The ADaM Basic Data Structure for Time-to-Event Analyses

Prepared by the

CDISC Analysis Data Model (ADaM) Team

[redacted]

Notes to Readers

- This Analysis model uses the principles, structures and standards described in the CDISC Analysis Data Model: Version 2.1 and Implementation Guide v1.0 documents

Revision History

Date	Version	Description
May 8, 2012	1.0	Final

Note: Please see APPENDIX A for Representations and Warranties; Limitations of Liability, and Disclaimers.

Contents

1. Introduction 3
2. Common Statistical Analysis Methods Supported by ADaM TTE 4
3. Points to Consider in this Document 5
4. ADaM Metadata 6
5. Example 1: Single Endpoint with Binary Values for Censoring 10
5.1 Examples of Time-to-Event Analysis Result Displays 11
5.2 Analysis Results Metadata 13
6. Example 2: Single Endpoint with Multiple Values for Censoring 17
7. Example 3: Composite Endpoints 18
7.1 Progression Free Survival (PFS) Example 18
7.2 Time to Hepatitis B e Antigen Seroconversion Example 21
8. References 30
APPENDIX A. Representations and Warranties; Limitations of Liability, and Disclaimers 31

1. Introduction

Survival analysis is a class of statistical methods for studying the occurrence and timing of events. Describing the timeline over which key disease-related events appear is an important feature of disease characterization. In many clinical studies, an outcome of interest is the time to an event. In these studies, the basis of analysis is the time from a defined starting point (e.g., the date of randomization or of an intervention) to the time of occurrence of the event of interest. Such events may be adverse, such as death or recurrence of a tumor; or positive, such as therapeutic response or discharge from hospital. Regardless of the nature of the event, survival analysis is the name that is most widely used and recognized.

The distinguishing feature of survival data is that at the end of the observation period, the event of interest may not have occurred for all subjects. For these subjects, the only information available is that the event did not occur within the duration of study. Therefore, the time to event for these subjects is said to be censored (i.e., right-censored). Subjects can be censored for other reasons. For example, if a subject prematurely discontinues from the study or experiences another type of event that prevents future assessment of the event of interest, the time to event for that subject would be censored at the time of discontinuation or occurrence of the specific event. Therefore, one can specify any set of values to indicate that a subject's time to event has been censored and for what reason. This ability is convenient when one has data in which a variable indicating a subject's status can have several values that represent different reasons for censoring.

The purpose of this document is to present the ADaM Basic Data Structure (BDS) for time-to-event (TTE) analyses. The TTE analyses can be applied to a broad range of clinical outcomes. The event might be single, composite, recurrent, or one of multiple potential events. The vast majority of TTE analyses are readily supported by analysis datasets that follow the ADaM BDS. However, because recurrent event analyses require more than one analysis variable as a dependent variable, an analysis dataset for recurrent events is not compliant with the ADaM BDS. Therefore, only the following TTE dataset examples that are compliant with the ADaM BDS are presented in this document:

1. Single event with binary values for censoring variable
2. Single event with multiple values for censoring variable
3. Composite event

The ADaM Implementation Guide (ADaM IG) [2] defines a few time-to-event specific variables. Additional ADaM variables are defined within this document to support a specific TTE analysis (refer to Section 4). The ADaM TTE analysis dataset implementation is therefore the ADaM BDS plus additional TTE variables. In this document, the ADaM TTE analysis dataset is simply referred to as an ADTTE dataset. It should be noted that this does not imply a required naming convention. The time-to-event analysis dataset should be named following the ADaM standard naming convention, as described in the Analysis Data Model, Version 2.1 (referred to in this document as the ADaM v2.1) [1].

Examples of increasing complexity using the event types described above are provided in this implementation document and demonstrate that the ADaM BDS is quite flexible. It can handle a number of outcomes and support a broad array of potential analyses. It is generally recommended that time-to-event data be stored separately from non-time-to-event data even if they both fit within the ADaM BDS. It is Sponsor's decision to determine how many ADTTE datasets would be adequate for a given study. There is no need to cram all time-to-event variables in one ADTTE dataset at the expense of clarity.

2. Common Statistical Analysis Methods Supported by ADaM TTE

Survival analysis is based on longitudinal data describing the occurrence of events. An event can be qualitative (i.e., transition from one discrete state to another) or can be a quantitative change (e.g., the change is large and sudden compared to the usual variation over time). The ADaM TTE analysis dataset structure is designed to support commonly employed time-to-event analysis methods, such as the Kaplan-Meier product moment curve, actuarial or cohort life table analyses, log-rank tests (stratified or trend), Wilcoxon tests, and Cox proportional hazards models.

The ADaM TTE analysis dataset structure can be used for a broad array of descriptive and inferential tabular and graphical data presentations, as well as diagnostic checks on appropriateness of the methods utilized. Illustrations of some graphical representations are included in this document as examples. The ADaM TTE analysis dataset structure also supports hypothesis tests and formal modeling with attendant assumption checks and diagnostics. However, illustrations of these operations are not presented in this document.

3. Points to Consider in this Document

In reviewing the metadata and examples in this document, the following points should be considered:

- **Ordering of variables:** Within this document, no specific ordering of variables within the illustrated datasets is applied. The ADaM v2.1 [1] states that ideally the ordering of the variables in the analysis dataset follows a logical ordering (not simply alphabetic). The ADaM v2.1 [1] does not provide a specific recommendation for the ordering of the variables. Within this document, the author of each example applied his or her own logical ordering.

- **Identification of source dataset:** When identifying the source dataset for a variable, the immediate predecessor is used, as described in the ADaM v2.1 [1]. For example, in ADSL the source is identified as DM.SUBJID in the analysis variable metadata. When AVAL used in an ADTTE dataset come from the lab collection date, the source is identified as LB.LBDTC.

- **Analysis-ready:** ADTTE should be "analysis-ready," meaning it should contain all of the variables needed for the specific analysis, so that the analysis can be replicated by performing the actual statistical test without first having to manipulate data. Analysis-ready does not mean that a formatted display can be generated in a single statistical procedure. In addition to required variables such as subject identifiers and treatment variables, the critical variables included in the analysis dataset will depend on the specific nature of the disease or indication, the analyses planned in the protocol, and the Statistical Analysis Plan.

- **Examples are for illustration only:** Note that the examples in this document are only intended as illustrations and should not be viewed as a statement of the standards themselves. In addition, the examples are intended to illustrate content and not appearance; it is understood that there are many different ways that data and results can be displayed. This document does not cover display formats.

- **Numbering scheme of the example in-text figure and tables in section 5.1:** Note that the in-text figure and table output numbers in Section 5.1 (Examples of Time-to-Event Analysis Display) were based on the International Conference of Harmonization E3 [5] guidance, rather than based on the section number as in the remaining sections. These figure and table numbers are later referenced in the subsequent Section 5.2 (Analysis Results Metadata) to show traceability from a result used in a statistical display to the data in the analysis datasets.

