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Neoadjuvant and Adjuvant Oncology Clinical Trials and Considerations for Designing the Subject Level Analysis Dataset (ADSL)

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ABSTRACT

Current ADaM classes (ADSL, BDS, OCCDS) support most cases of analysis datasets involving various study designs. However, the implementation of ADaM standards in complex study designs such as neoadjuvant and adjuvant oncology clinical trials can be challenging. Because of different treatments in different periods, and possible period baseline definitions and treatment emergent flags, one must carefully design Subject Level Analysis Dataset (ADSL) and other analysis datasets with a comprehensive understanding of analysis needs with the right interpretation of ADaM standards. In this paper, we focus on ADSL design with an emphasis on using the right phasing, period, sub-period and treatment variables for the needs of a neoadjuvant and adjuvant study. Further ADSL metadata describes the derivations and data origins for the variables.

INTRODUCTION

Clinical trials with complex study designs require careful attention to study details and proper interpretation and implementation of CDISC data standards to support successful regulatory submissions. Analysis datasets are designed based on ADaM fundamental principles: analysis ready and traceability between analysis data and source data (SDTM data). Analysis datasets are accompanied by metadata. They must follow standard data and metadata structures including standard variables and naming conventions for datasets and implement standard ADaM rules. ADaM defined four classes of data structures including Subject Level Analysis Data (ADSL), Occurrence Data (OCCDS), Basic Data Structure (BDS), and ADaM Other. Usually ADSL presents subject level data at one record per subject, and the BDS structure is used for most of the safety datasets such as ADLB, ADVS, ADEG and most efficacy datasets while the OCCDS class is used for ADAE, ADCM, and ADMH. Among these ADaM structures, ADSL is usually the first data structure to be implemented in a study. ADSL is required for submissions and it is essential to design it with appropriate variables that define phase or period and treatment. In contrast to parallel studies, complex study designs such as neoadjuvant and adjuvant studies are divided into phases or periods and periods can be further divided into multiple sub-periods.

Neoadjuvant or preoperative therapy is a systemic therapy given before surgery to reduce tumor activity or tumor size, increasing the success of surgical resection. Whereas adjuvant or post-operative therapies are the systemic therapies administered after definitive surgery. Neoadjuvant treatment has become an important part of the treatment strategy and works well in reducing cancer severity preoperatively and can be supplemented with adjuvant therapy to further improve outcomes. Here we present a study design that involves Neoadjuvant and Adjuvant settings and the design of subject level dataset (ADSL). In this design, it is expected that analyses will be performed by phase, period and sub-period and so this paper presents the most comprehensive implementation of these ADaM standard concepts. If a study analysis does not require all these concepts, then only some subset of these variables can be utilized in practice.

TRIAL SUMMARY

This is an example of a randomized, double-blind study design, where the subjects received treatment in Neoadjuvant and Adjuvant Treatment Periods after completing screening. In the Neoadjuvant Treatment Period the subjects either received (Placebo + Standard of care (SOC)) or (Investigational drug (ID) + Standard of care (SOC)). A safety follow-up occurs after the treatment and before the surgery. Post-surgery recovery (Post-Surg Rec) is allowed before the treatment in the Adjuvant Treatment Period. In the Adjuvant Treatment Period the subjects either receives ID or Placebo followed by safety follow-up. After the safety follow-up, subjects are followed for serious AEs in the long term-follow up.

The subjects are evaluated for pathological complete response (PCR) at the time of surgery and Event-Free Survival (EFS).

TRIAL DESIGN DETAILS AND ADSL DESIGN CONSIDERATIONS

The example study design (see the schematic representation in **Figure 1**) includes a Screening phase (day -28 to day -1) followed by a Neoadjuvant Treatment Period for about 27 weeks, where patients receive treatment in the Neoadjuvant Treatment Period. There are two treatment groups in the Neoadjuvant Treatment Period: Treatment 1= Placebo + SOC and Treatment 2 = ID + SOC. ID or Placebo is administered every 3 weeks in addition to the standard regimen of SOC. This treatment is followed by a 30-day safety follow-up prior to surgery. The Adjuvant Treatment Period starts after 30 to 60 days of post-surgery recovery. The Adjuvant Treatment Period is expected to last for 21 weeks. There are two treatment groups for Adjuvant Treatment Period: Treatment 1= Placebo and Treatment 2= ID. In this study the subjects are not allowed to cross over, and subjects remain on either treatment 1 or treatment 2 in both periods as per the randomization assignment. The treatment in adjuvant period is followed by a 30-day safety follow-up and after the 30-day safety follow-up, a long-term follow-up continues at scheduled intervals for the next few years.

