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Single Day Event

Efficient Construction of Analysis Datasets for Time-to-Event (ADTTE) for Safety endpoints and Presentation

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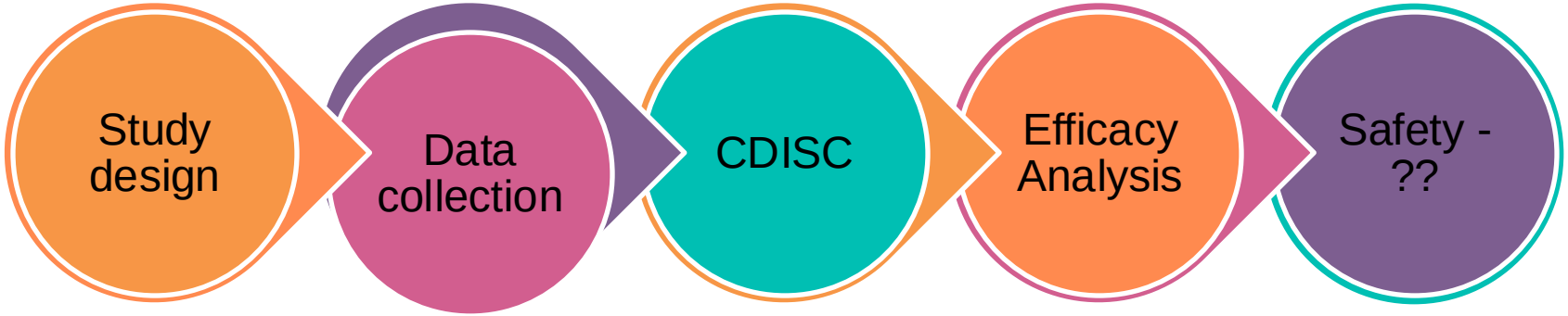
Agenda

- History and Rationale
- Collaborative Efforts Between FDA and PHUSE for Safety Analysis
- FDA recommendations
- New safety table templates
- Analysis Dataset set-up
- Lessons learned / Conclusion
- Q & A

History and Rationale



- Emergence of Adaptive design
- Integration of real-world evidence and patient centric approach

- Transition from paper based to EDC systems
- Integration of wearables and mHealth technologies
- Adoption of ePRO

- CDASH
- SDTM and ADAM

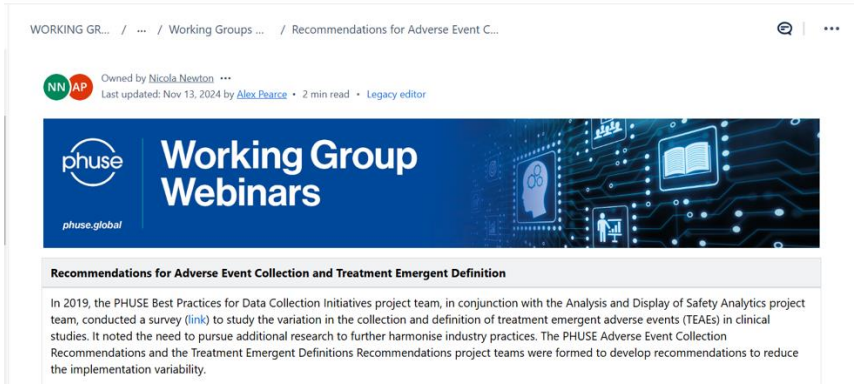
- Shift from traditional efficacy endpoints to more patient centric approach

Collaborative Efforts Between FDA and PHUSE for Safety Analysis

PHUSE Working Group for Safety Harmonization & Improvement:

The beginning of the effort leading to the PHUSE white papers came from the FDA computational statistics group (CBER and CDER). FDA identified key priorities and teamed up with PHUSE to tackle various challenges (Rosario, et. al. 2012). The FDA and PHUSE created several Computational Science Symposium (CSS) working groups to address a number of these challenges.

- PHUSE 2013 Central tendency
- PHUSE 2015 Outliers or Shifts
- PHUSE 2017 AE
- PHUSE 2018 Demographics Disposition and Medications
- PHUSE 2020 Safety Analytics Workshop
- PHUSE 2020 Treatment Emergence Issues
- PHUSE 2021 Safety Topics of Interest
- Paper 2020 Safety and Covid (PHUSE authors)



PHUSE Deliverables: Deliverables | PHUSE
PHUSE Safety Working Group: https://advance.phuse.global/display/WEL/Safety+Analytics

New FDA guidance on Premarket Safety Analytics

FDA led the development of two documents to facilitate review of safety data and improve safety signal detection.