- **Display of metadata for illustration of content only:** Though the metadata elements have been defined in the ADaM v2.1 [1], how the metadata are displayed is a function of the mechanism used to display the content. The presentation formats used in this document are for the purposes of contents illustration only, and are not intended to imply any type of display standard or requirement.

- **Examples not meant to be all inclusive regarding variables:** The examples describe some of the key variables and records that would be included in the dataset. They are not intended to illustrate every possible variable that might be included in the analysis dataset; for example core variables required for subgroup analyses are not included in all the illustrations.

- **No endorsement of vendors or products:** In an effort to provide illustrations of the ADaM concepts, examples are provided that refer to specific programming languages. As with other ADaM documents, references to specific vendor products are examples only and therefore should not be interpreted as an endorsement of these vendors or products.

4. ADaM Metadata

Table 4.1 shows how a typical Analysis Dataset Metadata is specified. Note that the ADaM TTE data structure adheres to the ADaM BDS, as is denoted in the "Class of Dataset" field.

Table 4.1 Example of ADTTE Dataset Metadata[1]

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADTTE	Data for the Time to Event Analyses	adtte.xpt	one record per subject per parameter	USUBJID, PARAMCD	BDS	ADTTE.SAS, SAP Section 10.1

Table 4.2 describes variables that one would commonly find in an ADaM TTE analysis dataset. The two rightmost columns ("Core" and "CDISC Notes") provide information about the variables to assist users in preparing their datasets. These columns are not meant to be metadata included in the define.xml. The "Core" column describes whether a variable is required (Req), conditionally required (Cond), or permissible (Perm). The "CDISC Notes" column provides more information about the variable relevant to the ADaM TTE analysis dataset. In addition, the "Type" column is being used to define whether the variable is character (Char) or numeric value (Num). More specific information will be provided in metadata (e.g., text, integer, or float).

Table 4.2 Time-to-Event Variables

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
STUDYID	Study Identifier	Char		Req	Must be identical to the ADSL variable.
USUBJID	Unique Subject Identifier	Char		Req	Must be identical to the ADSL variable.
ASEQ	Analysis Sequence Number	Num		Perm	Sequence number given to ensure uniqueness of subject record within the analysis dataset. As long as values are unique within a dataset, any valid number can be used for ASEQ. The use of this variable will be addressed in detail in the next version of ADaM IG.
TRTP	Planned Treatment	Char		Req	TRTP is a record-level identifier that represents the planned treatment attributed to a record for analysis purposes.

[1] The display presentation of the metadata should be determined between the sponsor and the recipient. The example presented here is only intended to illustrate content and not appearance.

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
TRTPN	Planned Treatment (N)	Num		Perm	The numeric code for TRTP. One-to-one map to TRTP.
TRTA	Actual Treatment	Char		Cond	TRTA is a record-level identifier that represents the actual treatment attributed to a record for analysis purposes.
TRTAN	Actual Treatment (N)	Num		Perm	The numeric code for TRTA. One-to-one map to TRTA.
TRTxxP	Planned Treatment for Period xx	Char		Cond	Subject-level identifier that represents the planned treatment for period xx. Must be identical to the ADSL variable. The letter "xx" in the variable name refer to a specific period where "xx" is replaced with a zero-padded two-digit integer (i.e., 01 – 99).
TRTxxPN	Planned Treatment for Period xx (N)	Num		Perm	The numeric code variable for TRTxxP. One-to-one map to TRTxxP. If included in ADSL, must be identical to the ADSL variable.
TRTxxA	Actual Treatment for Period xx	Char		Cond	Subject-level identifier that represents the actual treatment for period xx. If included in ADSL, must be identical to the ADSL variable.
TRTxxAN	Actual Treatment for Period xx (N)	Num		Perm	The numeric code variable for TRTxxA. One-to-one map to TRTxxA. If included in ADSL, must be identical to the ADSL variable.
PARAM	Parameter	Char	*	Req	The description of the analysis parameter. Examples include: "Time to Death (days)", "Time to First Hospitalization Through Day 168 (days)", "Time to Progression Free Survival (days)", and "Time to Hepatitis B Seroconversion (days)". PARAM should be sufficient to describe clear contents of AVAL, including the unit of the measurement, if applicable. PARAM may be longer than 40 characters in length (200-character limit).
PARAMCD	Parameter Code	Char	*	Req	The short name of the analysis parameter in PARAM. Values of PARAMCD should follow SAS 5 variable naming conventions (8 characters or less; starts with letter; contains only letters and digits). There must be a one-to-one mapping with PARAM. Examples include DEATH, PFS, and T2SERO.
AVAL	Analysis Value	Num		Req	AVAL is the elapsed time to the event of interest from the origin. For example, if AVAL is measured in days, AVAL would be ADT – STARTDT or ADT – STARTDT + 1.

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
STARTDT	Time to Event Origin Date for Subject	Num		Perm	The original date of risk for the time-to-event analysis. This is generally the time at which a subject is first at risk for the event of interest evaluation (as defined in the Protocol or Statistical Analysis Plan). For example, this may be the randomization date or the date of first study therapy exposure.
STARTDTM	Time to Event Origin Date/Time	Num		Perm	The date/time associated with STARTDT in numeric format.
STARTDTF	Origin Date Imputation Flag	Char	(DATEFL)	Cond	The level of imputation of the origin date. See General Timing Variable Convention #6 in the ADaM IG [2].
STARTTMF	Origin Time Imputation Flag	Char	(TIMEFL)	Cond	The level of imputation of the origin time. See General Timing Variable Convention #7 in the ADaM IG [2].
ADT	Analysis Date	Num		Perm	Analysis date of event or censoring associated with AVAL in numeric format.
ADTM	Analysis Date/Time	Num		Perm	Analysis date/time of event or censoring associated with AVAL in numeric format.
ADTF	Analysis Date Imputation Flag	Char	(DATEFL)	Cond	The level of imputation of ADT based on the source SDTM DTC variable. See General Timing Variable Convention #6 in the ADaM IG [2].
ATMF	Analysis Time Imputation Flag	Char	(TIMEFL)	Cond	The level of imputation of ATM based on the source SDTM DTC variable. See General Timing Variable Convention #7 in the ADaM IG [2].
AVISIT	Analysis Visit	Char	*	Cond	Analysis visit where event or censoring occurred. AVISIT may contain the visit names as observed (i.e., from SDTM VISIT), derived visit names, or conceptual description (e.g., endpoint).
CNSR	Censor	Num	*	Cond	CNSR is a required variable for a time-to-event analysis dataset, though it is a conditionally required variable with respect to the ADaM BDS. For example, CNSR = 0 for event and CNSR > 0 for censored records.
SRCDOM	Source Data	Char		Perm	The name of the SDTM domain (or dataset) or analysis dataset that relates to the analysis variable (e.g., AVAL). Allowing SRCDOM to be not only SDTM, but also ADaM dataset will be addressed in the next version of ADaM IG.

