



Syneos™
Health

PhUSE US Connect 2018

Adverse Event Analysis – One step forward!

- Anuja Rasal

05June2018

Disclaimer -

All views and opinions documented here are those of the author and do not necessarily represent the opinion, recommendation and practices of Syneos Health.

Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Adverse Event (AE) occurring in a subject can be elaborately referred as –

- Any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug.
- An event that can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.



Agenda

- Categories and Definitions
- Safety Analysis
- Adverse Event Analysis
 - Types of Analysis
 - Conventional AE analysis
- Categorical Analysis of Adverse events
- Exposure adjusted AE analysis
- AE's of Special Interest and their Analysis
 - Start Day of AE's
 - Duration of AE's
 - Tier-based Analysis of AE's
- Safety Signal Detection
- Conclusion

Adverse Event – Categories and Definitions

• Adverse Drug Reaction

- Cough, Nausea, Vomiting, Diarrhea, Headache. Skin reaction – Rashes, Itching

• Expected AE's

- In Diabetes, Hypoglycemia, Hyperglycemia, Blurred vision

• Unexpected AE's

- In Diabetes, skin disorders like Oedema

• Serious AE's

- Cardiac Arrest, Coronary Artery Stenosis

• Non Serious AE's

- Anything that is not life threatening. Cough, Headache

• Related AE's

- Any AE that is deemed related to the study drug by the PI

• Unrelated AE's

- Any AE that is deemed not related to the study drug by the PI

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Continued..

- **Adverse events of special interest (AESIs)** – An AE or a group of AEs of scientific and medical concern specific to the **sponsor's product or program**, which may require further investigation in order to characterize and understand them.
- Example AESIs include peripheral events, infections, and hypersensitivities etc.
- Some AESIs can be addressed using a Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA query (SMQ) and should be addressed with a MedDRA SMQ if one exists for the medical concept of interest.
- **Exposure Adjusted Incidence rate (EAIR)** – EAIR of AEs is defined as the number of subjects exposed to the drug and experiencing a certain event divided by the total exposure time of all subjects who are at risk for the event.
- Specifically, for subjects with **no event**, the exposure time is the time from the first drug intake to the last follow-up assessment;
- For subjects with at least **one event**, the exposure time is the time from the first drug exposure to first event.

Safety Analysis



Safety Analysis

• What is Safety Analysis ?

Safety Analysis comprises registering the side-effects produced by the drugs administered in a clinical trial and documenting and reporting them on an unbiased basis to the regulatory authorities. Comprises of various measurements.

- Adverse Events

- Site data

- Vital Signs

- Site and Diary data

- ECG

- Site data

- Laboratory Measurements

- Site Data

- Medical History

- Site data at baseline

Safety Analysis

Continued..

How are safety parameters analyzed?

Common but not usual methods include -

–Summary tables

- Descriptive summaries of change from baseline by visit / by treatment
- Descriptive summaries by different category subsets
- Categorical representation of data using n proportions
- Increase/Decrease in levels of various data

–Listings

- Listings by different categories
- Listings for data from/between definite periods

–Laboratory shift tables

- Overall summaries of shift tables
- Summaries for different subsets of laboratory data

