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A custom ADaM domain for time to event analysis in adverse events

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ABSTRACT

One of the primary objectives of first-in-human oncology clinical trials is to evaluate the safety of a drug and assess its maximum tolerated dose (MTD). To evaluate safety and MTD, it is important to study all the adverse events that are occurring during the trial. In particular, adverse events with severity grade 3 and above and adverse events that are recurring need to be analyzed in detail. In addition, when an AE first occurred in a patient and how long it took to improve to a better grade and/or complete resolution are endpoints of interest. In this paper, I am proposing a custom ADaM domain to capture onset, improvement and resolution of adverse events information following the basic data structure (BDS) as described in CDISC ADaM Implementation guide (v1.0). This approach facilitates in preparing Kaplan-Meier and time to event analysis TLFs in one proc away method and reduces time and effort on validation.

INTRODUCTION

In first-in-human clinical trials, to assess safety of a drug and safe dosage, it is important to collect and analyze all study relevant adverse events. To understand an adverse event that occurred in a patient while on trial, it is essential to understand certain parameters such as severity, treatment relatedness, seriousness, duration and time to event analysis (TTE) of AEs etc. Currently, as per CDISC implementation guideline, AE data is stored in AE SDTM domain and subsequently ADAE ADaM domain. Information about severity and treatment relatedness and seriousness details can be captured in both SDTM and ADaM AE datasets. However, TTE derivations such as first onset, duration and improvement or resolution of an AE may not be accommodated by ADAE in an intuitive way. This limitation can be overcome by creating a custom ADaM domain and may be called ADTTES. ADTTES stands for Analysis Dataset for Time to Event analysis of safety data. All TTE parameters of safety data can be stored in this domain while following BDS structure as described in ADaM Implementation guide.

Before discussing further, let us familiarize ourselves with the terms listed below that will be used in preparing the custom domain.

- **Adverse event (or AE):** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily need to have a causal relationship with this treatment. (As defined by International Conference of Harmonization)
- **Adverse event severity levels:** Severity of the AE as per CTCAE Grade 1 – Mild, Grade 2 – Moderate, Grade 3 – Severe, Grade 4 - life threatening, Grade 5 - Death related to AE
- **Treatment Emergent AE:** Event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state (as defined by ICH)
- **Time to AE Improvement or Resolution:** Time it takes for an adverse event to go from a higher grade to lower grade or complete resolution
- **Duration of AE:** The duration of AE is the time from start of AE to resolution

ADTTE vs ADTTES

Survival analysis refers to studying the occurrence and timing of events of interest. A CDISC guidance document was made available with ADaM Implementation guide v1.0 to capture survival analysis data. Proposed domain follows basic data structure (BDS) and a vast majority of TTE analyses, mostly efficacy related, are captured in ADTTE domain.

However, having a separate ADaM domain that captures TTE analysis information for safety data, adverse events in our example, is beneficial. As granularity of TTE analysis performed on safety data is extensive, combining both safety and efficacy TTE data will result in a complex program as well as a huge dataset. Moreover, if needed, it is easier to share safety data with the study team and external teams without exposing efficacy information.

ADTTES Domain

As described earlier, ADTTES dataset will follow BDS structure to accommodate all TTE related parameters. A sample ADTTES dataset will look as below. This dataset has information about when is the first onset of an AE, how long did an AE take to improve or resolve from a higher grade.