The study duration in the current trial can be divided into analysis timing elements such as phases, periods and subperiods described by a set of start and end timing variables. Here the study has three phases: Screening, Treatment and Follow-up. The Treatment phase has two analysis periods: Neoadjuvant Treatment and Adjuvant Treatment Periods. The Neoadjuvant Treatment Period is further divided into subperiods: Treatment in Period 01, SFU Period 01 and Post-Surg Rec Period 01. The Adjuvant Treatment Period is further divided into subperiods: Treatment in Period 02 and Safety Follow Up Period 02. The ADaM Implementation Guide defines a set of variables to define subject level timing elements in ADSL in addition to treatment variables.

Please see **Figure 1** which depicts the use of the subject level variables in the context of study design. Further, **Table 1**. ADSL Timing and Treatment Variables Used for Neoadjuvant and Adjuvant Oncology Clinical Trials provides general description of the variables

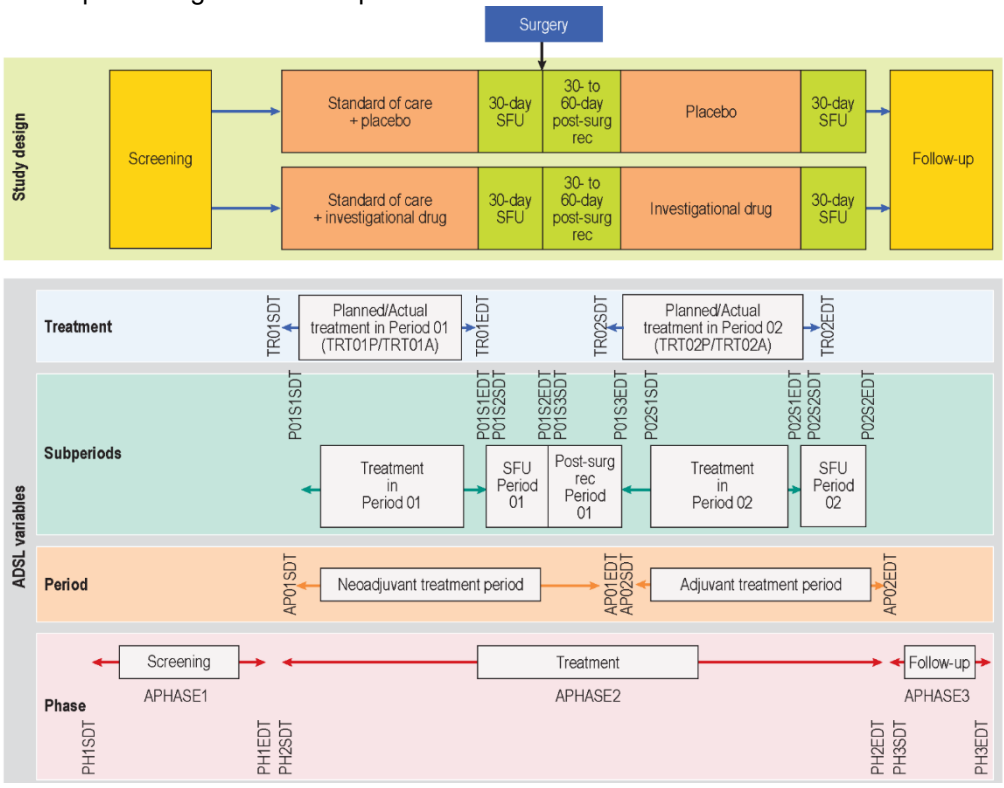

Figure 1. **The Design of a Neoadjuvant/Adjuvant study and the Use of ADSL Variables**

