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Two Approaches to Phase-Specific TRTEMFL in ADAE: A Neoadjuvant-Adjuvant Case with Surgery Between Phases

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ABSTRACT

Most ADAE implementations assume a single treatment phase. The standard TRTEMFL (treatment-emergent adverse event flag) derivation works well in single treatment phase setting, but it does not provide the flexibility to attribute adverse events (AEs) to distinct clinical phases (e.g., neoadjuvant vs adjuvant). In multi-phase trials, treatments, mechanisms, and risk windows often differ by phase; merging all AEs under a single TRTEMFL obscures phase-specific risk.

This paper uses a neoadjuvant–surgery–adjuvant oncology case to show how to define TRTEMFL in a multi-phase study without duplicate AE occurrence in each phase. The paper proposes two specification approaches for separating treatment-emergent AEs by phase: (1) assign APERIOD and derive a single TRTEMFL; and (2) derive phase-specific flags (TREM0xFL) alongside an overall TRTEMFL. Both approaches support phase-specific AE tables. With the practical specification and SAS code example from a neoadjuvant–adjuvant case, the paper explains the similarities and differences of the two approaches.

INTRODUCTION

In some oncology clinical studies, neoadjuvant therapy (e.g., chemotherapy) is given before surgery or other definitive treatment, to reduce tumor burden or assess response, while adjuvant therapy is given after surgery or other definitive treatment, to eliminate residual disease and reduce recurrence.

This multi-phase study design often requires careful considerations when developing ADaM specifications, particularly around defining phase-specific time windows. Papasani et al. (2021) provides a clear overview of neoadjuvant/adjuvant study design and related ADSL considerations.

In the discussion that follows, for a simplified case, the neoadjuvant phase uses TR01SDT, the surgery phase uses TR02SDT, and the adjuvant phase uses TR03SDT. While ADAE design for multi-phase studies has been discussed by Grewal (2023), this paper focuses specifically on TRTEMFL derivation in a neoadjuvant–surgery–adjuvant oncology setting.

These three-time windows (neoadjuvant – surgery – adjuvant) are consecutive, but not all participants will undergo the surgery phase or proceed to the adjuvant phase. Distinguishing TEAEs (treatment-emergent adverse events) that occur between these time windows requires careful definition. This paper presents example ADAE specifications and corresponding SAS code to support phase-specific adverse events attribution. The two approaches shown in the following sections, Approach 1 with APERIOD and a single TEAE flag is simpler but has limitations in practice, while Approach 2 with phase-specific TEAE flags is more general, flexible, and can be applied to many multi-phase studies.

STUDY DETAILS AND ADAE TRTEMFL DESIGN CONSIDERATIONS

Here is an example of the definition of AEs that happened in the neoadjuvant phase, adjuvant phase, and neoadjuvant and adjuvant phases combined.

- Neoadjuvant and Adjuvant Phase Combined AE Definition:

  Includes adverse events started from the first treatment and up to 30 days from the last treatment including last neoadjuvant therapy, definitive surgery, radiation therapy, or adjuvant treatment for nonserious adverse events and up to 90 days from the last treatment including neoadjuvant treatment, definitive surgery, radiation therapy, or adjuvant treatment for the serious adverse events

- Neoadjuvant Phase AE Definition:

Includes adverse events started from the first neoadjuvant treatment up to and including the last neoadjuvant treatment, definitive surgery or radiation therapy prior to the first adjuvant treatment or, if no adjuvant treatment, up to 30 days from last neoadjuvant treatment, definitive surgery, or radiation therapy (whichever is last) for non-serious adverse events and up to 90 days from last neoadjuvant treatment, definitive surgery, or radiation therapy (whichever is last) for serious adverse events.

- Adjuvant Phase AE Definition:

Includes adverse events started from the first adjuvant therapy after surgery and after any radiation therapy and up to 30 days of last adjuvant treatment for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.