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
SRCVAR	Source Variable	Char		Perm	The name of the column (in the domain or dataset identified by SRCDOM) that relates to the analysis variable. In the event that SRCDOM is a SUPPQUAL domain, then SRCVAR will be populated with the value of QNAM.
SRCSEQ	Source Sequence Number	Num		Perm	The sequence number --SEQ or ASEQ of the row (in the domain or dataset identified by SRCDOM) that relates to the analysis variable.
EVNTDESC	Event or Censoring Description	Char		Perm	Describe the event of interest or an event that warrants censoring. Values for EVNTDESC will be defined in the metadata as sponsor-defined controlled terminology (See Section 7.1).
CNSDTDSC	Censor Date Description	Char		Perm	Describe the circumstance represented by the censoring date if different from the event date that warrants censoring.

* indicates a user defined code list exists.

Note: Values in parenthesis are the names of CDISC Controlled Terminology codelists.

5. Example 1: Single Endpoint with Binary Values for Censoring

The first TTE example is for time to death. It incorporates a binary censoring variable that has a value of 0 for subjects who died and a value of 1 for subjects who were censored, either because they were lost to follow-up or completed the study assessment without experiencing the event (death).

In this example, STARTDT is used to indicate the time origin of the time-to-event calculation. This can be the numeric date version of RFSTDTC if the time origin is the same as the subject reference start date provided in the DM domain. The variable EVNTDESC describes either the event of interest or the reason for censoring. This variable should contain text clarifying what the event of interest is or the reasons for censoring for those subjects who did not have the event. These values should be included in the metadata as sponsor-defined controlled terminology. The rationale and use of EVNTDESC will be further explained in Section 7, which presents an example of a time-to-event analysis with a single endpoint and multiple values for censoring.

Table 5.1 Time-to-Event Data Structure for a Single Endpoint with a Binary Value for Censoring Variable

Row	USUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC
1	1001-0001	Time to Death (days)	DEATH	15	2007-01-01	2007-01-15	0	DEATH
2	1001-0002	Time to Death (days)	DEATH	168	2007-01-03	2007-06-19	1	COMPLETED THE STUDY
3	1001-0003	Time to Death (days)	DEATH	120	2007-01-03	2007-05-02	1	LOST TO FOLLOW-UP
4	1001-0004	Time to Death (days)	DEATH	168	2007-01-10	2007-06-26	1	COMPLETED THE STUDY
5	1001-1005	Time to Death (days)	DEATH	30	2007-01-11	2007-02-09	0	DEATH
6	1001-1006	Time to Death (days)	DEATH	4	2007-01-17	2007-01-20	1	ADVERSE EVENT

5.1 Examples of Time-to-Event Analysis Result Displays

This section presents analysis results for illustration purposes. Output presented in this section is not meant to imply any standard analysis presentation format or analysis method for all time-to-event data.

Figure 5.1.1 and Tables 5.1.2 and 5.1.3 contain example displays of analysis results for time-to-event for a single endpoint. The survival analysis results are presented in:

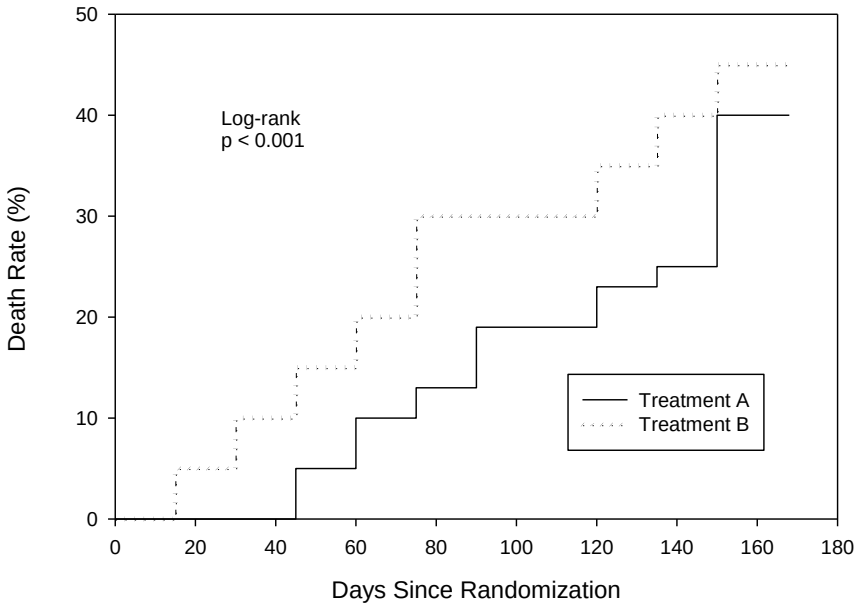
- a Kaplan-Meier plot
- a summary table of Kaplan-Meier estimates and inferential statistics
- a summary table of the hazard ratio along with inferential statistics

Figure 5.1.1 Example of Kaplan-Meier Plot Display[2]

Figure 12.3.1.1 (numbered based on ICH E3 [5])

Kaplan-Meier Plot

Time to Death (Days)



No. of Subjects at Risk									
Treat A 500	500	430	420	410	380	380	330	240	230
Treat B 500	440	420	410	320	310	300	290	230	230

KM Estimate	75%	50% (Median)	25%
Treat A	.	.	130
Treat B	.	.	69

[2] The style of the display of the results of an analysis will be determined by the sponsor. The examples presented here are intended to illustrate content and not appearance.

Table 5.1.2 Example of Time-to-Event Analysis Results Display[3]

Table 14.2.1.1 (numbered based on ICH E3 [5])

Time to Death Through Day 168 by Treatment Group

Analysis Population: Intent-to-Treat

Time to Death (days)	Treatment A (n=xxx)	Treatment B (n=xxx)	P value	Method
Median Time (95% CI)[a]	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	0.xxx	Log-rank Test
Event Rate (%) at Day 168 (95% CI) [a]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	0.xxx	Cox Regression Model[b]
N (%) Censored	xx (xx.x%)	xx (xx.x%)		

Note: Time to death is calculated as: date of death – date of randomization. For subjects who did not die on or prior to Week 24 (Day 168), they are censored at Day 168.

[a] Based on the Kaplan-Meier estimates

[b] The Cox regression model includes treatment group, age, and sex as covariates.

Table 5.1.3 Example of Time-to-Event Cox Regression Analysis Results Display[4]

Table 14.2.1.2 (numbered based on ICH E3 [5])

Time to Death Through Day 168 – Cox Regression Model

Analysis Population: Intent-to-Treat

Covariate	Hazard Ratio (95% CI)	P value
Treatment Group (Treatment B to Treatment A)	x.xx (x.xx, x.xx)	0.xxx
Age (< 65 to ≥ 65 years old)	x.xx (x.xx, x.xx)	0.xxx
Sex (Female to Male)	x.xx (x.xx, x.xx)	0.xxx

[3] The style of the display of the results of an analysis will be determined by the sponsor. The examples presented here are intended to illustrate content and not appearance.

[4] The style of the display of the results of an analysis will be determined by the sponsor. The examples presented here are intended to illustrate content and not appearance.