New FDA Safety Analysis Guidance based on PHUSE white papers

- Occurrence Tables includes columns for Risk-Difference & 95% CI, and option to use Exposure Adjusted Estimates
- Updated graphics for Labs, Vital Signs and Extreme Values
- On-treatment and On-study analysis periods

New FDA approach to grouping MedDRA PTs (FDA Medical Queries; FMQs)

- FMQs are new groupings of PTs, nested within SOCs
- Designed to improve adverse reaction section in the Label
- Algorithmic FMQs, in particular for AESI
- Defined by combinations of multiple components (PTs, labs, medication etc)

The new FDA documents have been made available for public FDA-created docket.

Workshop slides & recording on https://healthpolicy.duke.edu/events/advancing-pre-market-safety-analytics

Old Safety template

Table 14.3.2.x

Adverse events by system organ class and preferred term <<- Period>> (Safety set)

age by values>>

System organ class Preferred term (MedDRA version xx.x)	TRTA <<low dose>> N=xxx n (%)	TRTB <<high dose>> N=xxx n (%)	TRTC Total N=xxx n (%)	Control N=xxx n (%)
Any AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<System organ class A>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred term 1>>	x (x.x)	xx (xx.x)	x (x.x)	x (x.x)
<<Preferred term 2>>	xx (xx.x)	0	xx (xx.x)	0
…				
<<System organ class B>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred term 1>>	x (x.x)	x (x.x)	x (x.x)	x (x.x)
<<Preferred term 2>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…				
…				

New Safety template 1 of 2

	TRTA <<low dose>> N=xxx		TRTB <<medium dose>> N=xxx		TRTC <<high dose>> N=xxx		<<Control>> N=xxx		TRTA<<low dose>> vs <<Control>> TRTB<<medium dose>> vs <<Control>> TRTC<<high dose>> vs <<Control>>	
	n (%)	KM% (95% CI) at <<timepoint(s)>>	n (%)	KM% (95% CI) at <<timepoint(s)>>	n (%)	KM% (95% CI) at <<timepoint(s)>>	n (%)	KM% (95% CI) at <<timepoint(s)>>	Difference in KM% (95% CI) at <<timepoint>>	Hazard ratio (95% CI)
Any SAE	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any SAE with outcome death	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any immediately life-threatening SAE	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any SAE requiring hospitalization or prolongation of existing hospitalisation	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any SAE resulting in persistent or significant disability or incapacity	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any SAE of congenital anomaly or birth defect	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any other important medical event of SAE level	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any possibly related SAE [a]	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any AE	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx) x.xx (x.xx,x.xx)
Any AE leading to discontinuation of IP		x.x (x.x,x.x); ...		x.x (x.x,x.x); ...		x.x (x.x,x.x); ...		x.x (x.x,x.x); ...	x.x (x.x,x.x)	x.xx (x.xx,x.xx)

New Safety template 2 of 2

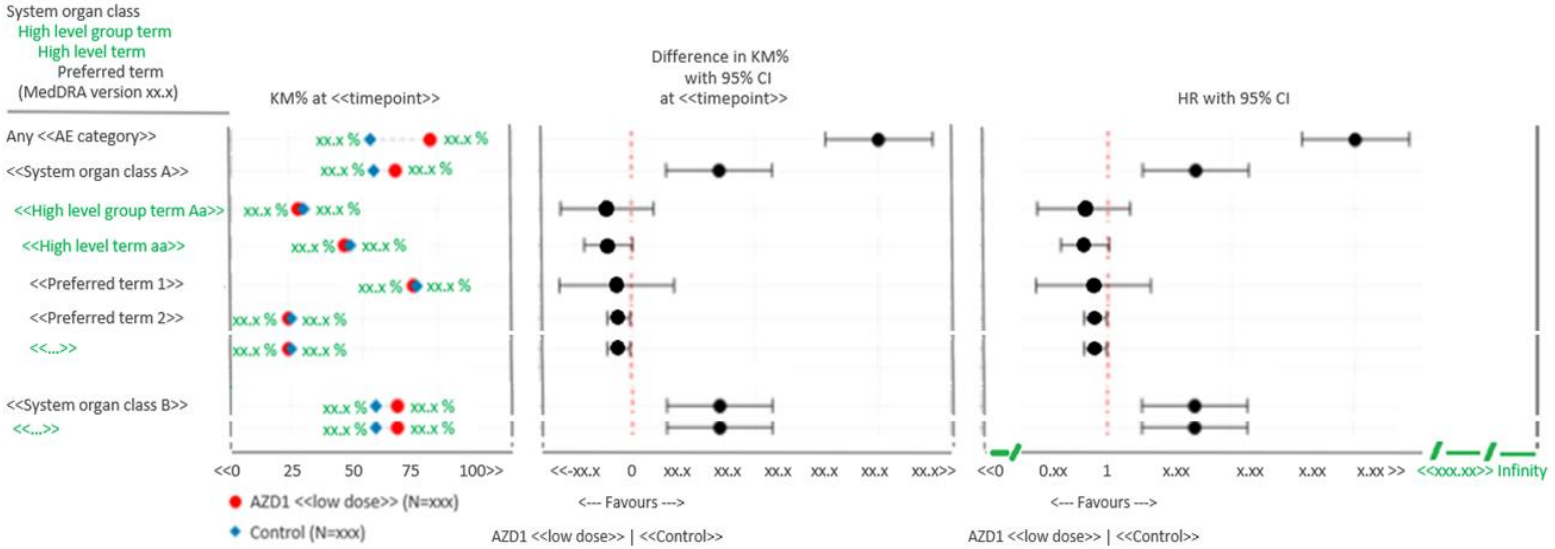
<<AE category>> by system organ class, high level group term, high level term and preferred term – <<Period>> (<<Population>>)