Please see **Figure 1** below, which depicts the definition of TEAE in different phases. +30 days for non-serious AEs and +90 days for serious AEs.

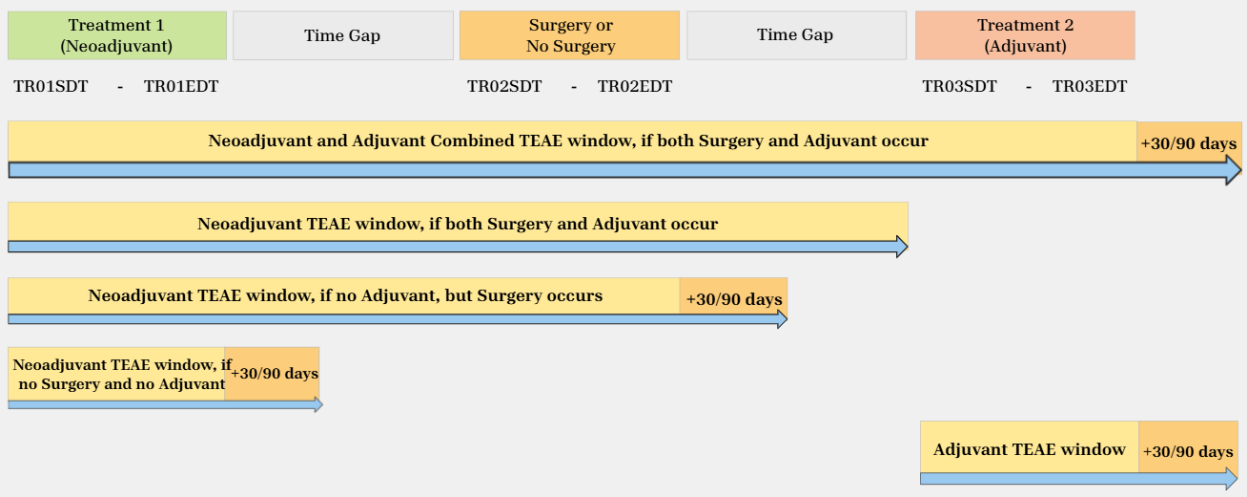

Figure 1. The Definition of AE in a Neoadjuvant/Adjuvant study

Usually, in single-phase studies, TRTEMFL is derived only for treated subjects. An example derivation logic in the ADAE specification is shown below in **Table 1**.

Variable Name	Variable Label	Define Derivation
TRTEMFL	Treatment Emergent Analysis Flag	Derive for treated subjects only. Set TRTEMFL = "Y", if ASTDT>=ADSL.TRTSDT and any of the following conditions is met: 1. study treatment was ongoing (ADSL.EOTSTT is not any of ('Completed', 'Discontinued')); or 2. study treatment ended (ADSL.EOTSTT is ('Completed' or 'Discontinued')) and AE is non-serious and ASTDT was within 30 days of ADSL.TRTEDT; or 3. study treatment ended and AE is serious and ASTDT was within 90 days of ADSL.TRTEDT

Table 1. The Derivation Logic of TRTEMFL in single-phase studies

This logic assumes a single exposure window (TRTSDT to TRTEDT) and a single set of post-treatment risk windows (30/90 days). It cannot distinguish which phase an AE is attributed to, nor can it support reporting TEAEs separately by phase.

TWO APPROACHES OF ADAE TRTEMFL DESIGN

APPROACH 1: APERIOD ASSIGNMENT PLUS A SINGLE TRTEMFL PER RECORD

Approach 1 separates phase-specific TEAEs by assigning an APERIOD value to each AE record and deriving a single TRTEMFL flag per record. Assign each AE to one phase (APERIOD) and then apply an updated TRTEMFL logic. This enables phase-specific AE tables by filtering on the corresponding APERIOD, while retaining a single TEAE flag for overall summaries.

