

Adverse Event Analysis - One step forward!

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ABSTRACT

From Headache (mild AE) to a 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 Events of special interests which are sometimes critical to the study report analysis or interim analysis of a trial are categorically analyzed for AE Onset Date, AE Duration along with their descriptive statistics. Statistical significance testing is done using Fischer's Exact, Chi-square test. Extrapolating incidences of adverse events is done by calculating exposure-adjusted incidence rate, 100-patient years. Risk-Rate analysis by calculating their odds ratios between treatment groups for AE's of special interest shows the power of statistical analysis in analyzing the safety avenue of a trial. We will look into more detail of such kind of Adverse Event analysis in the article to follow.

INTRODUCTION

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.

Similarly we have various classifications of adverse events depending on various factors. Adverse events can conventionally be analyzed by displaying frequency and percentages. They can also be analyzed by displaying incidences of their occurrences by treatment and reporting period and they can be statistically analyzed using tests for exact and goodness of fit like Fischer's and Chi-square test.

We will be looking into different methods available for analysis of adverse events. From this analysis, clinicians and statisticians interpret and report data to the regulatory agencies by means of clinical study report, safety narratives and manuscripts per patient to take appropriate action. Let's look into some AE definitions and categories required for such analysis.

ADVERSE EVENTS – CATEGORIES AND DEFINITIONS

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

- An adverse event (also referred to as an adverse experience) that can be 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 adverse 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.

Adverse Drug Reaction (ADR) – An undesirable effect, reasonably likely to be caused by a study drug and it may occur as part of the pharmacological action of the study drug or may be unpredictable in its occurrence.

Expected Adverse events – An expected AE is any adverse reaction whose nature and intensity have been previously observed and documented for the study product (e.g. in the investigator brochure, product information).

Unexpected Adverse Event – An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Serious Adverse Event (SAE) – An AE meeting one of the following conditions

- Death during the period of protocol defined surveillance.
- Life threatening (defined as a subject at immediate risk of death at the time of the event)
- Hospital admission during the period of protocol defined surveillance.
- Any event that results in congenital anomaly or birth defect.

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- Any event that results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Non-serious AE - These are all AEs that do not meet the above criteria for “serious”.

Intensity of the AE - All AEs in the database are assessed by the investigator using the protocol defined grading system. If the protocol has no defined grading system, then guidelines such as the following will be used to quantify intensity –

- Mild: Transient or mild discomfort (<48 hours) to the subject; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity of the subject - some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity of the subject, some assistance usually required; medical intervention/therapy required hospitalization possible.

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.

Treatment Emergent Adverse Events (TEAE) – A treatment-emergent adverse event is defined as any event not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment.

SAFETY ANALYSIS

Safety analysis in a clinical trial encompasses analyzing different measurements taken during the reporting period of the trial. Adverse events recorded by the principal investigators at the investigation sites are the primary ones as any reaction that the subject has during the period is or can be due to the administration of the study drug.

Other measurements include the vital signs, ECG, laboratory measurements that appear to be abnormal when compared to the ones that are acceptable as per the Investigator Brochure (IB) or product information. For example; Increase or decrease in systolic or diastolic blood pressure, or an abnormal ECG reading after a meal and the drug dose administration can signal into an adverse reaction happening in the subject’s body which should be analyzed.

Numerous different safety parameters are analyzed while monitoring the safety avenue of a clinical trial which is mentioned in the protocol and the type of analysis is mentioned in the statistical analysis plan after sponsor or client approval are done.

These measurements of safety for adverse events or vital signs or an abnormal laboratory reading are usually analyzed and displayed in a summary table with their occurrences and percentages of occurrences among the total number of subjects at risk or the safety population.

Shift tables are created for laboratory readings to find out the change in values of subjects showing low, normal or high readings at baseline and have a shift in these values after drug administration. It represents cross-frequencies of baseline values with post-dose values. The laboratory assessments include various measurements like Hemoglobin, Creatinine, Fasting Plasma Glucose, Bilirubin, BUN (Blood Urea Nitrogen) and many more.

