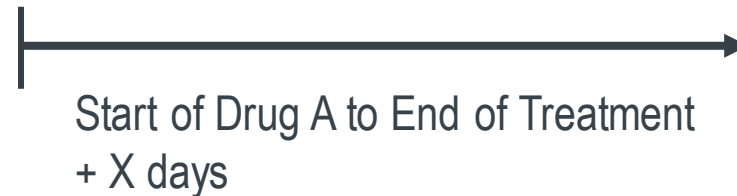
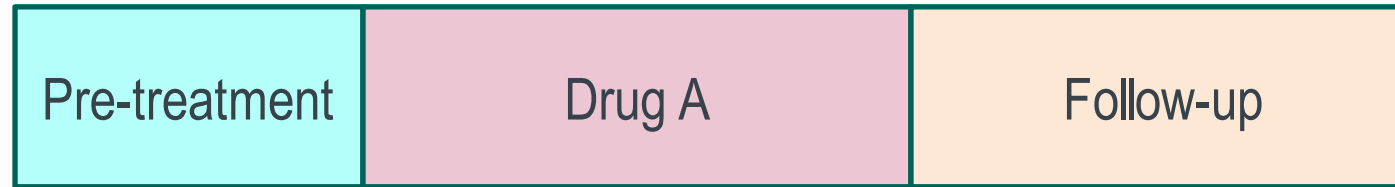
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Agenda

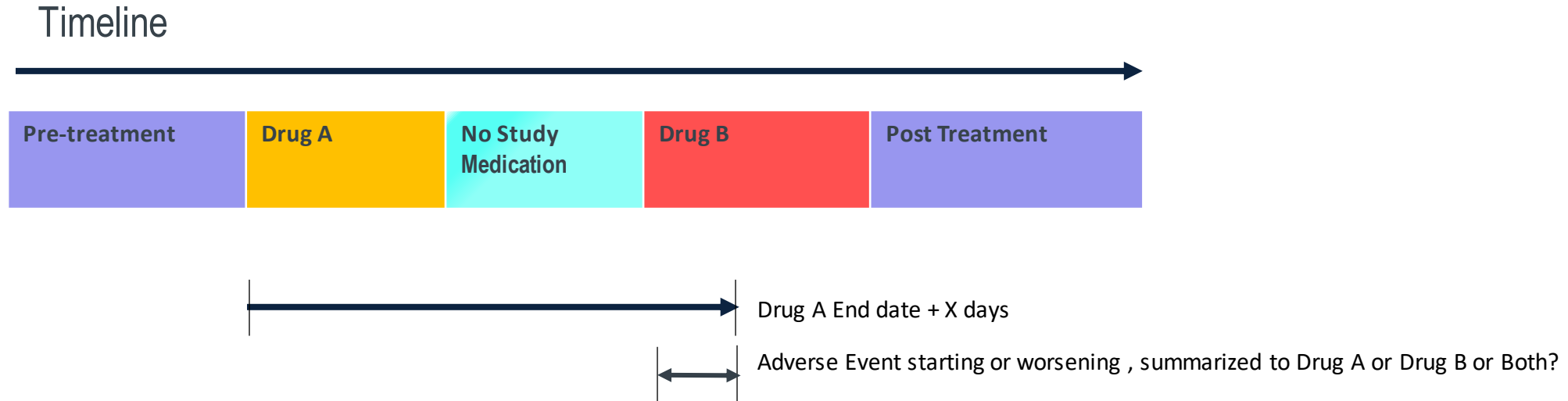
- Special AE reporting needs for a Multiple phase Trial vs Single Phase Trial
- Relevant CDISC ADaM OCCDS guideline
- Example cases showing how to design ADAE within guideline to address reporting needs
- Summarizing benefits

Typical AE reporting for Single Phase



All AE starts or worsening in this period are summarized under Drug A

AE reporting for Multiple Phase Trial



The decision is based upon Clinical know-how of the Drug and Safety Analysis Plan requirements.