An example derivation logic in the ADAE specification is shown below in **Table 2**.

Variable Name	Variable Label	Define Derivation
APERIOD	Period	For non-treated subjects, leave missing. For treated subjects, let APERIOD=z if 1) there is treatment beyond study treatment period 01 (ADSL.TRT0zSDT is non-missing for z>=2); and 2) ASTDT >= ADSL.TR0zSDT: and 3) ASTDT< ADSL.TR0(z+1)SDT or ADSL.TR0(z+1)SDT is missing. Otherwise APERIOD=1.
TRTEMFL	Treatment Emergent Analysis Flag	Derive for treated subjects only. Set TRTEMFL = "Y", if ASTDT>=ADSL.TRTSDT and any of the following conditions is met: 1. study treatment was ongoing (ADSL.EOTSTT is not any of ('Completed', 'Discontinued')); or 2. study treatment ended (ADSL.EOTSTT is ('Completed' or 'Discontinued')) and AE is non-serious and ASTDT was within 30 days of max(ADSL.TR01EDT, ADSL.TR02EDT, ADSL.TR03EDT); or 3. study treatment ended and AE is serious and ASTDT was within 90 days of max(ADSL.TR01EDT, ADSL.TR02EDT, ADSL.TR03EDT)

Table 2. The Derivation Logic of APERIOD and TRTEMFL in multi-phase studies

This logic assumes separate exposure windows for each phase, defined from the phase start dates (TR01SDT, TR02SDT, TR03SDT) to the corresponding phase end dates (TR01EDT, TR02EDT, TR03EDT). For each AE, if ASTDT falls on or after a given phase start date, APERIOD is set to that phase number. TRTEMFL is then set to "Y" if study treatment is ongoing, or if treatment has ended and ASTDT falls on or before the maximum of the relevant phase end date plus 30 days for non-serious AEs or 90 days for serious AEs. Using APERIOD and TRTEMFL together allows AEs to be attributed to specific phases.

An example of TRTEMFL SAS derivation code is shown below in **Program 1**.

```
%** TRTEMFL for AE records**;
  if missing(trtsdt) then do;
    if astdt>=trtsdt and ((upcase(eotstt) not in ('COMPLETED', 'DISCONTINUED'))
      or (upcase(eotstt) in ('COMPLETED', 'DISCONTINUED') and
      (astdt<=max(tr01edt, tr02edt, tr03edt) +30 and upcase(aeser) ="N") or
      (astdt<=max(tr01edt, tr02edt, tr03edt) +90 and upcase(aeser) ="Y"))) then
      trtemfl="Y";
  end;
```

Program 1. A sample SAS code of TRTEMFL in multi-phase studies using approach 1

Table 3 below provides illustrative participant-level examples showing how phase start/end dates (TR0xSDT, TR0xEDT) drive APERIOD assignment and TRTEMFL derivation.

USUBJID	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TR03SDT	TR03EDT	EOTSTT

A01	2015-01-18	2015-01-18	2016-04-26	2016-04-26	.	.	Discontinued
A02	2015-08-16	2015-09-08	2015-11-20	2015-11-20	.	.	Discontinued
A02	2015-08-16	2015-09-08	2015-11-20	2015-11-20	.	.	Discontinued
B01	2015-12-10	2015-12-31	2016-02-28	2016-02-28	.	.	Discontinued
B02	2014-05-16	2014-06-27	2014-08-09	2014-08-09	2014-09-11	2014-12-04	Discontinued

ASTDT	AESER	APERIOD	TRTEMFL
2015-02-20	N	1	Y
2015-11-21	N	2	Y
2015-12-12	Y	2	Y
2016-02-11	N	1	Y
2014-09-01	Y	2	Y

Table 3. Examples of participant-level derivation of APERIOD and TRTEMFL

APPROACH 2: MULTIPLE PHASE-SPECIFIC TEAE FLAGS (TREM01FL/TREM02FL/TREM03FL) PLUS OVERALL TRTEMFL PER RECORD

Approach 2 retains the overall TRTEMFL while also deriving separate TEAE flags for each phase (e.g., TREM01FL, TREM02FL, TREM03FL). This allows TEAE incidence to be summarized per phase without relying solely on APERIOD filtering and enables the same AE to be considered treatment-emergent in more than one phase when appropriate.