USUBJID	PARCAT	PARCAT1	PARAM	PARAMCD	ADY	ASTDT	AENDT
ABC-111239901	FEVER	Improve/Resolve after EOT	Grade 2 to resolution	grd2tor	22.1	21JAN2016	23JUN2016
ABC-111239902	FEVER	Improve/Resolve after EOT	Grade 2 ongoing	grd2ong	37.7	11JAN2016	
ABC-111239902	FEVER	Improve/Resolve after EOT	Grade 34 to grade 1 or resolution	grd34to1r	37.6	11JAN2016	29SEP2016
ABC-111239902	FEVER	Improve/Resolve after EOT	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	6.1	11JAN2016	22FEB2016
ABC-111239902	FEVER	Improve/Resolve after EOT	Grade 34 to resolution	grd34tor	37.6	11JAN2016	29SEP2016
ABC-111239902	FEVER	Improve/Resolve after EOT	Grade 2 ongoing	grd2ong	37.7	11JAN2016	
ABC-111239917	FEVER	Improve/Resolve after EOT	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	3.6	26SEP2016	20OCT2016
ABC-111239917	FEVER	Improve/Resolve after EOT	Grade 23 to grade 1 or resolution	grd23to1r	3.7	01SEP2016	26SEP2016
ABC-111239917	FEVER	Improve/Resolve after EOT	Grade 23 to resolution	grd23tor	3.7	01SEP2016	26SEP2016
ABC-111239917	FEVER	Improve/Resolve after EOT	Grade 2 to resolution	grd2tor	3.7	01SEP2016	26SEP2016
ABC-111269916	FEVER	Improve/Resolve after EOT	Grade 2 ongoing	grd2ong	18.9	28JUL2016	
ABC-111269916	FEVER	Improve/Resolve after EOT	Grade 1 to resolution	grd1tor	19.7	28JUL2016	12DEC2016
ABC-111029905	FEVER	Improve/Resolve of first episode	Grade 3 ongoing	grd3ong	0.1	23MAR2016	
ABC-111029914	FEVER	Improve/Resolve of first episode	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	0.7	20JUN2016	24JUN2016
ABC-111169904	FEVER	Improve/Resolve of first episode	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	3.1	29JAN2016	19FEB2016
ABC-111239901	FEVER	Improve/Resolve of first episode	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	22.1	21JAN2016	23JUN2016
ABC-111239902	FEVER	Improve/Resolve of first episode	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	6.1	11JAN2016	22FEB2016
ABC-111239917	FEVER	Improve/Resolve of first episode	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	3.6	26SEP2016	20OCT2016
ABC-111269916	FEVER	Improve/Resolve of first episode	Grade 34 to grade 2 or grade 1 or resolution	grd34to21r	0.6	18JUL2016	21JUL2016
ABC-111029905	FEVER	Onset of TEAE	first onset of any event	anyonset	3		
ABC-111029905	FEVER	Onset of TEAE	first onset of grade 1 event	grd1onset	3		
ABC-111029905	FEVER	Onset of TEAE	first onset of worst event	wstonset	3		
ABC-111029905	FEVER	Onset of TEAE	first onset of any event	anyonset	4.3		
ABC-111029905	FEVER	Onset of TEAE	first onset of grade 2 event	grd2onset	4.3		
ABC-111029905	FEVER	Onset of TEAE	first onset of grade 3 event	grd3onset	8.1		
ABC-111029905	FEVER	Onset of TEAE	first onset of worst event	wstonset	8.1		

Example : sample ADTTES dataset

First onset of an adverse event

First onset of an AE adverse event parameter captures the duration from the first dose date to the first onset of an adverse event of interest in a patient. This information can be further drilled down to capture by severity grade wise as seen in dataset above. First onset information informs a medical monitor about the number of patients with the same ae, the severity grade and average duration it takes for its first onset.

Improvement/Resolution of first episode

This parameter captures duration from onset of first episode of an ae to improvement or resolution. Here, first episode refers to first time an adverse event occurred in a patient while on trial. For instance, the same adverse event can occur multiple times over the course of a study. However, this parameter captures information about the improvement or resolution of the first episode alone. The first episode data can be captured at as granular a level as needed as per the study. Some of the data points calculated in the example dataset provided above are 'Grade 3 or 4 to Grade 1 or resolution' and 'Grade 3 or 4 to Resolution' etc.

Improvement/Resolution after EOT

After EOT visit, it may be important to follow up with a patient to study long term effects of a study treatment. Improvement/Resolution of an AE after EOT parameter data can be derived for all combinations of grades. For instance, in the example dataset above, after EOT, duration from a grade 3 or 4 to grade 2 or grade 1 or complete resolution and duration from grade 3 or 4 to complete resolution are derived. This kind of granularity about the each adverse event and its severity and the time it took for improvement provides a great deal of information for medical monitors and the study team to understand the safety of study drug and adjust the trial plan accordingly.

CONCLUSION

Though time to event analysis is usually done for efficacy evaluations, it can be very useful to perform it on safety data as well as it provides a comprehensive look at adverse events of interest which is essential in evaluating safety of a drug.

REFERENCES

- The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- CTCAE guide version 4.03
- CDISC SDTM Implementation guide v3.1.3
- CDISC ADaM Implementation Guide v1.0

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