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ADaM IG 1.1 Compliant ADEVENT and ADTTE development in a Cardiovascular Study

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ABSTRACT

Major adverse events such as death, stroke and myocardial Infarction are reported in cardiovascular studies. In addition to these major events, other important information about the clinical assessments is collected at different levels. In CV studies, the clinical assessments from different evaluators, typically investigators and adjudicators, are reported for the same event. Therefore, it is more complicated to build ADaM datasets to store and analyze the corresponding data.

In this paper, a CDISC compliant Basic Data Structure (BDS) dataset called ADEVENT is developed to store all collected major CV events and the corresponding detailed information. This dataset is used to generate the table of concordance between investigators and adjudicators. The time to event dataset ADTTE used for the primary analysis is derived from the ADEVENT dataset. The traceability between ADEVENT and ADTTE is described and discussed in this paper.

INTRODUCTION

Survival analysis is a class of statistical methods for studying the occurrence and timing of events. In many clinical studies, an outcome of interest is the time to an event which can be stored in ADTTE, but the structure of ADTTE is one record per subject per parameter and can't store all the related detailed information. Therefore, in order to develop a concordance table between the investigators and adjudicators or reoccurrence of events, another ADaM compliant dataset which can include all investigators reported events and adjudicators adjudicated events is needed. The examples of ADTTE and ADEVENT datasets are developed based on Heart Failure study in this paper.

ADEVENT – EVENT DATASET TO SUPPORT TABLES AND OTHER DATASETS

To create the concordance tables between investigators reported events and adjudicators adjudicated events, a CDISC compliant BDS dataset ADEVENT is created to store all events from both the reported and adjudicated data.

As shown in Figure 1, the concordance table contains the events from investigators reports as columns and the adjudicated events as rows. In order to generate this table, as shown in figure 2

each event will include two records in the ADEVENT dataset. One record is from investigators reported data, and the other is from adjudicated data. These two records are linked by a variable ADJREFID.

Fig. 1 Concordance Summary of Primary Reason of Hospitalization

	Investigator Reported Primary Reason of Hospitalization				
CEC Adjudication	**Heart Failure (N=xx)**	**Myocardial Infarction (N= xx)**	**Stroke (N=xx)**	**Other CV Event (N=xx)**	**Non-CV hospitalization (N=xx)**
Heart Failure	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Myocardial Infarction	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Stroke	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Other CV Event	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Non-CV Hospitalization	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Not Hospitalized	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)

- PARQUAL is used to indicate that the records are from investigators for adjudicated datasets.
- PARAMCD/PARAM is endpoints types at the collected CRF.
- AVALC is used to store the specified events from investigators endpoints dataset or adjudicated dataset.
- In a cardiovascular trial, it is normal that the criterion can have multiple responses for a given event. So MCRITy,MCRITyML,MCRITyMN are used to record the additional information for the given event. MCRITy, MCRITyML and MCRITyMN are not parameter-invariant. Therefore, MCRITy for one parameter can be different than MCRITy for a different parameter in the same dataset. Two levels of response are displayed in this example to store the additional information.
- ADJREFID is the reference ID used to link the same event between two evaluators.

Traceability is the property that enables the understanding where the analysis results come from. It facilitates transparency and is an essential component for building confidence in analysis results. for ADaM dataset(s), the traceability can be achieved by the combination of metadata traceability and data point traceability. Three source variables SRCDOM, SRCVAR, SRCSEQ are included to support data point traceability among ADEVENT and SDTM datasets related to AVAL or AVALC. Where SRCDOM is 2-character identifier of the SDTM domain;

SRCVAR is the name of the column identified by SRCDOM; SRCSEQ is the sequence number of xxSEQ used for AVAL/AVALC identified by SRCDOM and SRCVAR.

One example of ADEVENT is shown in Figure 2

Fig. 2 ADEVENT dataset

SUBJID	ASEQ	PARQUAL	PARAM	PARAMCD	AVALC	MCRIT1
002	1	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-Hf /Intestification Trt
002	2	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-New Or Worsening Symptom Indicator
002	3	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-Phy Exam And/Or Lab Fndng Indicator
002	4	INVESTIGATOR	HF Hospitalization	HFHOSP	Heart Failure	
002	5	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-Hf /Intestification Trt
002	6	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-Hf /Intestification Trt
002	7	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-New Or Worsening Symptom Indicator
002	8	ADJUDICATION COMMITTEE	HF Hospitalization	HFHOSP	Heart Failure	Adj-Phy Exam And/Or Lab Fndng Indicator
002	9	INVESTIGATOR	HF Hospitalization	HFHOSP	Heart Failure	
003	1	ADJUDICATION COMMITTEE	CV Death	CVDTH	Sudden Cardiac Death	
003	2	INVESTIGATOR	CV Death	CVDTH	Sudden Cardiac Death	