An example derivation logic in the ADAE specification is shown below in **Table 4**.

Variable Name	Variable Label	Define Derivation
TRTEMFL	Treatment Emergent Analysis Flag	Set to Y if any of TREM01FL, TREM02FL, TREM03FL is "Y"
TREM01FL	Treatment Emergent Flag – Phase 1	Set to Y if ASTDT>=TR01SDT and TR01SDT is not missing and one of the following: 1) TR02SDT is not missing and ASTDT <TR02SDT; 2) TR02SDT is missing and TR03SDT is not missing, and ASTDT<TR03SDT; 3) TR02SDT is missing and TR03SDT is missing, and EOTSTT is missing or equal to "Ongoing", 4) TR02SDT is missing and TR03SDT is missing, and EOTSTT is not missing and not equal to " Ongoing", and ((ASTDT <= TR01EDT+30 and upcase(AESER)='N') or (ASTDT <= TR01EDT+90 and upcase(AESER)='Y'))
TREM02FL	Treatment Emergent Flag – Phase 2	Set to Y if ASTDT>=TR02SDT and TR02SDT is not missing and one of the following: 1) TR03SDT is not missing and ASTDT <TR03SDT; 2) TR03SDT is missing and EOTSTT is missing or equal to " Ongoing"; 3) TR03SDT is missing and EOTSTT is not missing and not equal to "Ongoing", and ((ASTDT <= TR02EDT+30 and upcase(AESER)='N') or (ASTDT <= TR02EDT+90 and upcase(AESER)='Y'))
TREM03FL	Treatment Emergent Flag – Phase 3	Set to Y if ASTDT>=TR03SDT and TR03SDT is not missing and one of the following: 1. EOTSTT is missing or equal to "Ongoing":

		2. EOTSTT is not missing and not equal to "Ongoing", and ((ASTDT <= TRTEDT+30 and upcase(AESER)='N') or (ASTDT <= TRTEDT+90 and upcase(AESER)='Y'))

Table 4. The Derivation Logic of TREM01FL, TREM02FL, TREM03FL and TRTEMFL in multi-phase studies

Similarly to Approach 1, this derivation logic assumes separate exposure windows for each phase, defined from the phase start dates (TR01SDT, TR02SDT, TR03SDT) to the corresponding phase end dates (TR01EDT, TR02EDT, TR03EDT).

The key difference is that the treatment-emergent flag is split into three phase-specific flags (TREM0xFL). Each phase's flag can follow its own derivation rules, providing greater flexibility. If a particular phase requires different TEAE logic (e.g., a different risk window), the change is applied only to the corresponding phase flag. This makes Approach 2 more adaptable than Approach 1 for studies with phase-specific safety considerations.