5.2 Analysis Results Metadata

Analysis results metadata provide traceability from a result used in a statistical display to the data in the analysis datasets. Analysis results metadata are not required. However, it is a best practice to provide them as they help reviewers understand the content and sources of the analysis results by

- identifying the critical analyses and analysis variables,
- providing links between results, documentation, and datasets,
- documenting the analyses performed in a standard format and in a predictable location

The analysis results metadata for the example figure and tables in Section 5.1 are provided in Tables 5.2.1 to 5.2.4.

Table 5.2.1 Analysis Results Metadata[5] for the Example Kaplan-Meier Plot Display

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	Figure 12.3.1.1
DISPLAY NAME	Kaplan-Meier Plot: Time to Death (days)
RESULT IDENTIFIER	Time to Death (days)
PARAM	Time to Death (days)
PARAMCD	DEATH
ANALYSIS VARIABLE	AVAL, CNSR
REASON	Primary efficacy endpoint as pre-specified in protocol
DATASET	ADTTE
SELECTION CRITERIA	ITTFL='Y'
DOCUMENTATION	SAP Section 10.1.1. The time to death (in days) was plotted using Kaplan-Meier plot. P value was generated using a log-rank test.
PROGRAMMING STATEMENTS[a]	PROC LIFETEST DATA=ADTTE; TIME AVAL*CNSR (1 2 3); STRATA TRTPN; RUN;

[a] The same dataset as illustrated in Table 5.1, but uses multiple censor values can be found in Table 6.1 in this document. The TTE model statement was provided to show how multiple censor values can be included in the model.

[5] The style of the display of the results of an analysis will be determined by the sponsor. The examples presented here are intended to illustrate content and not appearance.

Because example Table 14.2.1.1 presents inferential statistics that are obtained using two different analysis methods, two analysis result metadata tables (i.e., Table 5.2.2 and Table 5.2.3) are created in order to describe each analysis method separately.

Table 5.2.2 Analysis Results Metadata[6] for Time-to-Event Results Using Log-Rank Test

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	Table 14.2.1.1
DISPLAY NAME	Time to Death Through Day 168 by Treatment Group; Analysis Population: Intent-to-Treat
RESULT IDENTIFIER	Treatment effect comparison between two treatment groups on time to death based on log-rank test
PARAM	Time to Death (days)
PARAMCD	DEATH
ANALYSIS VARIABLE	AVAL, CNSR
REASON	Primary efficacy endpoint as pre-specified in protocol; the treatment effect was evaluated using log-rank test.
DATASET	ADTTE
SELECTION CRITERIA	ITTFL='Y'
DOCUMENTATION	SAP Section 10.1.2. The time to death (in days) was analyzed using two analysis methods: 1) log-rank test and 2) Cox regression model with age (< 65 vs. ≥ 65 years) and sex as covariates.
PROGRAMMING STATEMENTS	PROC LIFETEST DATA=ADTTE; TIME AVAL*CNSR (1 2 3); STRATA TRTPN; RUN;

[6] The display presentation of the metadata should be determined between the sponsor and the recipient. The example presented here is only intended to illustrate content and not appearance.

Table 5.2.3 Analysis Results Metadata[7] for Time-to-Event Results Using Cox Regression Model

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	Table 14.2.1.1
DISPLAY NAME	Time to Death Through Day 168 by Treatment Group; Analysis Population: Intent-to-Treat
RESULT IDENTIFIER	Treatment effect comparison between two treatment groups on time to death based on Cox proportional hazard model
PARAM	Time to Death (days)
PARAMCD	DEATH
ANALYSIS VARIABLE	AVAL, CNSR
REASON	Primary efficacy endpoint as pre-specified in protocol; the treatment effect was evaluated using Cox proportional hazard model.
DATASET	ADTTE
SELECTION CRITERIA	ITTFL='Y'
DOCUMENTATION	SAP Section 10.1.2. The time to death (in days) was analyzed using two analysis methods: 1) log-rank test and 2) Cox regression model with age (< 65 vs. ≥ 65 years) and sex as covariates.
PROGRAMMING STATEMENTS	PROC PHREG DATA=ADTTE; MODEL AVAL*CNSR (1 2 3) = TRTPN AGEGR1N SEXN / ALPHA=0.05; RUN;

.

[7] The display presentation of the metadata should be determined between the sponsor and the recipient. The example presented here is only intended to illustrate content and not appearance.

Table 5.2.4 Analysis Results Metadata[8] for the Time-to-Event Hazard Ratio Display

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	Table 14.2.1.2
DISPLAY NAME	Time to Death Through Day 168 – Cox Regression Model, Analysis Population: Intent-to-Treat
RESULT IDENTIFIER	Hazard ratio
PARAM	Time to Death (days)
PARAMCD	DEATH
ANALYSIS VARIABLE	AVAL, CNSR
REASON	Primary efficacy endpoint as pre-specified in protocol
DATASET	ADTTE
SELECTION CRITERIA	ITTFL='Y'
DOCUMENTATION	SAP Section 10.1.2. The time to death (in days) was analyzed using a Cox regression model that includes age (< 65 vs. ≥ 65 years) and sex as covariates.
PROGRAMMING STATEMENTS	PROC PHREG DATA=ADTTE; MODEL AVAL*CNSR (1 2 3) = TRTPN AGEGR1N SEXN / ALPHA=0.05 RL; RUN;

[8] The display presentation of the metadata should be determined between the sponsor and the recipient. The example presented here is only intended to illustrate content and not appearance.

6. Example 2: Single Endpoint with Multiple Values for Censoring

In analyzing a time-to-event endpoint, reviewers are often interested in knowing reasons for subjects' censoring for better understanding of the data and also possible sensitivity analyses if applicable. The following example uses the exact same dataset as presented in Section 5, except for the values of the censor variable assignment. In this example, the censoring variable has more than two levels which uniquely identify the various reasons for censoring.

Table 6.1 Time-to-Event Data Structure for a Single Endpoint with Multiple Values for Censoring Variable

Row	USUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC
1	1001-0001	Time to Death (days)	DEATH	15	2007-01-01	2007-01-15	0	DEATH
2	1001-0002	Time to Death (days)	DEATH	168	2007-01-03	2007-06-19	1	COMPLETED THE STUDY
3	1001-0003	Time to Death (days)	DEATH	120	2007-01-03	2007-05-02	3	LOST TO FOLLOW-UP
4	1001-0004	Time to Death (days)	DEATH	168	2007-01-10	2007-06-26	1	COMPLETED THE STUDY
5	1001-1005	Time to Death (days)	DEATH	30	2007-01-11	2007-02-09	0	DEATH
6	1001-1006	Time to Death (days)	DEATH	4	2007-01-17	2007-01-20	2	ADVERSE EVENT

As displayed in this example, there would be as many levels for the CNSR variable as reasons for censoring. Having multiple levels of the censoring and event reason enables reviewers to better understand the data. It also provides the ability to conduct ad hoc analyses, including sensitivity of the results, from the ADaM TTE analysis dataset directly. The time-to-event analysis of a composite endpoint is another situation where multiple levels of the censor variable can be utilized. Section 7 provides an example of how multi-level censoring works with a composite endpoint when there are different types of event descriptions in addition to the multiple censoring descriptions.