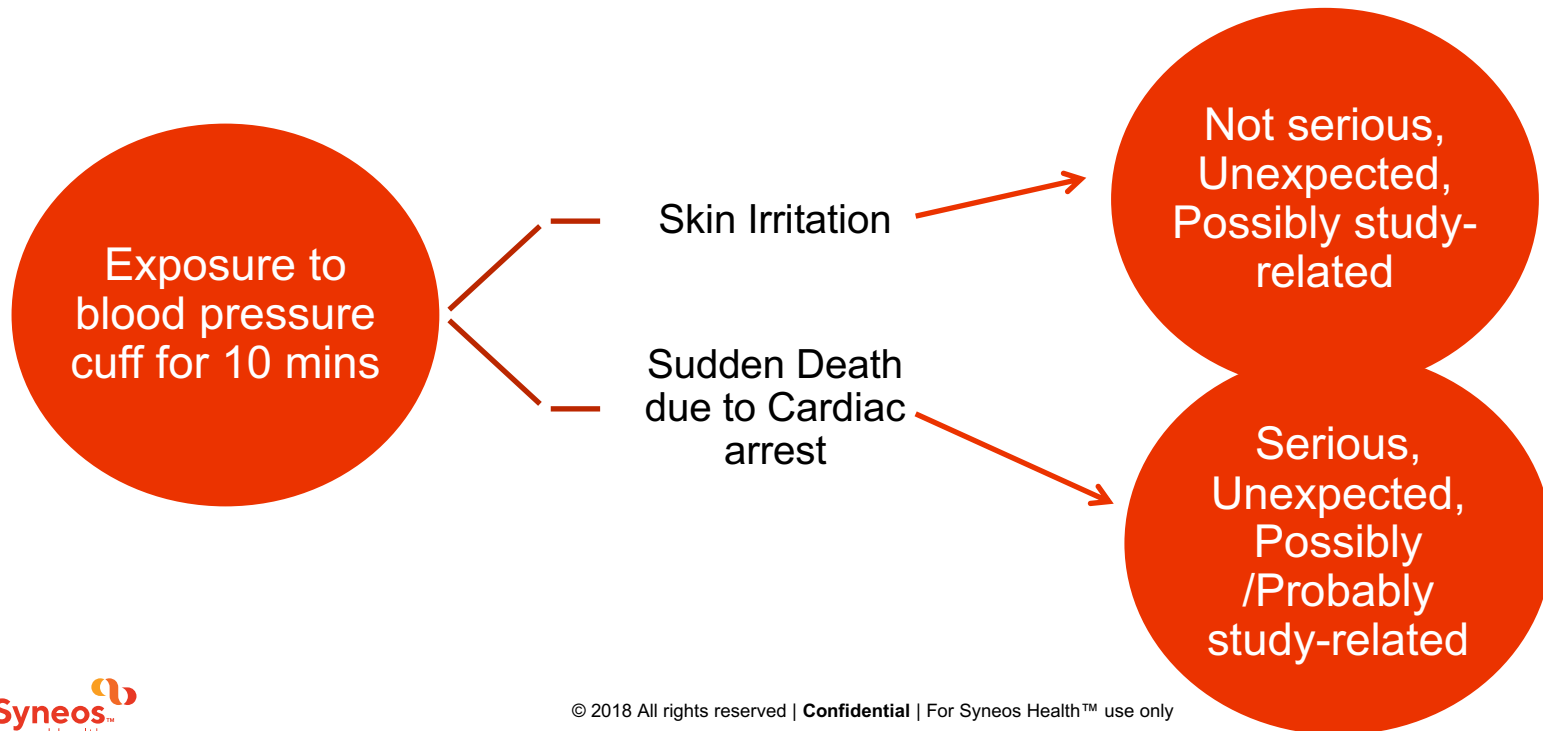
Adverse Event Analysis



Adverse Event Analysis

Headache(mild AE)  Cardiac Arrest(severe AE)

Every adverse event in a clinical trial is often summarized by their occurrence, percentage of occurrence, severity, seriousness, outcome, relation to treatment and so on.



Adverse Event Analysis

Continued..

- Data Monitoring Committee or Adjudication Committees
 - AE analysis for submission to DMCs/Adjudication Committees
 - Timely analysis helps in decision making for applying stopping rule/interim analysis
- CSR Analysis
 - AE analysis done for Clinical study reports and Blinded Data Review submissions help gauge trend of AE data and are therefore necessary.
- Adverse Events of Special Interest (AESI)
 - General set of summary reports created for all AE data is created for AESI along with some additional analysis reports by the sponsor statisticians and clinicians for better analysis.
- Adverse Events analysis as Endpoint analysis
 - Inferential Summary reports are created to judge the occurrence and significance (p-value) of all/a set of AEs by using various statistical procedures suitable to the data.

Conventional Adverse Event Analysis

- Adverse events are recorded as verbatim by principal investigators on site. These verbatim events recorded in the case report form (CRF) are coded into preferred terms and many other levels of terms as per the coding standard used for medical coding of adverse events which is available to us as **MedDRA (Medical Dictionary for Regulatory Activities)**. These levels of adverse event term coding hierarchy are used for further analyses.
- The commonly used coding levels of adverse event data are - **System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Lowest Level Term (LLT) and Preferred Term (PT)**.
- Adverse events are tabulated and are commonly presented in the form of occurrences and percentage of occurrences by SOC and PT.

Conventional Adverse Event Analysis

Continued..