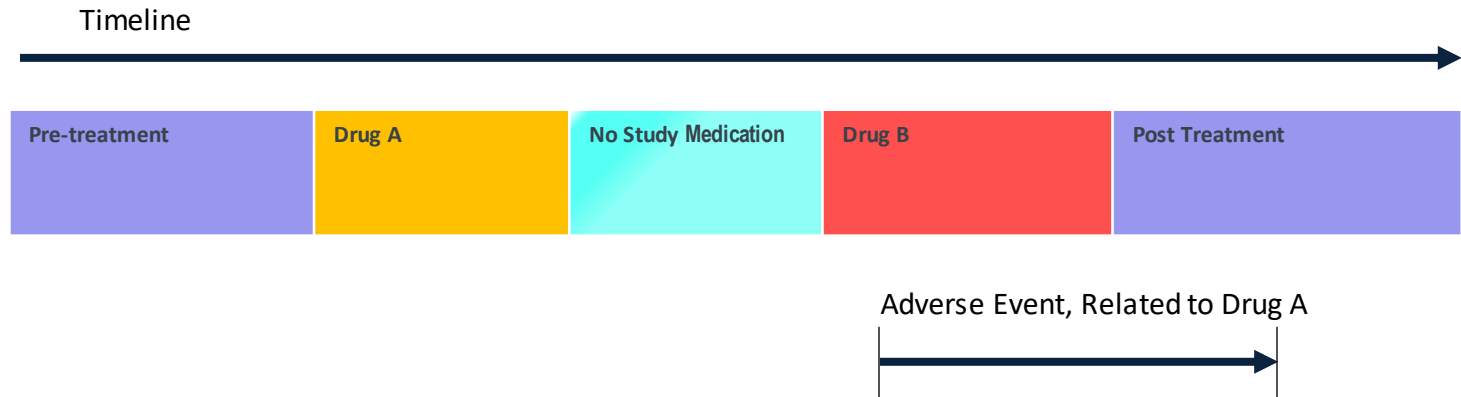
Reporting A Single AE Under Both Periods

- If same AE should be reported under two period, for better traceability from the summary result back to ADAE dataset , we can create more than one record for same AE.
- This is correct approach as per ADaM OCCDS Implementation Guide 1.1. It allows to create more than one record in following scenario.

If 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.

Example Case 1: Relationship to IP

- An AE is marked as related to Drug from previous phase.



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

USUBJID	AEDECOD	AESTDTC	AENDTC	SM1	REL1	SM2	REL2	AEREL	AESEQ
ABC-001	Pyrexia	2022-02-14	2022-02-25	Drug A	RELATED	Drug B	NOT RELATED	RELATED	3

Example Case 1: Relationship to IP

Clinical & Analysis Decision: To be counted under both Treatments

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

TRTA- Actual Treatment

APERIOD- Analysis Period

AREL- Analysis Causality

USUBJID	AEDECOD	AESTDTC	AENDTC	SM1	REL1	SM2	REL2	AEREL	AESEQ
ABC-001	Pyrexia	2022-02-14	2022-02-25	Drug A	RELATED	Drug B	NOT RELATED	RELATED	3

USUBJID	AEDECOD	ASTDT	AEENDT	SM1	REL1	SM2	REL2	AREL	APERIOD	TRTA	AESEQ	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	3	Y		Y
ABC-001	Pyrexia	2022-02-14	2022-02-15	Drug A	RELATED	Drug B	NOT RELATED	Related	Drug A	Drug A	3	Y	Y	

Example Case 1: Relationship to IP

USUBJID	AEDECOD	ASTDT	AEENDT	SM1	REL1	SM2	REL2	AREL	APERIOD	TRTA	AESEQ	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	3	Y		Y
ABC-001	Pyrexia	2022-02-14	2022-02-15	Drug A	RELATED	Drug B	NOT RELATED	Related	Drug A	Drug A	3	Y	Y	