7. Example 3: Composite Endpoints

7.1 Progression Free Survival (PFS) Example

A common efficacy endpoint in oncology trials is progression free survival (PFS). PFS is a composite endpoint defined in the FDA guidance document *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* [4] as "the time from randomization until objective tumor progression or death". The FDA guidance document also describes many scenarios that may warrant censoring of PFS data. The example below illustrates how PFS data with multiple event and censoring outcomes can be incorporated in the ADaM TTE analysis dataset structure.

Table 7.1.1 Time-to-Event Data Structure for a Composite Endpoint: PFS Example with Expansion of EVNTDESC to Explain Censoring Reason

Row	USUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC
1	1001-0001	Progression Free Survival (days)	PFS	15	2007-01-01	2007-01-15	0	DOCUMENTED PROGRESSION
2	1001-0002	Progression Free Survival (days)	PFS	168	2007-01-01	2007-06-17	1	COMPLETED STUDY. CENSORED AT TIME OF LAST ASSESSMENT.
3	1001-0003	Progression Free Survival (days)	PFS	120	2007-01-01	2007-04-30	3	NEW ANTI-CANCER THERAPY. CENSORED AT TIME OF LAST ASSESSMENT.
4	1001-0004	Progression Free Survival (days)	PFS	28	2007-01-01	2007-01-28	2	EARLY DISCONTINUATION. CENSORED AT TIME OF LAST ASSESSMENT.
5	1001-1005	Progression Free Survival (days)	PFS	30	2007-01-01	2007-01-30	0	DEATH
6	1001-1006	Progression Free Survival (days)	PFS	1	2007-01-01	2007-01-01	4	NO BASELINE ASSESSMENT. CENSORED AT TIME OF RANDOMIZATION.

In this example, two different types of events occur, a documented progression event for subject 1001-0001 and a death for subject 1001-1005. Both have a CNSR value of 0. EVNTDESC is populated using sponsor-defined controlled terminology to describe the event. All other subjects are censored, but for different reasons, as indicated by the different CNSR values. The EVNTDESC column describes both the *reason* for censoring (if CNSR > 0) and the *time* at which censoring occurs (i.e., a description of what ADT represents). Since an assessment of tumor progression may not occur at the same time as an event that warrants censoring, it is important to differentiate and describe these two dates. For example, an assessment of tumor progression may not occur when a subject discontinues from a study, so censoring occurs at the time when the subject was last known to have no documented

progression (refer to subject 1001-1004 in the above example). Note that this expanded use of EVNTDESC is only necessary when the event that warrants censoring and the event that represents the censoring time are not the same.

An alternative way to handle the difference in dates for censoring and onset of event that warranted censoring is illustrated in Table 7.1.2. Here, the CNSDTDSC column has been added to describe what the censoring date in ADT represents and EVNTDESC describes the event that warrants censoring. Note that adding CNSDTDSC provides additional information when there is a difference between the event date that warrants censoring and the actual date of censoring. If the event that warrants censoring is the same as the onset date of the event that represents the censoring date, then the CNSDTDSC column is not needed in the analysis dataset.

Table 7.1.2 Time-to-Event Data Structure for a Composite Endpoint: PFS Example Using CNSDTDSC to Describe the Censoring Date in addition to EVNTDESC to Describe the Reason for Censoring

Row	USUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC	CNSDTDSC
1	1001-0001	Progression Free Survival (days)	PFS	15	2007-01-01	2007-01-15	0	DOCUMENTED PROGRESSION	
2	1001-0002	Progression Free Survival (days)	PFS	168	2007-01-01	2007-06-17	1	COMPLETED STUDY	LAST RADIOLOGIC ASSESSMENT SHOWING NO PROGRESSION
3	1001-0003	Progression Free Survival (days)	PFS	120	2007-01-01	2007-04-30	3	NEW ANTI-CANCER THERAPY	LAST RADIOLOGIC ASSESSMENT SHOWING NO PROGRESSION
4	1001-0004	Progression Free Survival (days)	PFS	28	2007-01-01	2007-06-28	2	EARLY DISCONTINUATION	LAST RADIOLOGIC ASSESSMENT SHOWING NO PROGRESSION
5	1001-1005	Progression Free Survival (days)	PFS	30	2007-01-01	2007-01-30	0	DEATH	
6	1001-1006	Progression Free Survival (days)	PFS	1	2007-01-01	2007-01-01	4	NO BASELINE ASSESSMENT	RANDOMIZATION

7.2 Time to Hepatitis B e Antigen Seroconversion Example

Another composite TTE example is a time to Hepatitis B e Antigen (HBeAg) Seroconversion.

In this example, a subject must meet the following criteria in order to be considered as a responder for Hepatitis B e Antigen Seroconversion:

- antibody positive at baseline,
- antigen negative for two consecutive visits (which will be noted as Time to Confirmed HBeAg) and
- antibody positive for the same two consecutive visits (which will be noted as Time to Confirmed HBeAb).

Time to Confirmed Hepatitis B e Antigen (HBeAg) Seroconversion is defined as the first time to have:

- Hepatitis B e antigen negative results (HBeAg=Negative) either for two consecutive measurements or for the last observed measurement and concurrently
- Hepatitis B e antibody positive (HBeAb=Positive) in subjects with antigen positive at baseline.

Subjects who do not meet the definition above are censored at the last non-missing measurement during the analysis period. Subjects who are Hepatitis B e antigen negative (i.e., HBeAg=Negative) at baseline are excluded from the analysis.

One difference between this scenario and the examples in previous sections is that the event is determined by lab assays from samples drawn at discrete times generally determined by study visit schedules. It is known that the event occurred at some time between the visit when the subject first met the criterion and the visit when the subject no longer met the criterion, but the exact time the event occurred is not known. This is called interval censoring and requires the addition of the AVISIT variable to indicate which visit is associated with the event of interest. The STARTDT variable represents the initial study drug administration date in this example.

Multiple dataset creation steps will take place to create a final ADaM TTE analysis dataset for this example. First, an analysis dataset containing the lab information (ADLB) is created. In Table 7.2.1, the analysis dataset ADLB consists of several analysis parameters (PARAM) and values (AVALC) derived from the SDTM LB domain. For simplicity and ease of explanation, the example Table 7.2.1 contains only Hepatitis B seroconversion-related records. In order to provide traceability between the SDTM LB domain and the ADLB dataset, the Data Point Traceability variables, described in the ADaM IG, section 3.2.8. [2], are included in the ADLB domain. The variable SRCDOM provides the name of the input SDTM domain and has a value of LB. SRCVAR indicates the source variable in the SDTM LB domain, which is LBSTRESC. Finally, SRCSEQ is carried over from the original SDTM LB domain to link each value in ADLB to its corresponding record in the source SDTM LB domain. Together, SRCDOM, SRCSEQ, and SRCVAR provide data-point traceability via record-identifier variables that link the specific data value used as input for an analysis value. An alternative approach is to add only LBSEQ in the ADLB dataset to show record-level traceability because only the LB domain has been used to create the ADLB dataset in this example. However, if many domains and/or datasets (either SDTM or ADaM) are used to drive a composite endpoint, it will be necessary to add SRCDOM, SRCVAR, and SRCSEQ as this structure can handle sub-event input rows from many domains and datasets in only three standard supportive columns. Because this approach can be standardized, scaleable, and support analysis of sub-events, we chose to use this approach in this and subsequent analysis dataset examples.