- Below mentioned is a standard AE table in which **overall summary of incidence of treatment-emergent adverse events is given by system organ class by preferred term.**
- It is displayed as number of TEAE occurred within each treatment arm for subjects with percentage calculated as **number of adverse events** divided by the **total number of subjects at risk** for the given treatment arm into 100.

Protocol XXX Page 1 of y Incidence of Treatment-Emergent Adverse Events by System Organ Class (Safety Population)			
	PL (N=xxx) ----- n (%)	TRT 1 (N=xxx) ----- n (%)	TRT 2 (N=xxx) ----- n (%)
Number (%) of Subjects with TEAE by:			
System Organ Class and MedDRA (xxx) Preferred Term			
System Organ Class #1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term #1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term #2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class #2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term #1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term #2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class #3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term #1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred term #2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Conventional Adverse Event Analysis

Continued..

- Below shown is the **summary of incidence of treatment emergent adverse event displayed by descending frequency**.
- In this summary, the highest occurrence of any adverse event in the treatment group of higher dose, for e.g. TRT1 (10 mg) is displayed, followed by the second highest dose of treatment group.

Protocol XXX

Page 1 of y

Incidence of Treatment-Emergent Adverse Events by Descending Frequency (Safety Population)

	PL (N=xxx) ----- n (%)	TRT 1 (5 mg) (N=xxx) ----- n (%)	TRT 1 (10mg) (N=xxx) ----- n (%)
Number (%) of Subjects with Adverse Events by:			
MedDRA (xxx) Preferred Term			
Headache	11 (xx.x)	18 (xx.x)	20 (xx.x)
Nausea	4 (xx.x)	6 (xx.x)	7 (xx.x)
Shoulder Pain	5 (xx.x)	5 (xx.x)	7 (xx.x)
Neck Pain	3 (xx.x)	4 (xx.x)	7 (xx.x)
Arthralgia	8 (xx.x)	3 (xx.x)	6 (xx.x)

Subjects are counted only once per treatment in each row.

Adverse events are shown by descending frequency by the highest TRT1 dose, and in the case of a tie then for next lower TRT1 dose.

Conventional Adverse Event Analysis

Continued..

- For example, if we have 'Headache' as the highest occurring AE in TRT1 (10mg) with number 20 and we have other AEs like Nausea, Shoulder Pain and Neck pain having the same number of count – 7 in TRT1 (10 mg), then we will have descending sorting order displayed in TRT1 (5mg) for these respective AEs as 6, 5 and 4 within TRT1 (10 mg) as it is the treatment arm with next highest dose value.
- This analysis will give you **better knowledge of a particular AE occurrence** within the study and its **persistence** if analyzed over a period of time.

Categorical Analysis of Adverse Events



Categorical Analysis of Adverse Events

- The crude percentage (rate) is the simplest and also the most commonly used statistics for summarizing AEs in clinical trials.
- Contingency tables are often used to analyze AEs.
- Chi-square test and Fisher's exact test are two most popular approaches.
- How are they analyzed?
- Categories of interest –
 - Treatment-Emergent AE (TEAE)
 - Drug-related AE
 - Serious adverse event (SAE)
 - Higher intensity AE
 - Death
 - Adverse Event of Special Interest
 - Group of different list of AEs as per their significance to the protocol

Categorical Analysis of adverse events

Continued..

ORD	AECAT	TRT	OUTCOME	FREQ
1	Any TEAE	1	1	17
1	Any TEAE	1	2	23
1	Any TEAE	2	1	13
1	Any TEAE	2	2	52
2	Drug-Related TEAE	1	1	4
2	Drug-Related TEAE	1	2	36
2	Drug-Related TEAE	2	1	6
2	Drug-Related TEAE	2	2	59
3	Grade 3 or Higher TEAE	1	1	3
3	Grade 3 or Higher TEAE	1	2	37
3	Grade 3 or Higher TEAE	2	1	1
3	Grade 3 or Higher TEAE	2	2	64
4	Grade 3 or Higher Drug-Related TEAE	1	1	2
4	Grade 3 or Higher Drug-Related TEAE	1	2	38
4	Grade 3 or Higher Drug-Related TEAE	2	1	1
4	Grade 3 or Higher Drug-Related TEAE	2	2	64
5	Serious Adverse Event	1	1	3
5	Serious Adverse Event	1	2	37
5	Serious Adverse Event	2	1	2
5	Serious Adverse Event	2	2	63
6	On-study Death	1	1	1
6	On-study Death	1	2	39
6	On-study Death	2	1	0
6	On-study Death	2	2	65

```
proc freq data=ae;
  by ord;
  tables outcome*trt / CHISQ FISHER EXPECTED;
  weight freq;
  ods output FishersExact=Exact(where=(Name1='XP2_FISH'));
  ods output ChiSq=ChiSq(where=(Statistic='Chi-Square'));
  ods output CrosstabFreqs=Freqs(where=(Expected >.z));
run;
```

