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Summarizing Adverse Events of Interest – Onset, Duration, and Resolution

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ABSTRACT

One of the main objectives of clinical trials is to study the safety of the drug. To understand the safety of a drug in a first-in-human clinical trial, it is important to study adverse events and their corresponding severity grades. In most of the clinical trials there will be specific AE's of interest that need to be analyzed in detail. Summarizing the onset, duration and resolution of AE's of interest will provide the medical monitor with important information to determine the safety of the drug. In this paper, we will introduce the data analysis & presentation of treatment-emergent AE onset, AE duration and time-to-resolution of AE's of interest, after End-of-Treatment using SAS®. The onset data analysis provides a summary of time to first onset of AE of interest. The duration data analysis provides the duration of first occurrence of grade 3 or 4 events, to improvement or resolution. The AE resolution data analysis provides a summary of improvement or resolution of AE's of interest, after End of Treatment.

INTRODUCTION

While conducting a first in human clinical trials, it is of utmost importance to study the safety of the drug by monitoring the patient for Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and adverse reactions. Adverse reactions, commonly referred as adverse events, play a major role in determining the safety of the drug as both DLT and MTD are also based on AEs. There are some existing standard tables to present AE data. However, our team's curiosity to know more about a particular AE in detail led us to create a few AE tables to identify when an AE started, whether it is treatment emergent, what is its severity, how long it takes for its improvement or resolution. In this paper, we would like to discuss these tables that present AE data in a clear and concise manner for study team review or FDA submission.

Below are a few definitions to familiarize ourselves with before we move on to the tables.

Adverse event (or AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a Pharmaceutical product and which does not necessarily have 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.

Table for analyzing time to onset of AE

Time to onset is analyzed from the first dose of the investigational drug to first occurrence of the AE of interest. The dataset displayed below shows the AE of interest, start date, end date and first dose date. So the time to onset is calculated as the difference between ae start date and first dose date.

Subject	Aespid	Aeterm	Aedecod	AE toxicity Grade	AE start date	AE end date	First dose date
10001-0001	15:01	FATIGUE	FATIGUE	3	**17-Jul-14**	29-Jul-14	**20-Jun-14**
10001-0001	15:02	FATIGUE	FATIGUE	2	29-Jul-14	26-Aug-14	20-Jun-14
10001-0001	15:03	FATIGUE	FATIGUE	1	26-Aug-14	.	20-Jun-14
10001-0001	19:01	DYSPNEA	DYSPNEA	1	20-Aug-13	12-Nov-13	20-Jun-14

Following are some of the data steps that show the sub setting of data and calculation of onset days in weeks.

```
data ae;
set a.adae;
by usubjid;
if aedecod = 'AE of INTREST' and aetrtem='Y';
run;

proc sql;
/*time to onset of any  AE of intrest*/
create table onset as
select usubjid, (min(aestdy)/7)  as onsetday
from ae(where=(aestdt^=.))
group by usubjid;
quit;
```

The onset can be summarized in a table by calculating the mean and median by dose group. The following table shell shows the display of statistics.

SUMMARY OF ONSET OF TREATMENT-EMERGENT AE OF INTREST
All Treated Patients Set

	Dose 1 (N=xx)	Dose 2 (N=xx)	…	Dose X (N=xx)	Total (N=xx)
Time to onset of AE of interest among those with at least one event (weeks)					
N	xx	xx	xx	xx	xx
Mean (STD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Median	xx	xx	xx	xx	xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Median time to onset of any AE of interest (weeks)c					
n	xx	xx	xx	xx	xx
95% CI	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
25th-75th Percentile	xx	xx	xx	xx	xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Table for analyzing duration of AE

If a treatment related AE occurs there will be a great interest to know how long the subjects are experiencing the AE, and what is the time taken to improve from a grade 3 or 4 to a grade 1 or resolution. The duration for these events can be calculated and analyzed by dose group. The dataset below shows a grade 3 event, which recovers to a grade 2, grade 1, and to a complete resolution. The duration of the grade 3 event can be calculated as the difference between start dates of grade 3 events to start date of grade 2 event. The duration of the whole event is calculated as the difference between start date and the resolution date. In the Kaplan-Meier analysis, if the AE is ongoing and does not have a resolution date a date of last contact is imputed as minimum of treatment end date plus 30 days (30 days is AE follow-up time), end of study date and death date. The imputation of end date and creating censoring variables are shown in the code displayed below.