Classification	Variables	Description
PHASE	APHASEw, PHwSDT, PHwEDT	Phase is a higher-level categorization of timing within study and is independent of treatment period. APHASEw provides description of phase and the most common values include: Screening, Treatment and Follow-up etc. PHwSDT, PHwEDT provide the start date and end dates of APHASEw respectively
PERIOD	APxxSDT, APxxEDT	Period represents the analysis period within the study and APxxSDT, APxxEDT provide the start date and end date of the analysis period xx in the study.
SUBPERIOD	PxxSw, PxxSwSDT, PxxSwEDT	Subperiod within an analysis period. PxxSw provides the description of the subperiod. PxxSwSDT, PxxSwEDT provide the start date and end date of PxxSw respectively.
TREATMENT	TRTxxP, TRTxxPN, TRTxxA, TRTxxAN, TRxxSDT, TRxxEDT	TRTxxP, TRTxxPN, TRTxxA, TRTxxAN represents the planned or actual treatments for period xx. TRxxSDT and TRxxEDT represent dates of first exposure and last exposure to treatment in period xx respectively.

Table 1. ADSL Timing and Treatment Variables Used for Neoadjuvant and Adjuvant Oncology Clinical Trials

The letters “xx” (example: TRTxxP, APxxSDT) in variable names refer to analysis period where xx is two-digit number starting with 01. The lower-case letter w (example: PHwSDT, PxxSwSDT) in a variable name is an index for the w^{th} variable and is replaced with single integer. In short, “w” is an integer that indexes subperiods and phases while “xx” is reserved for use with periods and treatments.

DISCUSSION OF ADSL VARIABLES

PHASE

Study division that may or may not involve treatment of subjects, and usually used to represent higher level categorization of study. Examples of phase values include: Screening, Treatment and Follow-up. In the current example study, there are three phases: Screening, Treatment and Follow-up.

APHASEw

Provides descriptions of the different phases of study.
The values of APHASEw can be set as follows:

APHASE1= “Screening”,
APHASE2 = “Treatment”
APHASE3= “Follow-up”

PHwSDT, PHwEDT

Define the start and end of each phase.

PH1SDT/ PH1EDT: Start /End dates of Screening
PH2SDT/ PH2EDT: Start /End dates of Treatment
PH3SDT/ PH3EDT: Start /End dates of Follow-up

PERIOD

Analysis period within study and usually used to represent change of treatments within treatment phase. In the treatment phase, there are two analysis periods: Neoadjuvant Treatment and Adjuvant Treatment Periods, where subject received different treatments in two periods.

APxxSDT, APxxEDT

Define the start and end of each analysis treatment period, respectively.

AP01SDT/AP01EDT: Start /End dates of Neoadjuvant Treatment Period
AP02SDT/ AP02EDT: Start /End dates of Adjuvant Treatment Period

Please note xx in APxxSDT and APxxEDT is used to represent the concept of period. The value of “xx” is a zero-padded two-digit number (01-99) that represents a specific period within study. It is also a requirement that xx in APxxSDT and APxxEDT should correspond to xx of the treatment variables and if APxxSDT and APxxEDT are defined, then the treatment variables must exist: TRTxxP/TRTxxA. In the present study, TRT01P/ TRT01A represents treatment in Neoadjuvant Treatment Period (Analysis Period 01), and TRT02P/ TRT02A represents treatment in Adjuvant Treatment Period (Analysis Period 02). In this example, AP01SDT, is the start date of the Neoadjuvant Treatment Period (Analysis Period 01) and standard of care + placebo or standard of care + investigational drug are the treatments administered in this period. Therefore, TRT01P/ TRT01A and the related TR01SDT and TR01EDT are defined and represent the first and last exposure dates per subject to treatment in Analysis Period 01. Because of this one-to-one correspondence between analysis periods and treatment requirement, one should not use APxxSDT and APxxEDT to define either Screening or Follow Up as there is no treatment associated with these study intervals. Instead Screening and Follow Up must be defined as phases not periods.

SUBPERIOD

Periods can be further divided into multiple sub-periods.

PxxSw

Describes an analysis subperiod w within period xx. Note that the subperiod numbering starts over again with 1 for each new period.