Categorical Analysis of Adverse Events

Continued..

Category	Control (N=40)	Active (N=65)	P-value
Any TEAE	17 (42.5)	13 (20.0)	0.013
Drug-Related TEAE	4 (10.0)	6 (9.2)	1.000
Serious Adverse Event	3 (7.5)	2 (3.1)	0.367
Grade 3 or Higher TEAE	3 (7.5)	1 (1.5)	0.153
Grade 3 or Higher Drug-Related TEAE	2 (5.0)	1 (1.5)	0.556
On-study Death	1 (2.5)	0 (0.0)	0.381
Note: P-value is based on a chi-square test. If any cell has expected counts less than 5, then the Fisher's exact test is used instead.			

From the above table we can say that we could only get a **statistically significant p-value for the category 'Any TEAE'** in the Active treatment group with occurrence value to be lower as compared to the Control treatment group. **All other categories of AE classification did not show statistically significant results.**

Exposure-Adjusted Adverse Event Analysis



Exposure Adjusted Adverse Event Analysis

- **Crude Percentage** - The crude percentage is the most commonly used measurement for summarizing safety data.
 - It is defined as the number of subjects exposed to the drug and experiencing a certain event divided by the total number of subjects exposed to the drug, regardless of duration of follow-up.
 - The crude percentage is most appropriate where all subjects are treated and followed for the same period of time.
 - $n/N \times 100$ where n is the number of subjects experiencing a certain event
N is the total number of subjects exposed to the drug.
- **EAIR** – In situations where subjects have different durations of drug exposure, or a long-term follow-up, the crude percentage is not appropriate because it does not take into consideration of the duration of drug use.
 - It is defined as the number of subjects exposed to the drug and experiencing a certain event divided by the total exposure time of all subjects who are at risk for the event.
 - $n/D \times 100$ where n is the number of subjects experiencing an event
D is the duration calculated as the exposure years

Exposure Adjusted Adverse Event Analysis

Continued..

How is the below calculation done?

– $n/D \times 100$ where n is the number of subjects experiencing an event

D is the duration calculated as the exposure years.

- Exposure Years - Exposure years is calculated as last study drug exposure date minus first study drug exposure date plus one, divided by 365.25 which is the number of days count in a year.

$$\text{Expyears} = (\text{Last dose date} - \text{first dose date} + 1) / 365.25$$

- This exposure year calculated for each subject is then added cumulatively and is derived for each treatment arm. So each treatment arm will have one value of exposure years aka patient-years.

$$D = \text{Expyears } 1 + \text{Expyears } 2 + \text{Expyears } 3 + \dots + \text{Expyears } n.$$

- The exposure year calculation is different in case of subjects who have completed the study or discontinued from the study or have withdrawn from the study due to any reason.
- It is also different for crossover studies where the subject has moved from one treatment arm to another. In that case, drug exposure for both treatments is calculated and displayed separately in the summary table.

Exposure Adjusted Adverse Event Analysis

Continued..

Table 14.x.x.x Protocol			Page 1 of y
Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events			
Number of Subjects (rate per 100 patient- years) Preferred Term	P1 (N=XX)	TRT 1 (N=XX)	TRT 2 (N=XX)
Exposure Years	EY	EY	EY
Preferred term 1	n (e)	n (e)	n (e)
Preferred term 2	n (e)	n (e)	n (e)
Preferred term 3	n (e)	n (e)	n (e)

Here, EY is the exposure years calculated for all subjects in the treatment arm which is cumulative addition of exposure years for all subjects in days.

n is the frequency of adverse events per treatment arm

e is the percentage calculated as $n/EY * 100$ which gives the exposure adjusted rate of adverse events

- A key feature of this approach of analyzing adverse events for a long term study is that it is **easy to implement and interpret**.
- Statistical analysis of Exposure adjusted AE can be done in various ways depending upon the needs of the protocol. Like '**Exposure-adjusted incidence of TEAE by descending frequency**', '**Exposure-adjusted incidence of serious TEAE**', '**Exposure-adjusted incidence of TEAE leading to discontinuation**' and so on.