MCRIT1ML	MCRIT2	MCRIT2ML	ADT	ADJREFID	SRCDOM	SRCVAR	SRCSEQ
Intravenous Diuretic Or Vasoactive Agent	Adj-Hf /Intestification Trt	Iv Diuretic	8/22/2015	301	FA	FAOBJ	836
Y			8/22/2015	301	FA	FAOBJ	836
Y			8/22/2015	301	FA	FAOBJ	836
			8/22/2015	301	HO	HOINDC	711
Intravenous Diuretic Or Vasoactive Agent	Adj-Hf /Intestification Trt	Iv Diuretic	6/1/2016	302	FA	FAOBJ	846
Intravenous Diuretic Or Vasoactive Agent	Adj-Hf /Intestification Trt	Iv Vasodilator	6/1/2016	302	FA	FAOBJ	846
Y			6/1/2016	302	FA	FAOBJ	846
Y			6/1/2016	302	FA	FAOBJ	846
			6/1/2016	302	HO	HOINDC	721
			7/7/2016	101	FA	FASTRESC	902
			7/7/2016	101	DD	DDSCAT	751

ADTTE – TIME TO EVENT

The primary endpoint of the study is the time to first occurrence of the composite of CV death or HF hospitalization. If there is no event in the investigator dataset or adjudicated dataset, the event time is censored at the end of follow-up with CNSR = 1. One example is shown in Fig. 3, where the value PRIMARY in column PARAMCD indicates that it is the primary endpoint.

Fig. 3 ADTTE dataset

SUBJID	PARAMCD	EVAL	AVAL	STARTDT	ADT	CNSR
001	PRIMARY	ADJUDICATION COMMITTEE	575	7/12/2015	2/6/2017	1
001	PRIMARY	INVESTIGATOR	575	7/12/2015	2/6/2017	1
002	PRIMARY	ADJUDICATION COMMITTEE	37	7/17/2015	8/22/2015	0
002	PRIMARY	INVESTIGATOR	37	7/17/2015	8/22/2015	0
003	PRIMARY	ADJUDICATION COMMITTEE	381	6/22/2015	7/7/2016	0
003	PRIMARY	INVESTIGATOR	381	6/22/2015	7/7/2016	0

EVNTDESC	ADREFID	SRCDOM	SRCVAR	SRCSEQ
End date of follow-up		ADSL		
End date of follow-up		ADSL		
HF Hospitalization: Heart Failure	301	ADEVENT	ADT	1
HF Hospitalization: Heart Failure	301	ADEVENT	ADT	4
CV Death: Sudden Cardiac Death	101	ADEVENT	ADT	1
CV Death: Sudden Cardiac Death	101	ADEVENT	ADT	2

- EVAL is evaluator indicating that the data of the events is from Investigators or adjudicators.
- AVAL is the time to the first HF hospitalization or death event or censoring time where AVAL is measured in days, AVAL would be ADT – STARTDT or ADT – STARTDT + 1.
- STARTDT is the original date at risk for the time-to-event analysis. For example, randomization date is used for Intention-to-Treat (ITT) population; the first dose date is used for on-treatment population.
- ADT is the first occurrence analysis date of specified endpoint or composite endpoint associated with AVALC. If the event is not found in the investigator datasets or adjudicated dataset, then ADT is censored with the end date of follow-up.
- CNSR is used to indicate that a given record is event or censored. CNSR = 0 is assigned for event and CNSR > 0 is assigned for censored records.
- EVNTDESC is used to describe the event of interest or an event that warrants censoring. For example, CV death of MI is for event, and End date of follow-up is for censor.
- SRCDOM, SRCVAR, and SRCSEQ contain the name of the source ADaM dataset ADEVENT, the variable name ADEVENT.ADT, and the ADEVENT.ASEQ value of the row where the source data point is located, respectively

As shown in Fig.3, subject 001 does not have adjudicated event at row 1 nor investigator reported event at row 2. The subject is censored at the end of follow up (CNSR = 1). Subject 002 has an

investigator reported event which was confirmed by adjudication committee. Therefore, CNSR is 0 in rows 3 and 4.

CONCLUSION

As you can see from this paper, ADEVENT ADaM dataset is an efficient way to record and derive the clinical events, especially the additional information with multiple assessments for the clinical events. This dataset can not only be used to produce analysis tables such as the concordance table, but can also serve as the source data to generate other ADaM datasets such as ADTTE. This paper presents the basic framework of ADEVENT and ADTTE and provides a clear picture of traceability between these datasets. The clear traceability facilitates the reviewer to understand how the endpoints are derived and related to their source data.

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