All AE Table

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

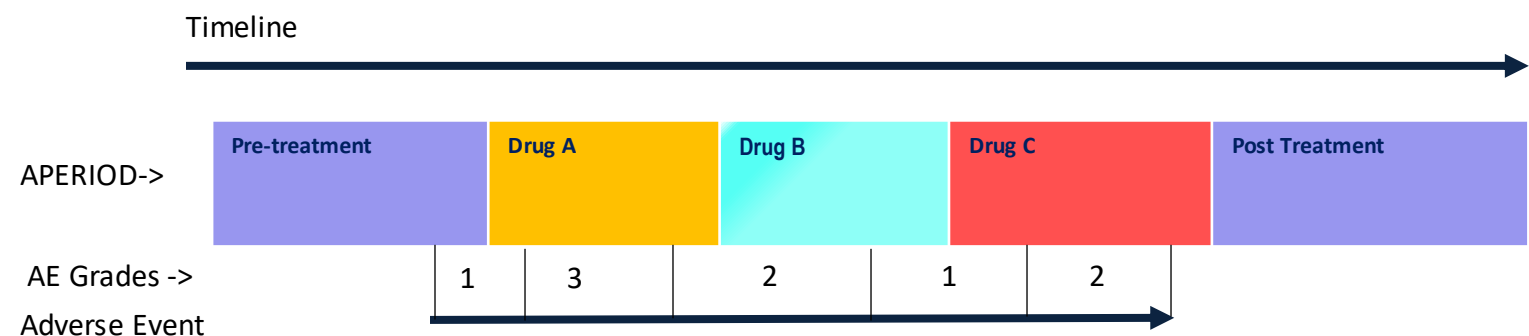
Example Case 1: Relationship to IP

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	

All Drug- Related AE Table

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

Example Case 2: AE toxicity grade changing across treatment Periods



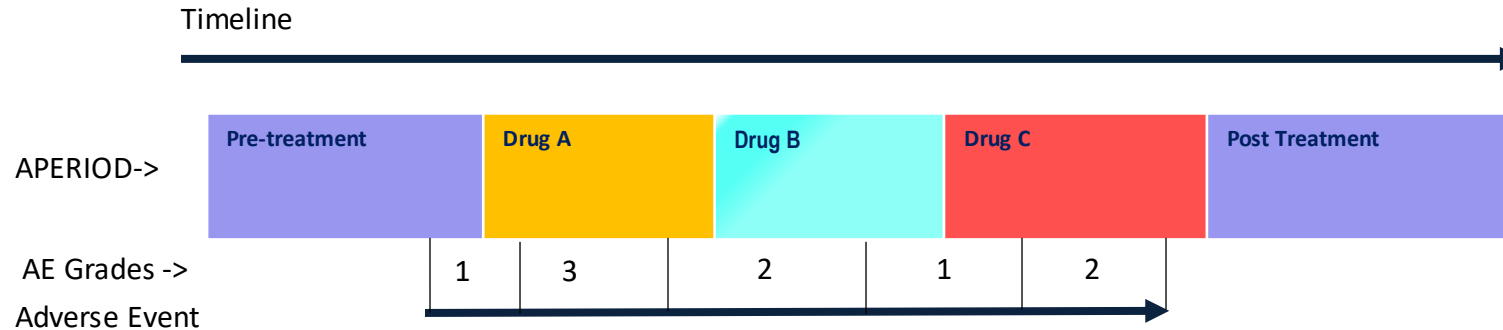
ADSL:

USUBJID	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TR03SDT	TR03EDT	TRT01A	TRT02A	TRT03A
ABC-004	2022-01-13	2022-01-25	2022-02-10	2022-02-22	2022-03-01	2022-03-10	Drug A	Drug B	Drug C

AE:

USUBJID	AEDECOD	AESTDTC	AENDTC	AETOXGR	AESEQ
ABC-004	Nausea	2022-01-12	2022-03-10	3	4

Example Case 2: AE toxicity grade changing across treatment Periods



USUBJID	FASEQ	FAOBJ	FAGRPI D	FATESTC D	FATEST	FAORR ES	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

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

Example Case 2: AE toxicity grade changing across treatment Periods

Clinical & Analysis Decision: To be counted under Treatment Phase where it worsened.

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

Example Case 2: AE toxicity grade changing across treatment Periods

USUBJID	FASEQ	FAOBJ	FAGRPI D	FATESTC D	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

ADAE records from FAAE

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

Example Case 2: AE toxicity grade changing across treatment Periods

ADAE records from FAAE

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 Summary Records

USUBJID	AESEQ	AEDECOD	ACAT1	ATOXGR	AESEQ	AESTDTC	AEENDTC	ASTDT	AENDT	TRTA	APERIOD	TRTEMFL
ABC-004	101	Nausea	ADVERSE EVENTS SUMMARY	3	4	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	4	2022-01-12	2022-03-09	2022-03-06	2022-03-09	Drug C	Drug C	Y

Example Case 2: AE toxicity grade changing across treatment Periods

ADAE Summary Records

USUBJID	AESEQ	AEDECOD	AESEQ	ACAT1	ATOXGR	AESTDTC	AEENDTC	ASTDT	AENDT	TRTA	APERIOD	TRTEMFL
ABC-004	101	Nausea	4	ADVERSE EVENTS SUMMARY	3	2022-01-12	2022-03-09	2022-01-15	2022-02-12	Drug A	Drug A	Y
ABC-004	101	Nausea	4	ADVERSE EVENTS SUMMARY	2	2022-01-12	2022-03-09	2022-03-06	2022-03-09	Drug C	Drug C	Y

AE Maximum Toxicity Grade Table

	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 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.

THANK YOU



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