Subperiods in Neoadjuvant Treatment Period (Period 01):

P01S1= “Treatment in Period 01”
P01S2= “SFU Period 01”
P01S3= “Post-Surg Rec Period 01”

Subperiods in Adjuvant Treatment Period (Period 02):

P02S1= “Treatment in Period 02”
P02S2= “SFU Period 02”

PxxSwSDT/PxxSwEDT

Define the start and end of each subperiod

Dates of subperiods within Neoadjuvant Period (Period 01):

P01S1SDT/ P01S1EDT: Start /End dates of Treatment in Period 01
P01S2SDT/ P01S2EDT: Start /End dates of SFU Period 01
P01S3SDT/ P01S3EDT: Start /End dates of Post-Surg Rec Period 01

Dates of subperiods within Adjuvant Treatment Period (Period 02):

P02S1SDT/ P02S1EDT: Start /End dates of Treatment in Period 02
P02S2SDT/ P02S2EDT: Start /End dates of SFU Period 02

TREATMENT

Represents planned/actual treatment for period xx and start and end dates of exposure in period xx.

TRTxxP, TRTxxPN

TRTxxP represents the planned treatment for period xx. TRTxxPN is a numeric version of TRTxxP.

TRT01P = “Standard of care + Placebo” or “Standard of care + Investigational drug”
TRT02P = “Placebo” or “Investigational drug”
TRT01PN = 1 for “Standard of care + Placebo” ; 2 for “Standard of care + Investigational drug”
TRT02PN = 1 for “Placebo”; 2 for “Investigational drug”

TRTxxA, TRTxxAN

TRTxxA represents the actual treatment for period xx. TRTxxAN is a numeric version of TRTxxA.

TRT01A = “Standard of care + Placebo” or “Standard of care + Investigational drug”
TRT02A = “Placebo” or “Investigational drug”
TRT01AN = 1 for “Standard of care + Placebo” ; 2 for “Standard of care + Investigational drug”
TRT02AN = 1 for “Placebo”; 2 for “Investigational drug”

TRxxSDT, TRxxEDT

TRxxSDT, TRxxEDT represent the dates of first exposure and last exposure in period xx.

TR01SDT/TR01EDT: Start /End dates of Treatment in Period 01
TR02SDT/TR02EDT: Start /End dates of Treatment in Period 02

Table 2 shows the sample data for ADSL for the subject-level variables across a series of tables. Note that each subject has defined boundaries for phases, periods, subperiods and treatments. The values of phases are captured in APHASE1, APHASE2, and APHASE3 variables and corresponding start and end date values are presented in PH1SDT/ PH1EDT, PH2SDT/ PH2EDT and PH3SDT/ PH3EDT.

The analysis period boundaries within the treatment phase are defined by AP01SDT, AP01EDT for the Neoadjuvant Treatment Period and AP02SDT, AP02EDT for the Adjuvant Treatment Period. Please note that period end date/time could be different from the treatment end date/time. In the data example, AP01EDT ≠ TR01EDT and AP02EDT ≠ TR02EDT. For example, USUBJID=101 has TR01EDT=2018-01-27, but AP01EDT = 2018-04-26 that is TR02SDT – 1 (TR02SDT=2018-04-27). Similarly, TR02EDT = 2018-09-21 but AP02EDT = 2018-10-22. The first analysis period starts with the start of the first dosing in

Neoadjuvant Treatment Period and ends prior to first dose in the Adjuvant Treatment Period. Similarly, the second analysis period starts with the first dosing in the Adjuvant Treatment Period and ends 30 days after last treatment dose so are no gaps in time between analysis periods. Events or findings that occur from TR01SDT through a day before TR02SDT are reported under the Neoadjuvant Treatment Period with corresponding: TRT01P/TRT01A with APERIOD=1. Similarly, events/findings that occur from first dose in Adjuvant Treatment Period until 30 days from last dose are reported under the Adjuvant Treatment Period with corresponding: TRT02P/TRT02A with APERIOD=2. Further, subperiod variables P01S1, P01S2 and P01S3 describe subdivisions in Neoadjuvant Treatment Period and P02S1 and P02S2 describe subdivisions in Adjuvant Treatment Period. The boundaries of each subdivision are presented with PxxSwDT/ PxxSwEDT variables.