In the ADLB analysis dataset, we introduce a new ADaM sequence variable ASEQ. Because ADLB is going to be used as an input dataset to generate an intermediate time-to-event analysis dataset (called ADTTE1 in this example), ASEQ is created to provide record-level traceability between two analysis datasets (ADLB and ADTTE1). ASEQ will contain sequence numbers that are unique for each record to ensure uniqueness of subject record within the ADLB dataset as illustrated in Table 7.2.1.

Table 7.2.1 Hepatitis B Seroconversion Source Analysis Dataset (ADLB)

Row	USUBJID	ASEQ	PARAM	PARAMCD	STARTDT	AVISIT	AVALC	ADT	ADY	SRCDOM	SRCVAR	SRCSEQ
1	1001-1001	1	Hepatitis B e antigen	HBeAg	2003-08-11	Baseline	Positive	2003-08-11	-2	LB	LBSTRESC	2800
2	1001-1001	2	Hepatitis B e antigen	HBeAg	2003-08-11	Week 2	Negative	2003-08-27	15	LB	LBSTRESC	2801
3	1001-1001	3	Hepatitis B e antigen	HBeAg	2003-08-11	Week 3	Negative	2003-09-03	22	LB	LBSTRESC	2802
4	1001-1001	4	Hepatitis B e antigen	HBeAg	2003-08-11	Week 4	Negative	2003-09-09	28	LB	LBSTRESC	2803
5	1001-1001	5	Hepatitis B e antigen	HBeAg	2003-08-11	Week 5	Negative	2003-09-16	35	LB	LBSTRESC	2804
6	1001-1001	6	Antibody to Hepatitis B e antigen	HBeAb	2003-08-11	Baseline	Positive	2003-08-11	-2	LB	LBSTRESC	2805
7	1001-1001	7	Antibody to Hepatitis B e antigen	HBeAb	2003-08-11	Week 2	Positive	2003-08-27	15	LB	LBSTRESC	2806
8	1001-1001	8	Antibody to Hepatitis B e antigen	HBeAb	2003-08-11	Week 3	Positive	2003-09-03	22	LB	LBSTRESC	2807
9	1001-1001	9	Antibody to Hepatitis B e antigen	HBeAb	2003-08-11	Week 4	Positive	2003-09-09	28	LB	LBSTRESC	2808
10	1001-1001	10	Antibody to Hepatitis B e antigen	HBeAb	2003-08-11	Week 5	Positive	2003-09-16	35	LB	LBSTRESC	2809
11	1001-1002	11	Hepatitis B e antigen	HBeAg	2003-08-19	Baseline	Positive	2003-08-19	1	LB	LBSTRESC	3000
12	1001-1002	12	Hepatitis B e antigen	HBeAg	2003-08-19	Week 2	Negative	2003-08-31	13	LB	LBSTRESC	3001
13	1001-1002	13	Hepatitis B e antigen	HBeAg	2003-08-19	Week 3	Negative	2003-09-07	20	LB	LBSTRESC	3002

Row	USUBJID	ASEQ	PARAM	PARAMCD	STARTDT	AVISIT	AVALC	ADT	ADY	SRCDOM	SRCVAR	SRCSEQ
14	1001-1002	14	Hepatitis B e antigen	HBeAg	2003-08-19	Week 4	Negative	2003-09-15	28	LB	LBSTRESC	3003
15	1001-1002	15	Hepatitis B e antigen	HBeAg	2003-08-19	Week 5	Positive	2003-09-22	35	LB	LBSTRESC	3004
16	1001-1002	16	Antibody to Hepatitis B e antigen	HBeAb	2003-08-19	Baseline	Negative	2003-08-19	1	LB	LBSTRESC	3005
17	1001-1002	17	Antibody to Hepatitis B e antigen	HBeAb	2003-08-19	Week 2	Negative	2003-08-31	13	LB	LBSTRESC	3006
18	1001-1002	18	Antibody to Hepatitis B e antigen	HBeAb	2003-08-19	Week 3	Negative	2003-09-07	20	LB	LBSTRESC	3007
19	1001-1002	19	Antibody to Hepatitis B e antigen	HBeAb	2003-08-19	Week 4	Negative	2003-09-15	28	LB	LBSTRESC	3008
20	1001-1002	20	Antibody to Hepatitis B e antigen	HBeAb	2003-08-19	Week 5	Negative	2003-09-22	35	LB	LBSTRESC	3009
21	1001-1003	21	Hepatitis B e antigen	HBeAg	2003-08-01	Baseline	Negative	2003-08-01	1	LB	LBSTRESC	3200
22	1001-1003	22	Hepatitis B e antigen	HBeAg	2003-08-01	Week 2	Negative	2003-08-14	14	LB	LBSTRESC	3201
23	1001-1003	23	Hepatitis B e antigen	HBeAg	2003-08-01	Week 3	Negative	2003-08-21	21	LB	LBSTRESC	3202
24	1001-1003	24	Hepatitis B e antigen	HBeAg	2003-08-01	Week 4	Negative	2003-08-28	28	LB	LBSTRESC	3203
25	1001-1003	25	Antibody to Hepatitis B e antigen	HBeAb	2003-08-01	Baseline	Positive	2003-08-01	1	LB	LBSTRESC	3204
26	1001-1003	26	Antibody to Hepatitis B e antigen	HBeAb	2003-08-01	Week 2	Positive	2003-08-14	14	LB	LBSTRESC	3205