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ADVERSE EVENT ANALYSIS

Existing statistical methodology to evaluate the efficacy of a study drug in clinical trials is well-developed. However, the research on the safety analysis, including AE data, is very limited. In a clinical trial requiring statistical analysis, sample size determination generally requires patient enrollment to meet the efficacy criteria, while safety analysis is done only for exploratory purposes. Therefore, the majority of clinical trials simply request AEs to be tabulated and/or listed without any inferential statistical analysis. However, recent research demands rigorous analysis on AE datasets in clinical trials.

When preparing the statistical reports, clinical investigators and medical writers often ask biostatisticians and SAS programmers to provide statistical analysis on safety profiles, more often for a submission to regulatory authority such as the Data Monitoring Committee (DMC) or Adjudication Committees. These committees aid in implementing appropriate stopping rule or undertaking interim analysis which were not originally decided as per the protocol.

Often the interim analyses are pre-decided by the clinicians and statisticians and other stakeholders of the study or compound in cases of rare diseases or therapeutic areas where safety of a subject is the primary endpoint. However, at times when these interim analyses are not adjudicated before-hand, they are then decided by analyzing the interim data provided by the SAS programmers on a timely basis by these committees put in place. It is therefore necessary for practitioners to apply statistical approaches to AE and other safety profiles of a subject.

Most adverse event (AE) summary tables display the number of subjects experiencing an AE in each treatment group and include a standard percentage calculation. This standard way of calculating percentage is the number of subjects experiencing an AE divided by the number of subjects at risk who received a particular treatment. But in studies with long-term follow-up, this percentage calculation may not be appropriate because there is a potential for differences in the follow-up duration between treatment groups. A more appropriate measure under this scenario is the exposure-adjusted incidence rate.

Adverse Event data is also analyzed by displaying the number of subjects that have had the same AE of special interest and have started on the same start date called as 'Summary of start day of treatment emergent adverse events'. The duration for which the AE has occurred which is calculated as AE end date minus the AE start date plus one is also displayed as a 'Summary of duration of treatment emergent adverse events'.

AEs of special interest are summarized by their occurrence and are displayed in various ways viz. 'Summary of treatment emergent AESI by descending frequency of treatments', 'Incidence of treatment emergent AESI by treatments' and so on.

ADVERSE EVENT ANALYSIS AS ENDPOINT ANALYSIS

In multicenter trials occurring in different countries with different legal requirements of data collection involving thousands of subjects at the same time creates the need of analyzing adverse event data as a primary or secondary endpoint in order to track and analyze AE data with maximum accuracy and optimum integrity. AE data is usually but not necessarily analyzed as primary endpoint in Phase I and/or exploratory trials.

CONVENTIONAL ADVERSE EVENT ANALYSIS

Adverse Event data is collected verbatim by the investigator from the subjects or a suitable legally acceptable representative during subject visits or over telephone during telephone contact visits. 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 as their occurrences and percentage of occurrences by SOC and PT. Statistical analysis of adverse events by showing their occurrences and percentage of occurrences in the given population is shown by summarizing the incidence of TEAE by descending frequency of treatments.

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.

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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 Preferred term #1 Preferred term #2	xxx (xx.x) xxx (xx.x) xxx (xx.x)	xxx (xx.x) xxx (xx.x) xxx (xx.x)	xxx (xx.x) xxx (xx.x) xxx (xx.x)
System Organ Class #2 Preferred term #1 Preferred term #2	xxx (xx.x) xxx (xx.x) xxx (xx.x)	xxx (xx.x) xxx (xx.x) xxx (xx.x)	xxx (xx.x) xxx (xx.x) xxx (xx.x)
System Organ Class #3 Preferred term #1 Preferred term #2	xxx (xx.x) xxx (xx.x) xxx (xx.x)	xxx (xx.x) xxx (xx.x) xxx (xx.x)	xxx (xx.x) xxx (xx.x) xxx (xx.x)

Below mentioned 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 highest and second highest order of number of adverse events in the next higher treatment group.