Adverse Events of Special Interest and their Analysis



Adverse Events of Special Interest and their Analysis

- Adverse Events of Special Interest are those events thought to be [potentially] associated with the **investigational compound or disease** under study. Reporting on Adverse Events of Special Interest is an emerging and ever more critical aspect related to **characterizing the safety profile** of a compound.
- **Standard MedDRA Queries (SMQs)** - presented by the MedDRA group of coding, or grouping of terms that relate to the defined medical condition or area of interest, exists to select all events similar in some way (e.g., Peripheral sensations).
- In addition, as Events of Special Interest lists become more numerous and detailed, the potential coding changes caused by **MedDRA updates** every six months necessitate the team re-review these lists twice a year (after each upgrade) in order to ensure the list of adverse events of special interest remain accurate.

Adverse Events of Special Interest and their Analysis

Adverse Event Start Day Analysis

- Summaries of AE start day for these selective terms of interest as per the clinicians and statisticians in relation to their first dose of drug administration (AESTDY) are done.
- Categories from 0 weeks to 4 weeks, 4 weeks to 8 weeks, 8 weeks to 16 weeks and so on. The **descriptive statistics** of the start days of these adverse events can also be derived for better analysis. The summary table for such analysis looks like below.

Table 14.X.X.X.X

Page 1 of y

Protocol

Summary of start day of adverse events of special interest

Start day of Adverse
Event (days)

Start of Adverse Event after First Dose (weeks) [1]

	0-<4 n (%)	4-<8 n (%)	8-<16 n (%)	Total n (%)	Mean, Median	Min, Max
Pl (N=XXX)						
Preferred term 1	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x, xx.x	(xx, xx)
Preferred term 2	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x, xx.x	(xx, xx)
TRT1 (N=XXX)						
Preferred term 1	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x, xx.x	(xx, xx)
Preferred term 2	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x, xx.x	(xx, xx)
TRT2 (N=XXX)						
Preferred term 1	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x, xx.x	(xx, xx)
Preferred term 2	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x, xx.x	(xx, xx)

[1] Start of first adverse event in each adverse event group is summarized in relation to date of first dose.

Preferred term 1 and Preferred term 2 belong to the list of Adverse Events of special interest.

Adverse Events of Special Interest and their Analysis

Duration of Adverse Event Analysis

- Summaries of AE duration for these selective terms of interest as per the clinicians and statisticians in relation to their first dose of drug administration and time for which the AE continues is done by using the categories of weeks and displaying the duration of the AEs falling within these week categories.
- Duration is calculated as AE stop date minus AE start date plus one.
- For e.g. Categories from 0 weeks to 2 weeks, 2 weeks to 4 weeks, 4 weeks to 6 weeks and so on.
- These AEs can be displayed and spit into two parts – resolved and still present.
- In cases of AEs that are shown in the later part where the AEs are still present, the **AE stop date** is usually considered as to be the **study completion or the study discontinuation date** for that particular subject. The descriptive statistics of these adverse events can also be derived for better analysis. The summary table for such analysis looks like below.

Adverse Events of Special Interest and their Analysis

Continued..

Table 14.X.X.X.X

Page 1 of y

Protocol

Summary of duration of adverse events of special interest

Adverse Events resolved/Adverse Events still present/All Adverse Events

Duration of Adverse Event (weeks)							
	0-<2	2-<4	4-<6	Total	Mean, Median		Min, Max
	n (%)	n (%)	n (%)	n (%)			

P1 (N=XXX)							
Preferred term 1	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x,	xx.x	(xx, xx)
Preferred term 2	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x,	xx.x	(xx, xx)
TRT1 (N=XXX)							
Preferred term 1	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x,	xx.x	(xx, xx)
Preferred term 2	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x,	xx.x	(xx, xx)
TRT2 (N=XXX)							
Preferred term 1	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x,	xx.x	(xx, xx)
Preferred term 2	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	xx.x,	xx.x	(xx, xx)

Preferred term 1 and Preferred term 2 belong to the list of Adverse Events of special interest.