USUBJID	TRT01P	TRT02P	TRT01A	TRT02A	TR01SDT	TR01EDT	TR02SDT	TR02EDT
101	Standard of care +Placebo	Placebo	Standard of care +Placebo	Placebo	2017-07-25	2018-01-27	2018-04-27	2018-09-21
102	Standard of care + Investigatio nal drug	Investigatio nal drug	Standard of care + Investigatio nal drug	Investigatio nal drug	2017-11-21	2018-05-29	2018-06-28	2018-11-22

AP01SDT	AP01EDT	AP02SDT	AP02EDT	P01S1	P01S2	P01S3	P02S1	P02S2
2017-07-25	2018-04-26	2018-04-27	2018-10-22	Treatment in Period 01	SFU Period 01	Post-Surg Rec Period 01	Treatment in Period 02	SFU Period 02
2017-11-21	2018-06-27	2018-06-28	2018-12-23	Treatment in Period 01	SFU Period 01	Post-Surg Rec Period 01	Treatment in Period 02	SFU Period 02

P01S1SDT	P01S1EDT	P01S2SDT	P01S2EDT	P01S3SDT	P01S3EDT	P02S1SDT	P02S1EDT	P02S2SDT	P02S2EDT
2017-07-25	2018-01-27	2018-01-28	2018-02-27	2018-02-28	2018-04-26	2018-04-27	2018-09-21	2018-09-22	2018-10-22
2017-11-21	2018-05-29	2018-05-30	2018-06-30	2018-06-31	2018-06-27	2018-06-31	2018-11-22	2018-11-23	2018-12-23

AHASE1	AHASE2	AHASE3	PH1SDT	PH1EDT	PH2SDT	PH2EDT	PH3SDT	PH3EDT
Screening	Treatment	Follow UP	2017-06-25	2017-07-24	2017-07-25	2018-09-21	2018-09-22	2020-09-22
Screening	Treatment	Follow UP	2017-10-21	2017-11-20	2017-11-21	2018-11-22	2018-11-23	2020-11-23

Table 2. Sample ADSL Data for Timing and Treatment Variables Used for Neoadjuvant and Adjuvant Oncology Clinical Trials

Please refer to metadata **Table 3** for derivations of these variables. The list of subject level variables for phase, period and subperiod that are provided here is comprehensive. Depending on the study analysis needs, one needs to determine if all or some of the variables for phase, period and subperiod variable are needed in the design of analysis datasets. For example: if a study only needs to summarize the data separately during screening, treatment and follow up then the use of phase variables would be appropriate, and period variables would not be necessary. On the other hand, if study only needs to

summarize the data based on treatment periods then use of period variables is appropriate and use of phase variables would not be necessary. If the study division represents a subset of an analysis period and required for analysis, then the use of subperiod variables would be appropriate.

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core	Notes
AHASE1	Description of Phase 1	Char		Perm	Screening
APHASE2	Description of Phase 2	Char		Perm	Treatment
APHASE3	Description of Phase 3	Char		Perm	Follow-Up
PH1SDT	Phase 1 Start Date	Num		Perm	Start of the Screening Phase. Date corresponding to -28 day (+1 day is the day of treatment start day in Neoadjuvant Treatment Period)
PH1EDT	Phase 1 End Date	Num		Perm	End of the Screening Phase. Date corresponding to -1 day
PH2SDT	Phase 2 Start Date	Num		Perm	Date corresponding to first administered dose (+1 day)
PH2EDT	Phase 2 End Date	Num		Perm	Date corresponding to last administered dose + 30 days
PH3SDT	Phase 3 Start Date	Num		Perm	Date corresponding to the last administered + 31 days
PH3EDT	Phase 3 End Date	Num		Perm	Date corresponding to study completion or lost to follow up or death, whichever is the earliest
AP01SDT	Period 01 Start Date	Num		Perm	Date corresponding to first administered dose in the Neoadjuvant Treatment Period
AP01EDT	Period 01 End Date	Num		Perm	Date corresponding to discontinuation from the Neoadjuvant Treatment Period or the date one day prior to the start of the Adjuvant Treatment Period.
AP02SDT	Period 02 Start Date	Num		Perm	Date corresponding to first dose in the Adjuvant Treatment Period.
AP02EDT	Period 02 End Date	Num		Perm	Date corresponding to discontinuation from the Adjuvant Treatment Period or the Adjuvant Treatment Period end date + 30 days.
P01S1	Description of Period 01 Subperiod 1	Char		Perm	Treatment in Period 01
P01S2	Description of Period 01 Subperiod 2	Char		Perm	SFU Period 01

