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Timing is Everything: Defining ADaM Period, Subperiod and Phase

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ABSTRACT

The CDISC Analysis Data Model Implementation Guide (ADaMIG) provides several timing variables for modeling clinical trial designs in analysis datasets. APHASE, APERIOD and ASPER can be used in conjunction with related treatment variables to meet a variety of analysis requirements, from single-period parallel studies to much more complicated situations involving multiple treatment periods and even different studies. The goal of this paper is to illustrate how some of these study designs may be handled in ADaM, and provide guidelines for selecting when to use the different timing variables that are available.

INTRODUCTION

Many clinical trials still follow a simple design consisting of a pre-treatment Screening epoch, a Treatment epoch during which a subject receives a single investigational product, and a Follow-up epoch during which safety information is collected. However, a growing number of trials are more complex. Open-label extensions of double-blind studies, cross-over designs, dose titrations and varieties of adaptive study designs pose a challenge to statistical programmers and biostatisticians who need to set up analysis datasets that account for the effect of the study design on the analysis requirements. Oncology studies with repeated treatment cycles can also be difficult to model.

The ADaMIG provides three standard variables, along with their corresponding numeric or character counterparts, which can be used in ADaM datasets to represent different types of epochs or time divisions within a study. These definitions are taken from Table 3.3.3.1 in the ADaMIG v1.1, which was the current version at the time this paper was written.

Variable Name	Variable Label	Variable Type	CDISC Notes
APHASE	Phase	Char	APHASE is a categorization of timing within a study, for example a higher-level categorization of APERIOD or an analysis epoch. For example, APHASE could describe spans of time for SCREENING, ON TREATMENT, and FOLLOW-UP.
APERIOD	Period	Num	APERIOD is a record-level timing variable that represents the analysis period within the study associated with the record for analysis purposes. The value of APERIOD (if populated) must be one of the xx values found in the ADSL TRTxxP variables.
ASPER	Subperiod within Period	Num	The numeric value characterizing a sublevel within APERIOD to which the record belongs. Within each APERIOD, the first ASPER is 1 (i.e., it resets to 1 when the APERIOD value changes).

Table 1. Primary ADaMIG Timing Variables

Let's take a closer look at these variables and how they can be used.

DIFFERENCE BETWEEN SDTM AND ADAM

The main reason for the creation of the primary timing variables in ADaM is the need for analyzing study results using different time divisions than what has been collected or modeled in SDTM using EPOCH. For example, the SAP may define visit or time division windowing in order to guarantee that observations

collected at a similar time interval from the start of the summary are summarized together, regardless of the CRF page on which they were recorded. Additionally, analysis time divisions may view the study epochs differently than how the data was collected. ADaM timing variables should reflect the analysis requirements, and not simply copy values from SDTM epochs or visits.

PRIMARY TIMING VARIABLES

As indicated in the ADaMIG, APHASE represents the analysis phase associated with the record, which is a study time division that may or may not involve the administration of an investigational product. Examples of APHASE values are Screening, Treatment and Follow-up, but there is no controlled terminology associated with APHASE, so anything that reflects the wording displayed on the tables is acceptable.

APERIOD represents the analysis period associated with the record. As noted in the ADaMIG, the value of APERIOD must correspond to one of the analysis periods defined by the TRTxxP variables in ADSL. APERIOD contains a numeric value ranging from 1 to 99.

ASPER denotes a subperiod within an analysis period. It also contains a numeric value; the first subperiod within a period is always assigned a value of 1, and the counter starts again for any subperiods defined within subsequent analysis periods.

The first step in deciding which of these variables to use is to determine whether there is a change in analysis study treatment when a subject moves between study epochs. If there is no study treatment involved, or the treatment assignment does not change when the next study epoch begins, then APHASE should generally be used to represent the study division needed for analysis. If the subject moves from one treatment to another when the study division changes, then APERIOD should generally be used, especially if the treatment is represented by one of the TRTxxP variables in ADSL. Finally, if the study division represents a subset of an analysis period, then ASPER is generally appropriate.