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.

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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.			

Listing of adverse events in the entire study with their demographic characteristics, adverse event data like start date, end date, severity, seriousness, treatment start date, treatment end date, crossover drug data in case of crossover studies is presented. Along with this listing, listing of serious adverse events, listing of subjects discontinued from study due to adverse events is also created as a part of adverse event analysis submission. These listings give us comparative view with the summaries created for the submissions. Adverse event listing looks as displayed below.

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Listing of Adverse Events						
System Organ Class	MedDRA Preferred term/ Investigator term	Trt Phase	Adverse Event/ Study Start day/ Study Stop day	Intensity/ Outcome	Action/ Causality	
1001/100/1001 Yes	M/54yrs/WHITE/78kg	Active	7/	Severe/	Discontinued	
MUSCULOSKELE TAL TISSUE DISORDERS	Musculoskeletal pain/ Shoulder pain		12	Still Pres ent	from study/ Study Drug	
...						
...						
...						
...						

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.

A chi-square test is any statistical hypothesis test in which the sampling distribution of the test statistic is a chi-square distribution when the null hypothesis is true, or asymptotically true. This means that the 2 sampling distribution (if the null hypothesis is true) can be made to approximate a chi-square distribution as closely as desired when the sample size is large enough. The FREQ procedure in SAS provides several chi-square tests and the default one is Pearson's Chi-Square test for independence (or test for goodness of fit).

Fisher's exact test is an alternative statistical test to the chi-square test in the analysis of contingency tables when sample sizes are small. It is named after its inventor, R. A. Fisher, and is one of a class of exact tests, so called because the significance of the deviation from a null hypothesis can be calculated exactly, rather than relying on an approximation that becomes exact in the limit as the sample size grows to infinity, or asymptotically. FREQ procedure in SAS calculates and prints Fisher's exact test for 2 X 2 tables by default. For larger tables (either row or column is greater than 2), exact tests must be explicitly requested with the EXACT option on the TABLES statement.

Consider a randomized clinical trial with two treatment groups. 40 subjects receive control and 65 subjects receive active treatment. The trial lasts for about 3 months. Note that not every subject has an AE and some subjects may have two or more AEs during the study.

In order to comprehensively assess AE, the following information is generally of interest to the investigators:

- 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

Before assessing AEs between groups, we need to present the original AE data with a contingency table. Because not every subject has an AE during the study, the subject level data (e.g. demographic data) should be used to calculate each cell count. In the FREQ procedure, we use CHISQ and FISHER options in the TABLES statement to output two separate datasets with results from chi-square tests and Fisher's exact tests, and also use EXPECTED option to output another table of expected cell counts, which is similar to the contingency table with observed cell counts.

If the AE data looks like this, you can apply the Proc freq procedure to get the results as displayed in the table below.