An example of TRTEMFL and TREM0xFL SAS derivation code is shown below in **Program 2**.

```
%** Derive TREM01FL, TREM02FL, TREM03FL, TRTEMFL**;
  if .<tr01sdt<=astdt and
    ((^missing(tr02sdt) and astdt<tr02sdt) or
    (missing(tr02sdt) and missing(tr03sdt) and upcase(eotstt) in ('', 'ONGOING') or
    (missing(tr02sdt) and ^missing(tr03sdt) and astdt<tr03sdt)) or
    ((missing(tr02sdt) and missing(tr03sdt) and upcase(eotstt) not in ('', 'ONGOING'))
     and ((astdt<=tr01edt+30 and upcase(aeser) = "N") or (astdt <=tr01edt+90 and
upcase(aeser) = 'Y'))))
  then trem01fl = 'Y';

  if .<tr02sdt<=astdt and
    ((^missing(tr03sdt) and astdt<tr03sdt) or
    (missing(tr03sdt) and upcase(eotstt) in ('', 'ONGOING')) or
    ((missing(tr03sdt) and upcase(eotstt) not in ('', 'ONGOING')) and
    ((astdt<=tr02edt+30 and upcase(aeser) = "N") or (astdt <=tr02edt+90 and upcase(aeser)
= 'Y'))))
    then trem02fl = 'Y';

  if .<tr03sdt<=astdt and
    ((upcase(eotstt) in ('', 'ONGOING')) or
    (upcase(eotstt) not in ('', 'ONGOING') and
    ((astdt<=trtedt+30 and upcase(aeser) = "N") or (astdt <=trtedt+90 and upcase(aeser) =
'Y'))))
    then trem03fl = 'Y';

if trem01fl = 'Y' or trem02fl = 'Y' or trem03fl = 'Y' then trtemfl ='Y';
```

Program 2. A sample SAS code of TREM0xFL in multi-phase studies using approach 2

Table 5 below provides illustrative participant-level examples showing how APERIOD and TRTEMFL are derived under Approach 1, and how phase-specific flags (TREM01FL, TREM02FL, TREM03FL) are derived under Approach 2.

USUBJID	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TR03SDT	TR03EDT	EOTSTT
A01	2015-01-18	2015-01-18	2016-04-26	2016-04-26	.	.	Discontinued
A02	2015-08-16	2015-09-08	2015-11-20	2015-11-20	.	.	Discontinued
A02	2015-08-16	2015-09-08	2015-11-20	2015-11-20	.	.	Discontinued
B01	2015-12-10	2015-12-31	2016-02-28	2016-02-28	.	.	Discontinued
B02	2014-05-16	2014-06-27	2014-08-09	2014-08-09	2014-09-11	2014-12-04	Discontinued

ASTDT	AESER	APERIOD	TRTEMFL	TREM01FL	TREM02FL	TREM03FL
2015-02-20	N	1	Y	Y		

2015-11-21	N	2	Y		Y	
2015-12-25	Y	2	Y		Y	
2016-02-11	N	1	Y	Y		
2014-09-01	Y	2	Y		Y	

Table 5. Examples of participant-level derivation of APERIOD, TRTEMFL, TREM01FL, TREM02FL, and TREM03FL

From the participant-level examples in **Table 5**, the combination of APERIOD and TRTEMFL in Approach 1 can mimic the effect of the phase-specific flags in Approach 2. For example, APERIOD = 1 and TRTEMFL = Y is functionally equivalent to TREM01FL = Y.

CONCLUSION

Multi-phase oncology trials require careful handling of treatment-emergent adverse events to preserve phase-specific safety signals. This paper demonstrated two practical ADAE implementation strategies using a neoadjuvant–surgery–adjuvant example, including detailed specification concepts and SAS code to support practical application.

Approach 1 keeps the ADAE structure simple and enables phase-specific tables by subsetting on APERIOD, while retaining a single TEAE flag for overall summaries.

Approach 2 gives greater flexibility to apply different risk windows or rules by phase and allows an AE to be considered treatment-emergent in multiple phases when appropriate.

Both approaches support TEAE summaries overall and by period, but only Approach B can flexibly assign TEAEs by different risk windows to multiple phases and handle phase-specific modification.

In practice, Approach 1 is suitable when a simpler dataset and straightforward subsetting are sufficient for phase-specific AE summaries, whereas Approach 2 is preferred when the SAP requires explicit per-phase indicators or more complex phase-specific TEAE derivation rules (Grewal, 2023).

The examples and code provided can serve as templates for implementing phase-aware TEAE derivations in future multi-phase trials, improving clarity, consistency, and interpretability of safety outputs.

REFERENCES

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