Figure 1 represents a flowchart that models these decision rules:

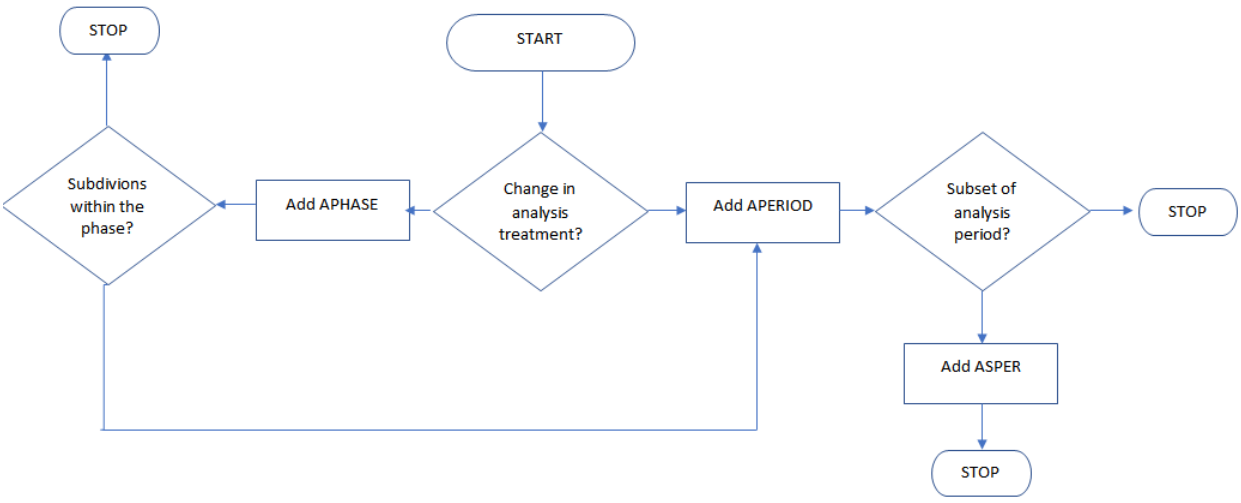

Figure 1. Timing Variable Decision Flowchart

Let's apply this process for modeling some different types of study designs.

SINGLE-PERIOD PARALLEL-DESIGN STUDY

A single-period parallel-design study is one of the simplest study designs, and is still widely used. In this scenario, subjects are assigned to a single treatment arm, and receive one or more doses of a single investigational product during the course of the study. A schematic of the study design might look something like this:

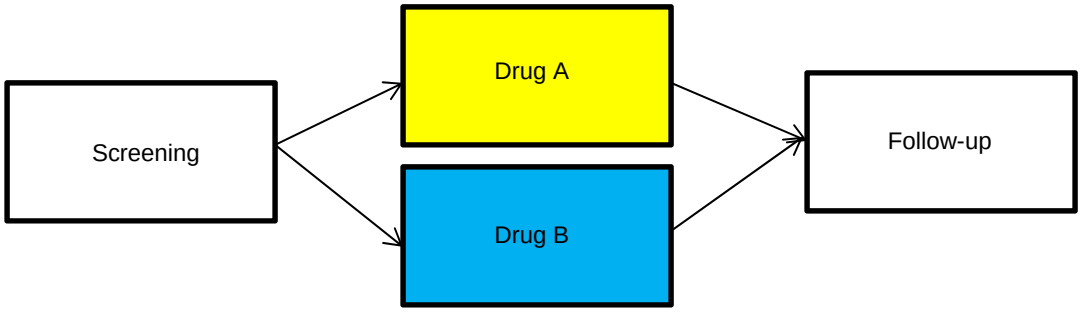

Figure 2. Single-Period Parallel Design Example

The main question to answer here is whether we will need to summarize data separately during the Screening, Treatment (Drug A/Drug B) and Follow-up epochs. If so, since there is no change in treatment, other than the subject completing treatment before starting the Follow-up epoch, this design can be modeled by using APHASE, set to values of “Screening”, “Treatment” and “Follow-up”, as appropriate, on each of the records in the BDS. If we only need to summarize data during the Treatment epoch, then none of these variables are needed, and TRTP, if used, will take on the values of ADSL.TRT01P.

CROSSOVER DESIGN STUDY

In a crossover study, subjects are assigned to two or more different study treatments during the course of the study. There also may be washout epochs, or gaps, between the administration of each treatment.