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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;

```

SAS output generally gives a warning as “XX% of the cells has expected counts less than 5. Chi-Square may not be a valid test.” The warning message could be used as guidance for choosing between chi-square tests and Fisher’s exact tests. However, it couldn’t be used for programming purpose. Instead, we will use the output data by EXPECTED option to investigate whether any cell count is less than 5. We recommend using the chi-square test by default; if any category has a cell count less than 5, then the Fisher’s exact test will be used.

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 to be lower as compared to the Control treatment group. All other categories of AE classification did not show statistically significant results.

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EXPOSURE ADJUSTED ADVERSE EVENT ANALYSIS

Several measurements have been used to estimate rates of occurrence of adverse events associated with exposure to a drug. 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.

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. To adjust for potential differences on duration of drug exposure, the exposure adjusted incidence rate (EAIR), which is also referred to as incidence density, may be used. 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.

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. The EAIR is a measure of average events per unit time of exposure or follow-up.

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. 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. 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. The follow-up period, reporting period here and the subject by subject difference in start day and end date of exposure leads to the calculation of exposure years for accurate calculation of exposure adjusted incidence of adverse events.

A typical exposure adjusted adverse event summary report will look like below.

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	Pl (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 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). However, SMQs may be either too general or, in some cases, too specific for a project team to use 'straight out of the box'. It's also possible that there are not enough existing MedDRA SMQs to accommodate the needs of a project team.

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.

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The analysis of these special terms is done for subjects that show withdrawal from the study due to this adverse event or is marked as a serious adverse event or whose severity has changed after drug exposure. Various summary reports for these events are created in order to derive correct analysis of the safety of the drug when requested by the DMC or adjudication committees. Some detailed analysis that can be done for these events are documented below.

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. This is done by displaying the start days of the AEs falling within these week categories. For e.g. 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

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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.

This table 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.

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 split 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.

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Table 14.X.X.X.X
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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 n (%)	2-<4 n (%)	4-<6 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)	

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

This table 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.

Adverse Events of special interest can also be summarized by displaying the incidences and the percentages of incidence by descending frequency of the treatment groups. They can also be summarized for their seriousness and whether any AE among this list lead to discontinuation of the subject from the trial.

This list of adverse events of interest keeps updating as per the sponsor clinicians and statistician requirements based on previous analysis. A timely submission of such reports helps the clinicians and statisticians analyze the trend of the event occurrence.

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. If certain adverse event percentage occurrence is greater than 3 or 5, they can be analyzed for their risk differences between treatment groups and the comparator with 95% confidence intervals using exact methods.

Tier 1 adverse events can be summarized as below.

Table 14.X.X.X.X Protocol				Page 1 of y		
Summary and Analysis of Tier 1 Treatment-Emergent Adverse Events						
	Treatment			95% Confidence Interval		
System Organ Class and MedDRA Preferred Term	TRT1 (N=xxx)	Comparator (N=xxx)	Risk Difference	Lower Limit	Upper Limit	p- value
	----- n (%)	----- n (%)				
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.						

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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.

SAFETY SIGNAL DETECTION OF ADVERSE EVENTS

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.

Two methods of monitoring can be applied to find out the signal in multiple trials or in a large trial carried over a period of time.

Qualitative methods are based on clinical evaluation by clinicians and statisticians who review data reported by the SAS programmers for a single case or series of cases through patient profiling of subjects that show SAE or increased intensity of existing AE/SAE or discontinuation due to AE.

Quantitative ('automated' or 'data mining') techniques complement the medical review by making use of computational power to analyze the large volume of data. These statistical techniques provide estimates of the extent of how the number of observed cases differs from the number of expected cases. The underlying principle is to explore indicators of disproportionality that may then reveal associations of interest. Different measures include ranking of incidence rates and risks within time periods, risk and/or rate ratios between time periods, and reasons for treatment withdrawal. The data may also be compared with the expected frequencies (e.g. from prescribing information), or from external data sources.

CONCLUSION

This paper introduces several statistical methods in assessing AEs. Readers may have been familiar with some of these methods in efficacy analysis instead of in safety analysis. As we have mentioned in the beginning, the logic of statistical analysis of AEs is different from that of efficacy analysis. 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.

All statistical methods introduced in this paper are limited to AEs in safety profiles, and we also recommend using simple methods if possible.

The statistical methods introduced in this paper are definitely not a comprehensive list. The appropriate applications depend on study design and investigating purpose. SAS can provide lots of procedures to easily apply these methods, or we can use DATA steps or macros to implement them.

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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.

RECOMMENDED READING

Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents - PhUSE Computational Science Standard Analyses and Code Sharing Working Group - Standard Analyses and Code Sharing-Analysis and Display White Papers Project Team – Version 1.0 – 2017-FEB-03

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