Adverse Events of Special Interest and their Analysis

Continued..

- Conclusion :

- This Summary of start day analysis shows the number of adverse events **starting during which part of the trial** as per the weeks. This shows the trend of **when** and **how** the adverse event of special interest occurred during the trial reporting period. This helps in better analysis for the clinicians and stakeholders to take decisions about the trial.
- This Summary of duration of adverse event analysis shows the number of adverse events categorized by **duration for which** they might have occurred during **which** part of the trial as per the weeks. This shows the trend of **when** and **how** long the adverse event of special interest occurred during the trial reporting period. This helps in better analysis for the clinicians and stakeholders to take decisions about the trial.
- Along with trend analysis, this kind of start day & duration analysis along with the study of Concomitant Medications helps the statisticians to analyze and approve of any other Concomitant/Study Medications that will help reduce/decrease the intensity of the AE. It helps the study more, if the AE in question is of special interest to the program.

Tier based AE analysis

- Among standard reporting of adverse events of special interest, other AE analysis includes classification of adverse events into various tier system, viz. **1-Tier, 2-Tier, 3-Tier system** based on their **percentage of occurrence** and their importance to the trial.
- They can be analyzed for their risk differences between treatment groups and the comparator with 95% confidence intervals using exact methods.

Table 14.X.X.X.X Protocol Summary and Analysis of Tier 1 Treatment-Emergent Adverse Events				Page 1 of y		
	Treatment			95% Confidence Interval		
System Organ Class and MedDRA Preferred Term	TRT1 (N=xxx) ----- n (%)	Comparator (N=xxx) ----- n (%)	Risk Difference	Lower Limit	Upper Limit	p- value
System organ class #1						
Preferred term #1	xxx (xx.x)	xxx (xx.x)	x.xxxx	x.xxxx	x.xxxx	x.xxxx
System organ class #2						
Preferred term #1	xxx (xx.x)	xxx (xx.x)	x.xxxx	x.xxxx	x.xxxx	x.xxxx
...						
...						
P-values and confidence intervals are not adjusted for multiplicity and should be used for screening purpose only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference is computed as 'TRT1 vs. Comparator'. Exact methods are used for 95% confidence intervals and significance tests.						

Tier based AE analysis

Continued..

- Here, risk differences calculated is the **estimate of difference in proportions** of incidence of particular AE of special interest falling under the respective treatment arm.
- 95% confidence intervals give us the lower limit and the upper limit estimates of the risk difference calculated for that particular adverse event.
- Any significance between the risk differences of these adverse events occurrence in this hypothesis testing can be seen if the p-value is less than 0.05 where alpha (Type I error)=0.05.

Safety Signal Detection

- A 'signal' consists of reported information on a possible causal relationship between **an adverse event and a drug**, the relationship being unknown or incompletely documented previously.
- Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.
- **'Signal detection', 'signal generation' or 'signaling'** refers to a process that aims to find, as soon as possible, any indication of an unexpected drug safety problem which may be either **new ADRs or a change of the frequency of ADRs** that are already known to be associated with the drugs involved during the course of the trial or during the post-marketing surveillance of the drug.
- Timely analysis, usually **quarterly**, by creating summaries of adverse events and other safety measurements such as **Vital signs, ECG, Laboratory abnormal findings** is done to keep a check on the increase in intensity of observations taken at baseline and/or new findings arisen after baseline.

Conclusion

- A powerful study is generally designed for evaluating drug's efficacy, while safety profiles, including AEs, are for **exploratory** purposes only. In other words, the determination of sample size of the trial (if needed) can't guarantee the statistical power for assessing any variables other than efficacy. Therefore, we must be cautious when explaining the p-values or confidence intervals for AE parameters.
- We always recommend **stressing the results of statistical analysis on AEs as of guidance or exploratory nature, rather than statistically confirmative.**
- The statistical methods introduced in this paper are definitely not a comprehensive list. The appropriate applications **depend on study design and investigating purpose.**

Acknowledgements

I would like to thank my colleagues and peers who helped me with their valuable feedback which helped me in improvising the paper. I would like to thank my manager Akhil Mishra for providing valuable feedback and support throughout. I would also like to thank my family for their constant support.

Shortening the Distance From Lab to Life™

Questions?