Subject	Aespid	Aeterm	Aedecod	Outcome	AE toxicity Grade	AE start date	AE end date	censoring variable
10001-0008	15:01	FATIGUE	FATIGUE	RECOVERING/RESOLVING	3	**17-Jul-14**	29-Jul-14	
10001-0008	15:02	FATIGUE	FATIGUE	RECOVERING/RESOLVING	2	29-Jul-14	26-Aug-14	
10001-0008	15:03	FATIGUE	FATIGUE	RECOVERED/RESOLVED	1	**26-Aug-14**	**30-Aug-14**	0
10001-0008	19:01	DYSPNEA	DYSPNEA	RECOVERED/RESOLVED	1	20-Aug-13	12-Nov-13	0
10001-0009	17:02	HEADACHE	HEADACHE	NOT RECOVERED/NOT RESOLVED	2	20-Aug-13	**12-Nov-13**	1

Following are some of the data steps that show the calculation of ae duration, creating censoring variable and proc lifetest.

```
data ae;
set a.adae;
by usubjid;

 if aedecod = 'AE of INTREST' and aetrtem='Y';

/** creating a censoring variable **/
 if ^nmiss(aeendt,aestdt) then aescens=0;
else if aeendt=. then aescens=1;

/** imputing missing end date for Km analysis**/
if aeendt=. then aeendt_i=round(min((trtendt+30), eosdt,dthdt));
run;

proc sql;

  create table adae_stdt as
  select   distinct usubjid , min(aestdt) as startdt format date9.
  from ae
           group by usubjid
           order by usubjid;
quit;

proc sort data=ae;
by usubjid decending aeendt_i;
run;

data adae_endt;
set ae;
by usubjid ;
 if first.usubjid;
 enddt=aeendt_i;
 keep usubjid aeendt_i aeendt aescens enddt;

run;
```

```
data adae_dt1;
merge adae_stdt adae_endt;
by usubjid;
/***** Calculating duration from AE start and end dates ***/
if ^nmiss(startdt,enddt) then aedur=round((enddt - startdt + 1)/7,0.1);
run;

ods output quartiles=quartiles;
proc lifetest data=surv0 method=pl alpha=.05 outsurv=ci95;
  time aedur*aescens(1);
  by trt1pn;
run;
ods output close;
```

The following table shows the display of statistics by dose group. Duration of AE's of interest will be analyzed using Kaplan-Meier methodology. The median duration of events and its two-sided 95% CI are calculated using the complementary log-log transformation method.

Summary of Improvement or Resolution of Treatment-Emergent AE of Interest
All Treated Patients Set

	Dose 1 (N=xx) n (%)	Dose 2 (N=xx) n (%)	Dose 3 (N=xx) n (%)	DoseX (N=xx) n (%)	Total (N=xx) n (%)
Subjects with grade >=3 adverse events, n (%)	xx	xx	xx	xx (xx)	xx (xx)
Duration from 1st Grade 3 or 4 to improvement to Grade 2 or Grade 1 event or resolution (wks)					
n	xx	xx	xx	xx	xx
Mean (STD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Median	xx	xx	xx	xx	xx
Min, Max	xx,xx	xx, xx	xx, xx	xx, xx	xx, xx
Duration from 1st Grade 3 or 4 to Gr 1 event or resolution (wks)					
n	xx	xx	xx	xx	xx
Mean (STD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Median	xx	xx	xx	xx	xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

The duration can be calculated at different time points in the study. If the subject experiences an AE we want to know how long it took for the first episode to resolve. This kind of information may be helpful for medical monitors working with investigators on dose modifications if the AE is related to drug. The following table summarizes the duration of first episode.