Row	USUBJID	ASEQ	PARAM	PARAMCD	STARTDT	AVISIT	AVALC	ADT	ADY	SRCDOM	SRCVAR	SRCSEQ
27	1001-1003	27	Antibody to Hepatitis B e antigen	HBeAb	2003-08-01	Week 3	Positive	2003-08-21	21	LB	LBSTRESC	3206
28	1001-1003	28	Antibody to Hepatitis B e antigen	HBeAb	2003-08-01	Week 4	Positive	2003-08-28	28	LB	LBSTRESC	3207
29	1001-1004	29	Hepatitis B e antigen	HBeAg	2003-09-20	Baseline	Positive	2003-09-20	1	LB	LBSTRESC	3900
30	1001-1004	30	Hepatitis B e antigen	HBeAg	2003-09-20	Week 2	Negative	2003-10-02	13	LB	LBSTRESC	3901
31	1001-1004	31	Hepatitis B e antigen	HBeAg	2003-09-20	Week 3	Negative	2003-10-09	20	LB	LBSTRESC	3902
32	1001-1004	32	Hepatitis B e antigen	HBeAg	2003-09-20	Week 4	Negative	2003-10-17	28	LB	LBSTRESC	3903
33	1001-1004	33	Hepatitis B e antigen	HBeAg	2003-09-20	Week 5	Negative	2003-10-24	35	LB	LBSTRESC	3904
34	1001-1004	34	Antibody to Hepatitis B e antigen	HBeAb	2003-09-20	Baseline	Negative	2003-09-20	1	LB	LBSTRESC	3905
35	1001-1004	35	Antibody to Hepatitis B e antigen	HBeAb	2003-09-20	Week 2	Negative	2003-10-02	13	LB	LBSTRESC	3906
36	1001-1004	36	Antibody to Hepatitis B e antigen	HBeAb	2003-09-20	Week 3	Negative	2003-10-09	20	LB	LBSTRESC	3907
37	1001-1004	37	Antibody to Hepatitis B e antigen	HBeAb	2003-09-20	Week 4	Negative	2003-10-17	28	LB	LBSTRESC	3908
38	1001-1004	38	Antibody to Hepatitis B e antigen	HBeAb	2003-09-20	Week 5	Positive	2003-10-24	35	LB	LBSTRESC	3909

Because the derivation algorithms to define the final composite endpoint are complex, an intermediate analysis dataset (called ADTTE1 in this example) is created and illustrated in Table 7.2.2. This intermediate ADaM TTE analysis dataset (ADTTE1) will show how the final composite endpoint data are generated as well as what records are included in the final analysis dataset (called ADTTE2 in this example). The values for SRCSEQ of the composite endpoint row in the ADDTTE1 dataset were left blank for the time to confirmed hepatitis B e Antigen Seroconversion (i.e., PARAMCD='T2HBeAg') as there are more than one record that are to be taken into account to determine confirmation. Because SRCSEQ does not allow more than one value, this is the traceability method we chose to use in this example. This does not mean that this is the only method one can use to provide the traceability between two datasets. The final dataset that will be used in the analysis of time to Hepatitis B e Antigen Seroconversion (ADTTE2) is illustrated in Table 7.2.3. For simplicity and ease of use, only records that are eligible for the time to Hepatitis B e Antigen Seroconversion analysis are retained in the ADTTE2 dataset.

The composite endpoint in this analysis consists of two parameters: HBeAg and HBeAb from the source analysis dataset (ADLB) illustrated in Table 7.2.1 (PARAMCD= 'HBeAg' and PARAMCD= 'HBeAb').

The two PARAMCD values from ADTTE1 that are used as components of the composite endpoint are:

- PARAMCD= 'T2HBeAg' indicates the time to negative Hepatis B e antigen confirmed which will be determined based on whether a subject met the analysis definition for confirmed HBeAg (two consecutive or the last observed HBeAg measurement= 'Negative').
- PARAMCD= 'T2HBeAb' indicates the time to positive Hepatis B e antibody confirmed which will be determined based on whether a subject met the analysis definition for confirmed HBeAb (two consecutive or the last observed HBeAb measurement= 'Positive').

Note that even though the individual components (T2HBeAg and T2HBeAb) have met the definition of the events for the post-treatment records, combining them together does not necessarily mean that they will be considered having the event for the composite endpoint analysis unless subject's antigen is positive at baseline. As shown in the example, subject 1001-1003 is considered as having an event in both 'Time to Confirmed HBeAg' and 'Time to Confirmed HBeAb'; however, this subject is excluded from the analysis because the subject's baseline Hepatitis B antigen was 'Negative'.

AVAL in the ADaM TTE analysis datasets (i.e., ADTTE1 and ADTTE2) contains the number of days from the time of origin (STARTDT) to the date where the earliest event of the two consecutive events met the confirmed Hepatitis B e Antigen Seroconversion criteria (or the date of the last measurement if the last measurement met the criteria). EVNTDESC describes why a subject was either qualified for an event or censored. The final ADaM TTE analysis dataset (ADTTE2) includes only those records with PARAMCD= 'T2SERO' and a non-missing censor value (i.e., CNSR not missing). When the analysis datasets utilize traceability variables to provide record-level traceability from the source dataset(s) to the final analysis dataset, it is desirable to provide intermediate analysis dataset(s) for easier review.

The following is an example of intermediate ADaM TTE analysis dataset (ADTTE1):

Table 7.2.2 Time-to-Event Data Structure for a Composite Endpoint: An Intermediate Dataset for Time to Hepatitis B e Antigen Seroconversion (ADTTE1)

Row	USUBJID	ASEQ	PARAM	PARAMCD	AVAL	STARTDT	ADT	AVISIT	CNSR	SRCDOM	SRC SEQ	EVNTDESC
1	1001-1001	1	Time to Confirmed HBeAg (days)	T2HBeAg	15	2003-08-13	2003-08-27	Week 2	0	ADLB	2	Two consecutive HBeAg= Negative
2	1001-1001	2	Time to Confirmed HBeAb (days)	T2HBeAb	15	2003-08-13	2003-08-27	Week 2	0	ADLB	7	Two consecutive HBeAb = Positive
3	1001-1001	3	Time to HBeAg Seroconversion (days)	T2SERO	15	2003-08-13	2003-08-27	Week 2	0	ADLB		HBeAg=Positive at baseline and two consecutive HBeAg = Negative and two consecutive HBeAb = Positive
4	1001-1002	4	Time to Confirmed HBeAg (days)	T2HBeAg	13	2003-08-19	2003-08-31	Week 2	0	ADLB	12	Two consecutive HBeAg = Negative
5	1001-1002	5	Time to Confirmed HBeAb (days)	T2HBeAb	35	2003-08-19	2003-09-22	Week 5	1	ADLB	20	No two consecutive or last HBeAb = Positive
6	1001-1002	6	Time to HBeAg Seroconversion (days)	T2SERO	35	2003-08-19	2003-09-22	Week 5	1	ADLB		Two consecutive HBeAg = Negative but no two consecutive or last HBeAb = Positive
7	1001-1003	7	Time to Confirmed HBeAg (days)	T2HBeAg	14	2003-08-01	2003-08-14	Week 2	0	ADLB	22	Two consecutive HBeAg = Negative
8	1001-1003	8	Time to Confirmed HBeAb (days)	T2HBeAb	14	2003-08-01	2003-08-14	Week 2	0	ADLB	26	Two consecutive HBeAb= Positive

Row	USUBJID	ASEQ	PARAM	PARAMCD	AVAL	STARTDT	ADT	AVISIT	CNSR	SRCDOM	SRC SEQ	EVNTDESC
9	1001-1003	9	Time to HBeAg Seroconversion (days)	T2SERO	.	2003-08-01	.		.	ADLB		Excluded from analysis due to Baseline HBeAg = Negative
10	1001-1004	10	Time to Confirmed HBeAg (days)	T2HBeAg	13	2003-09-20	2003-10-02	Week 2	0	ADLB	30	Two consecutive HBeAg = Negative
11	1001-1004	11	Time to Confirmed HBeAb (days)	T2HBeAb	35	2003-09-20	2003-10-24	Week 5	0	ADLB	38	Last HBeAb = Positive
12	1001-1004	12	Time to HBeAg Sero-conversion (days)	T2SERO	35	2003-09-20	2003-10-24	Week 5	0	ADLB		HBeAg=Positive at baseline and two consecutive HBeAg = Negative and last HBeAb = Positive

The final ADaM TTE analysis dataset (ADTTE2) for the time to confirmed Hepatitis B e Antigen Seroconversion example is shown in Table 7.2.3. Note that subject 1001-1003 was excluded from the ADTTE2 dataset because this subject had a negative Hepatitis B e antigen at baseline.