<<Page by values>>

System organ class High level group term High level term Preferred term (MedDRA version xx.x)	TRTA <<low dose>> N=xxx n (%)	KM% (95% CI) at <<timepoint(s)>>	TRTB <<medium dose>> N=xxx n (%)	KM% (95% CI) at <<timepoint(s)>>	TRTC <<high dose>> N=xxx n (%)	KM% (95% CI) at <<timepoint(s)>>	Control N=xxx n (%)	KM% (95% CI) at <<timepoint(s)>>	TRTA<<low dose>> vs <<Control>> TRTB <<medium dose>> vs <<Control>> TRTC<<high dose>> vs <<Control>> Difference in KM% (95% CI) <<at timepoint>>	Hazard ratio (95% CI)
Any <<AE category>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<System organ class A>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<High level group term Aa>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<High level term aa>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<Preferred term 1>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<Preferred term 2>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<…>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<System organ class B>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<High level group term Bb>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<High level term bb>>	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x (x.x)	x.x (x.x,x.x); ... ; x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)	x.x (x.x,x.x) x.x (x.x,x.x) x.x (x.x,x.x)
<<Preferred term 1>>	x (x.x)	x.x (x.x,x.x); ...	x (x.x)	x.x (x.x,x.x); ...	x (x.x)	x.x (x.x,x.x); ...	x (x.x)	x.x (x.x,x.x); ...	x.x (x.x,x.x)	x.x (x.x,x.x)

The Safety Figures - template

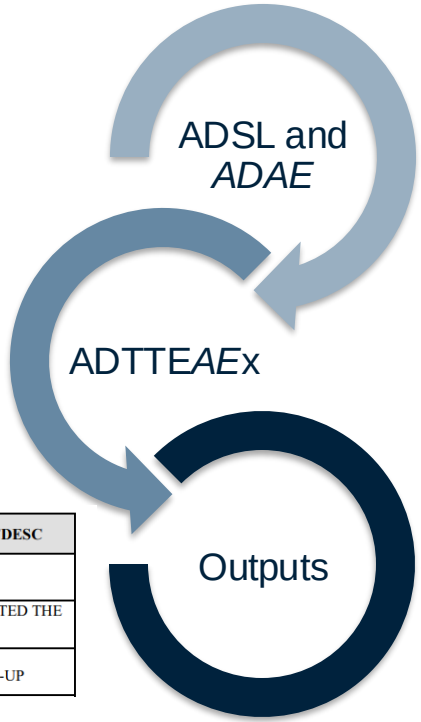
Dot plot of KM estimate and forest plot for treatment comparison



Analysis dataset setup (ADTTEAEx)

Process flow

- Treatment information
- Population flags
- Demographics variables
- Different dates
- Adverse event coded variables
- Additional Adverse event variables



- ADaM Basic Data Structure for Time-to-Event Analyses
- Parameter Categories
- Parameter Codes
- Derived Time to event analysis variables

Row	USUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC
1	1001-0001	Time to Death (days)	DEATH	15	2007-01-01	2007-01-15	0	DEATH
2	1001-0002	Time to Death (days)	DEATH	168	2007-01-03	2007-06-19	1	COMPLETED THE STUDY
3	1001-0003	Time to Death (days)	DEATH	120	2007-01-03	2007-05-02	1	LOST TO FOLLOW-UP