A schematic of a crossover study with 2 treatment periods might look like this:

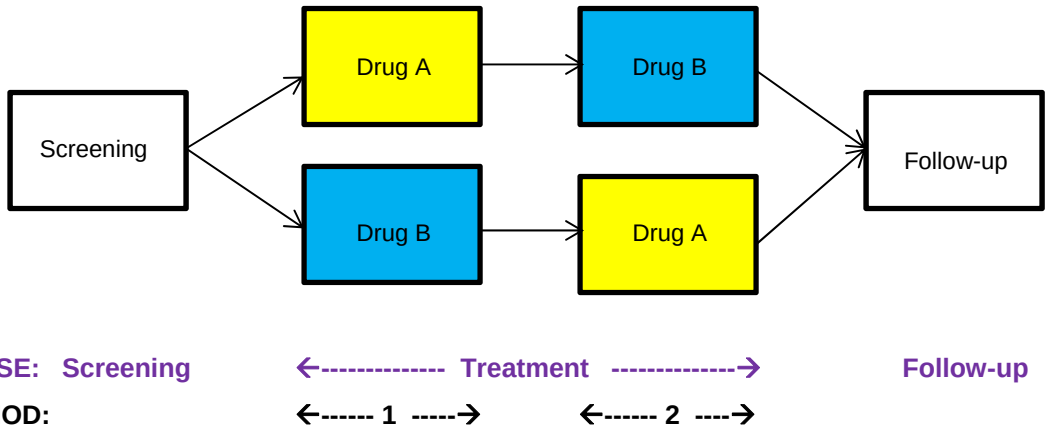

Figure 3. Crossover Design Example

Since the study treatment changes during each of the crossover epochs, this design can be modeled by assigning each of the treatment epochs to a different analysis period (APERIOD). Note that APERIOD is numeric. If desired, we could also create APERIODC to contain a character description of APERIOD; there must be a 1-1 relationship between the values of APERIOD and APERIODC within a dataset when both are populated. However, APERIOD is considered to be the primary variable, so APERIODC may only be used when APERIOD is also present.

Note that again, we only need to create APHASE when we need to summarize Screening, Treatment and Follow-up records separately. If we are only summarizing Treatment records, then simply using APERIOD will suffice.

However, what if there are washout segments, or gaps, between the crossover epochs? Again, we have to determine whether values occurring during the washout segments should be summarized as part of the preceding treatment period, or whether they are to be either handled separately, or excluded altogether. If they are to be included with the previous treatment period, or excluded, then the model proposed above will handle them correctly. However, if we need to summarize them separately, we may consider creating active treatment and washout subperiods within the treatment periods. Such a model might look something like this:

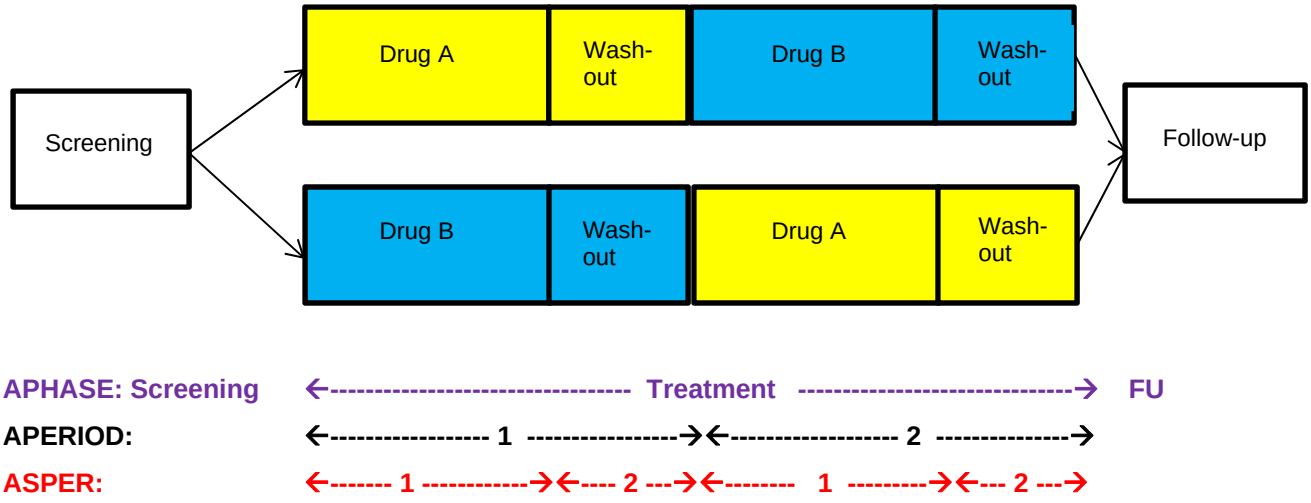

Figure 4. Crossover Design with Subperiods

In this case, there are no gaps between the treatment periods. TRTP would be assigned the value of TRT01P for records occurring during Analysis Period 1, and the value of TRT02P for records occurring during Analysis Period 2. Note also that the subperiod numbering starts over again with 1 for each new period.