Duration of First Episode of AE of Interest

All Treated Patients Set

	Dose 1 (N=xx)	Dose 2 (N=xx)	…	Dose X (N=xx)	Total (N=xx)
Duration of first occurrence of AE of Interest (weeks)					
Median	x.x	x.x		x.x	x.x
95% CI	-, -	-, -		-, -	-, -
25th-75th Percentile	x.x, x.x	x.x, x.x		x.x, x.x	x.x, x.x
Min, Max	x.x, x.x+	x.x, x.x+		x.x, x.x+	x.x, x.x+

Time to Resolution of AE's of Interest, After End of Treatment

Some treatment emergent, investigational drug related AE's will be ongoing as the subject is getting dosed in multiple cycles, so it will be hard to summarize the resolution of AE during treatment. In such cases there will be an interest to find out about the improvement or resolution of the AE after EOT, so the status of the AE is followed and flagged for analysis. The following dataset is an example of how we flag the AE's to determine their status after EOT.

Subject	Aespid	Aeterm	Aedecod	Outcome	AE toxicity Grade	AE start date	AE end date	Improve	Worsening	Resolve
10001-0008	15:01	LEFT HEAD PAIN	HEADACHE	RECOVERING/ RESOLVING	3	**17-Jul-14**	29-Jul-14	Y		Y
10001-0008	15:02	LEFT HEAD PAIN	HEADACHE	RECOVERING/ RESOLVING	2	29-Jul-14	26-Aug-14	Y		Y
10001-0008	15:03	LEFT HEAD PAIN	HEADACHE	RECOVERED/RESOLVED	1	**26-Aug-14**	**30-Aug-14**	Y		Y
10001-0008	16:01	LYMPHOMA PAIN (HEAD/TEMPORAL MUSCLE)	HEADACHE	RECOVERED/RESOLVED	2	29-Jul-14	26-Aug-14			Y
10001-0009	17:01	HEADACHE	HEADACHE	NOT RECOVERED/NOT RESOLVED	1	**26-Aug-14**	**30-Aug-14**		Y	
10001-0009	17:02	HEADACHE	HEADACHE	NOT RECOVERED/NOT RESOLVED	2	20-Aug-13	12-Nov-13		Y	
10001-0009	17:03	HEADACHE	HEADACHE	NOT RECOVERED/NOT RESOLVED	3	**17-Jul-14**	29-Jul-14		Y	

The AEs can be analyzed in a table shown below. The table has the counts of subjects with resolution, improvement, or worsening after EOT.

Summary of Improvement or Resolution of Treatment-Emergent AE's of Interest after Last Dose
All Treated Patients Set

	Dose 1 (N=xx)	Dose 2 (N=xx)	…	Dose X (N=xx)	Total (N=xx)
Patients with any AE of interest on or after last dose, n (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with resolution or improvement of AE of interest	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with resolution of all AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with improvement of AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with no improvement of AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with worsening AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with any worst grade 3 or 4 AE of interest on or after last dose, n (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with resolution or improvement of AE of interest	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with resolution of all AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with improvement of AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with no improvement of AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Patients with worsening AE of interest events	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

	Dose 1 (N=xx)	Dose 2 (N=xx)	…	Dose X (N=xx)	Total (N=xx)
Patients with improvement to grade 1 or below	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

CONCLUSION

To correctly determine the safety of a study drug, it is important to study adverse events that arise during the clinical trial, either drug related or not. This paper illustrates a few approaches to analyzing adverse events of interest at a micro level and preparing publication ready AE tables for onset, time to resolution or improvement and duration of adverse events.

REFERENCES

- The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- CTCAE guide version 4.03

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