P01S3	Description of Period 01 Subperiod 3	Char		Perm	Post-Surg Rec Period 01
P02S1	Description of Period 02 Subperiod 1	Char		Perm	Treatment in Period 02
P02S2	Description of Period 02 Subperiod 2	Char		Perm	SFU Period 02
P01S1SDT	Period 01 Subperiod 1 Start Date	Num		Perm	Date corresponding to first administered dose in the Neoadjuvant Treatment Period
P01S1EDT	Period 01 Subperiod 1 End Date	Num		Perm	Date corresponding to last administered dose in the Neoadjuvant Treatment Period
P01S2EDT	Period 01 Subperiod 2 End Date	Num		Perm	Date corresponding to a day prior to date of surgery
P01S3SDT	Period 01 Subperiod 3 Start Date	Num		Perm	Date corresponding to the surgery
P01S3EDT	Period 01 Subperiod 3 End Date	Num		Perm	Date corresponding to a day prior to the start of the treatment in the Adjuvant Treatment Period
P02S1SDT	Period 02 Subperiod 1 Start Date	Num		Perm	Date corresponding to first administered dose in the Adjuvant Treatment Period
P02S1EDT	Period 02 Subperiod 1 End Date	Num		Perm	Date Corresponding to last administered dose in Adjuvant Treatment Period
P02S2SDT	Period 02 Subperiod 2 Start Date	Num		Perm	Date corresponding to last administered dose in Adjuvant Treatment Period +1 day
P02S2EDT	Period 02 Subperiod 2 End Date	Num		Perm	Date corresponding to last administered dose in Adjuvant Treatment Period + 30 days
TRT01A	Actual Treatment for Period 01	Char		Req	Treatment administered in Neoadjuvant Treatment Period
TRT01P	Planned Treatment for Period 01	Char		Cond	Treatment planned for Neoadjuvant Treatment Period

TRT02A	Actual Treatment for Period 02	Char	Cond		Treatment administered in Adjuvant Treatment Period
TRT02P	Planned Treatment for Period 02	Char	Cond		Treatment planned for Adjuvant Treatment Period
TR01SDT	Date of First Exposure in Period 01	Num	Cond		Date corresponding to first administered dose in the Neoadjuvant Treatment Period
TR01EDT	Date of Last Exposure in Period 01	Num	Cond		Date corresponding to last administered dose in the Neoadjuvant Treatment Period
TR02SDT	Date of First Exposure in Period 02	Num	Cond		Date corresponding to first administered dose in the Adjuvant Treatment Period
TR02EDT	Date of Last Exposure in Period 02	Num	Cond		Date corresponding to last administered dose in the Adjuvant Treatment Period

Table 3. ADSL Metadata

CONCLUSION

In this paper, a comprehensive implementation of subject level phase, period, subperiod and treatment variables in the context of neoadjuvant/adjuvant studies has been illustrated. The example study has three phases: Screening, Treatment and Follow-up. The Treatment phase consists of two analysis periods: The Neoadjuvant Treatment Period and the Adjuvant Treatment Period. In Neoadjuvant Treatment Period, there are three subperiods: Treatment in Period 01, SFU Period 01 and Post-Surg Rec Period 01. Whereas, the Adjuvant Treatment Period has only two subperiods: Treatment in Period 02 and SFU Period 02. Depending on the study analysis needs, one needs to determine if all or some of the phase, period and subperiod variables are needed in the design of analysis datasets. After designing ADSL, BDS/OCCDS datasets would be designed with appropriate record level variables such as APHASE, APERIOD, ASPER (Subperiod within Period), TRTP, TRTA for analysis reporting.

REFERENCES

Please refer to https://www.cdisc.org for all CDISC documents discussed in this paper.

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