PHASE VERSUS PERIOD

Sometimes, it's harder to determine changes in study treatment, or whether to model a particular study epoch using APHASE or APERIOD. Let's look at the following design, taken from an oncology study. In this case, study treatment was administered via injection at various intervals. Subjects were randomized to one of 2 possible treatment arms, and remained on that arm for the duration of the study. If a subject experienced disease progression, they were allowed to receive additional anticancer therapy, which was not considered as study treatment for analysis purposes. If they subsequently experienced a second disease progression, they were discontinued from the study. The efficacy analysis summarized responses from the beginning of the study until the start of the first additional anticancer therapy, and then from there until the end of the study.

A schematic of the study design looked something like this:

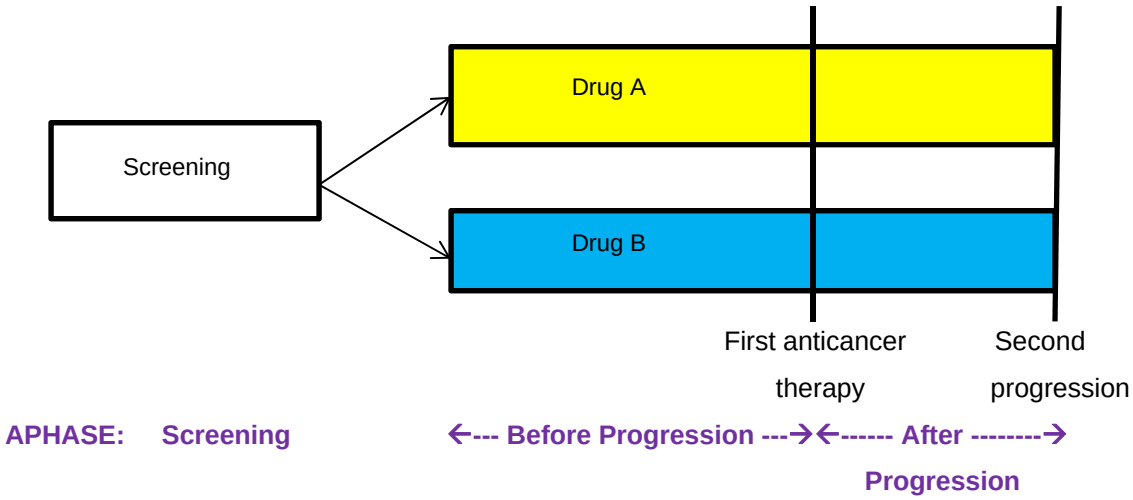

Figure 5. Multi-Phase Study Design Example

Since the study treatment was not changed after the start of the first anticancer therapy, we decided to use APHASE, instead of APERIOD, to model the study segments. TRT01P was defined in ADSL, and used to populate TRTP on the BDS dataset records.

PHASES, PERIODS AND SUBPERIODS - OH MY!

Recently, we encountered a study that consisted of a Screening epoch, followed by a Double-Blind Treatment epoch, and finally an Open-Label Extension (OLE) epoch. The Double-Blind Treatment epoch was further subdivided into Titration, Maintenance and Taper segments, before subjects moved on to the Open-Label Extension. Data needed to be summarized separately for the Double-Blind Treatment and Open-Label Extension epochs, and also for the Titration, Maintenance and Taper segments. However, subjects were summarized within a single treatment group for all of the Double-Blind epoch, and within a single treatment group for all of the Open-Label epoch.

A schematic of the study design looked something like this:

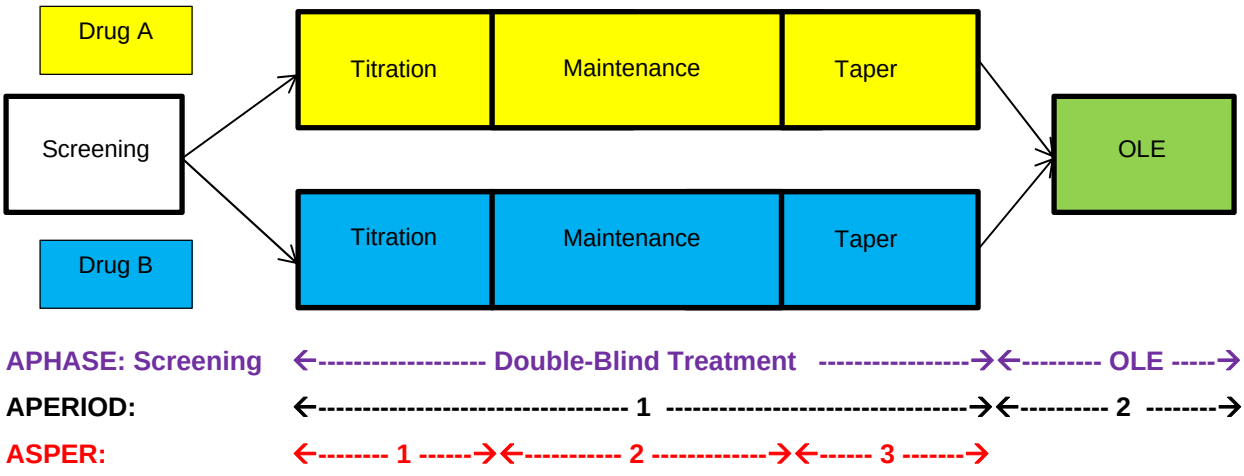

Figure 6. Example of Phase, Period and Subperiod

The key point at which study treatment changed for analysis purposes was at the end of Double-Blind Treatment epoch. Thus, we decided to model the Double-Blind Treatment and Open-Label Extension epochs as analysis periods, using TRT01P and TRT02P to populate TRTP in the BDS datasets. The Titration, Maintenance and Taper segments were assigned to subperiods, since subjects were summarized in the same treatment group for all 3 segments. APHASE was used to handle the tables summarizing Screening, Double-Blind and Open-Label values separately.

ONCOLOGY TREATMENT CYCLES

Another type of dosing strategy occurs in many oncology studies, where subjects receive one or more doses of study medication for a set period of time, followed by a rest period; this on-again, off-again dosing pattern is repeated until the subject achieves a response, or experiences disease progression. A common example of this is a 28-day treatment cycle, where a subject receives medication daily for 21 days, and then goes for 7 days with no medication, before starting back up again.

Such a study design is extremely difficult to model with analysis period, subperiod and/or phase due to the long-term nature of these studies and potentially large number of treatment cycles. The ADaM oncology sub-team is currently developing a methodology for handling this type of dosing schedule. One possible approach for now is the use of the variable ACYCLE (Analysis Cycle) to indicate the cycle in which a visit or event occurs.

The schematic of an oncology with treatment cycles may look something like this, as shown in the SDTMIG v3.2:

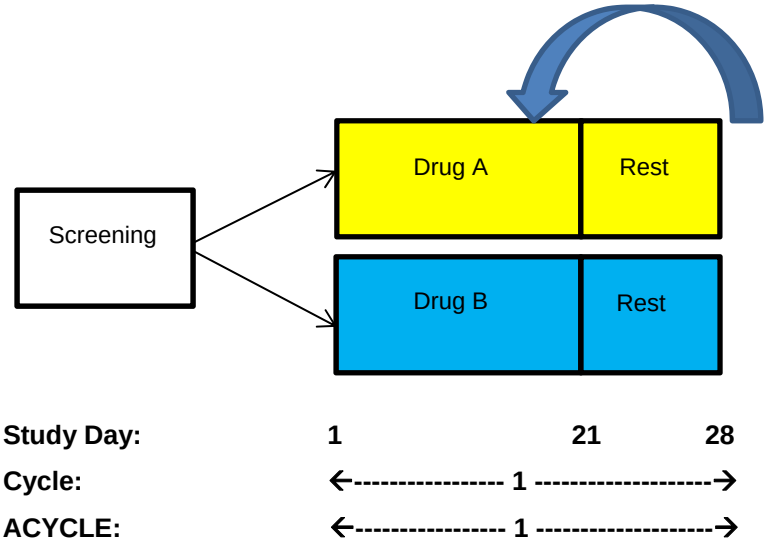

Figure 7. Example of Oncology Treatment Cycles

CONCLUSION

The ADaMIG defines the variables APERIOD, ASPER and APHASE, which can be used for modeling different types of study designs, based on analysis requirements. The flowchart shown earlier in this paper may be helpful in determining which variables to use for a given study, depending on the design and analysis needs. The first question to answer is whether there is a change in analysis treatment from one study segment to the next. The response to that question determines where to proceed from there, and should help guide you to the correct choice of variables to use in modeling your study design.

REFERENCES

CDISC ADaM Implementation Guide v1.1 Release Package. Accessed March 3, 2019. https://www.cdisc.org/standards/foundational/adam.

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CONTACT INFORMATION

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