Table 7.2.3 Time-to-Event Data Structure for a Composite Endpoint: The Final Analysis Dataset for Time to Hepatitis B e Antigen Seroconversion (ADTTE2)

Row	USUBJID	ASEQ	PARAM	PARAMCD	AVAL	STARTDT	ADT	AVISIT	CNSR	SRCDOM	SRCSEQ	EVNTDESC	CNSDTDSC
1	1001-1001	1	Time to HBeAg Sero-conversion (days)	T2SERO	15	2003-08-13	2003-08-27	Week 2	0	ADTTE1	3	HBeAg= Positive at baseline and two consecutive HBeAg = Negative and two consecutive HBeAb = Positive	
2	1001-1002	2	Time to HBeAg Sero-conversion (days)	T2SERO	35	2003-08-19	2003-09-22	Week 5	1	ADTTE1	6	Two consecutive HBeAg = Negative but no two consecutive or last HBeAb = Positive	Date of last non-missing lab data.
3	1001-1004	3	Time to HBeAg Sero-conversion (days)	T2SERO	35	2003-09-20	2003-10-24	Week 5	0	ADTTE1	12	HBeAg= Positive at baseline and two consecutive HBeAg = Negative and last HBeAb = Positive	

As shown above, very complex derivations may require the creation of intermediate analysis datasets. In these situations, traceability may be accomplished by retaining and including intermediate analysis datasets along with their associated metadata. Traceability would then involve several steps. The analysis results would be linked by appropriate metadata, including results metadata, to the data which directly supports the analytical procedures; those data would be linked to the intermediate analysis data; the intermediate data would in turn be linked to the source SDTM data. Because ADTTE is not a required dataset name for all time-to-event analysis datasets, one can assign a logical name to identify the intermediate and final time-to-event analysis datasets for clarity.

8. References

1. Analysis Data Model (ADaM) version 2.1
   http://www.cdisc.org/adam
2. Analysis Data Model (ADaM) Implementation Guide version 1.0
   http://www.cdisc.org/adam
3. Alan B. Cantor. SAS Survival Analysis Techniques for Medical Research. Second Edition, SAS Institute Inc. September 2005
4. FDA Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, May, 2007
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf
5. International Conference of Harmonization E3 "Structure and Content of Clinical Study Reports"
   http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf
6. Paul D. Allison. Survival Analysis Using the SAS System. A Practical Guide, Second Edition. SAS Institute Inc. 2010

APPENDIX A. Representations and Warranties; Limitations of Liability, and Disclaimers

CDISC Patent Disclaimers

It is possible that implementation of and compliance with this standard may require use of subject matter covered by patent rights. By publication of this standard, no position is taken with respect to the existence or validity of any claim or of any patent rights in connection therewith. CDISC, including the CDISC Board of Directors, shall not be responsible for identifying patent claims for which a license may be required in order to implement this standard or for conducting inquiries into the legal validity or scope of those patents or patent claims that are brought to its attention.

Representations and Warranties

Each Participant in the development of this standard shall be deemed to represent, warrant, and covenant, at the time of a Contribution by such Participant (or by its Representative), that to the best of its knowledge and ability: (a) it holds or has the right to grant all relevant licenses to any of its Contributions in all jurisdictions or territories in which it holds relevant intellectual property rights; (b) there are no limits to the Participant's ability to make the grants, acknowledgments, and agreements herein; and (c) the Contribution does not subject any Contribution, Draft Standard, Final Standard, or implementations thereof, in whole or in part, to licensing obligations with additional restrictions or requirements inconsistent with those set forth in this Policy, or that would require any such Contribution, Final Standard, or implementation, in whole or in part, to be either: (i) disclosed or distributed in source code form; (ii) licensed for the purpose of making derivative works (other than as set forth in Section 4.2 of the CDISC Intellectual Property Policy ("the Policy")); or (iii) distributed at no charge, except as set forth in Sections 3, 5.1, and 4.2 of the Policy. If a Participant has knowledge that a Contribution made by any Participant or any other party may subject any Contribution, Draft Standard, Final Standard, or implementation, in whole or in part, to one or more of the licensing obligations listed in Section 9.3, such Participant shall give prompt notice of the same to the CDISC President who shall promptly notify all Participants.

No Other Warranties/Disclaimers. ALL PARTICIPANTS ACKNOWLEDGE THAT, EXCEPT AS PROVIDED UNDER SECTION 9.3 OF THE CDISC INTELLECTUAL PROPERTY POLICY, ALL DRAFT STANDARDS AND FINAL STANDARDS, AND ALL CONTRIBUTIONS TO FINAL STANDARDS AND DRAFT STANDARDS, ARE PROVIDED "AS IS" WITH NO WARRANTIES WHATSOEVER, WHETHER EXPRESS, IMPLIED, STATUTORY, OR OTHERWISE, AND THE PARTICIPANTS, REPRESENTATIVES, THE CDISC PRESIDENT, THE CDISC BOARD OF DIRECTORS, AND CDISC EXPRESSLY DISCLAIM ANY WARRANTY OF MERCHANTABILITY, NONINFRINGEMENT, FITNESS FOR ANY PARTICULAR OR INTENDED PURPOSE, OR ANY OTHER WARRANTY OTHERWISE ARISING OUT OF ANY PROPOSAL, FINAL STANDARDS OR DRAFT STANDARDS, OR CONTRIBUTION.

Limitation of Liability

IN NO EVENT WILL CDISC OR ANY OF ITS CONSTITUENT PARTS (INCLUDING, BUT NOT LIMITED TO, THE CDISC BOARD OF DIRECTORS, THE CDISC PRESIDENT, CDISC STAFF, AND CDISC MEMBERS) BE LIABLE TO ANY OTHER PERSON OR ENTITY FOR ANY LOSS OF PROFITS, LOSS OF USE, DIRECT, INDIRECT, INCIDENTAL, CONSEQUENTIAL, OR SPECIAL DAMAGES, WHETHER UNDER CONTRACT, TORT, WARRANTY, OR OTHERWISE, ARISING IN ANY WAY OUT OF THIS POLICY OR ANY RELATED AGREEMENT, WHETHER OR NOT SUCH PARTY HAD ADVANCE NOTICE OF THE POSSIBILITY OF SUCH DAMAGES.

Note: The CDISC Intellectual Property Policy can be found at
http://www.cdisc.org/about/bylaws_pdfs/CDISCIPPolicy-FINAL.pdf .