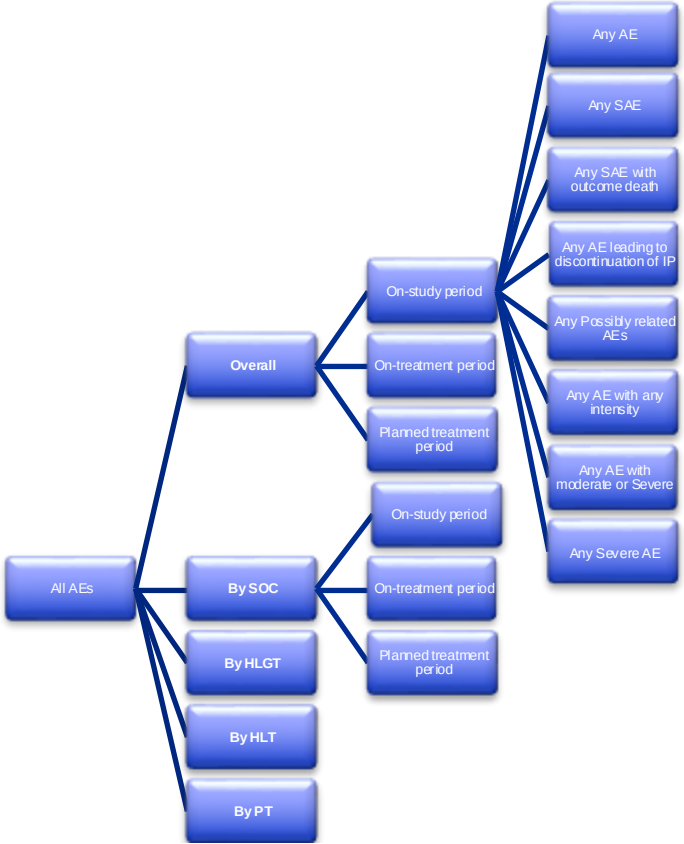
- Output macro package
- Quick analysis for Kaplan-Meier and Hazard Ratio

ADAE to ADTTEAEx Transformation Concept

- The ADTTEAEx (TTE for AEs Analysis Datasets), dataset is designed to create a ***Time to Event dataset based on each event recorded in the adverse events*** dataset of the study.
- It derives the below mentioned ***8 adverse event categories for each subject*** included in the study:
    - Any Adverse Event (AE)
    - Any Serious Adverse Event (SAE)
    - Any SAE resulting in death
    - Any AE leading to discontinuation of the Investigational Medicinal Product (IMP)
    - Any Possibly related AEs
    - Any AE with maximum intensity
    - Any AE with moderate or severe intensity
    - Any Severe AE.
- Input takes ***11 ADSL*** variable, ***17 ADAE*** variables and generates the ***16 derived variables*** for time to event analysis
- These categories are essential for generating unique time-to-event records and can be accessed based on the unique PARAM or PARAMCD created for the ***subgroup analysis at the table level.***
- This dataset is specifically created to utilize the ***censor variables for each group of Adverse events*** based on the PARAMCD and PARCAT combination.

ADTTEAEx Analysis Categories Structure: Branched Structure for different AE categories

Derived Variables	Value levels
PARCAT1	All AEs SAEs SAEs with outcome death AEs leading to discontinuation of IP Possibly related AEs AE with any intensity AE with moderate or Severe Severe AE
PARCAT2	Overall By SOC By HLGT By HLT By PT
PARCAT3	On-study period On-treatment period Planned treatment period
PARCAT4	Any AE Any SAE Any SAE with outcome death Any AE leading to discontinuation of IP Any Possibly related AEs Any AE with any intensity Any AE with moderate or Severe Any Severe AE



Well defined purpose of each derived variable for sub setting: Grouping AE Category

Derived Variables	Variable Description	Source	Purpose
PARCAT1	Parameter Category 1	AETERM, AESER, AEOUT, AEACN, AEREL, AESEV	Sub-setting variable used to subset main category of AE for safety reports.
PARCAT1N	Parameter Category 1 (N)		Numeric equivalent of PARCAT1
PARCAT2	Parameter Category 2	AESOCCD, AESOC, AEHLGTCD, AEHLGT, AEHLTCD, AEHLT, AEPTCD, AEDECOD	Categorization of AE based on Overall, SOC, HLGT, HLT and PT
PARCAT2N	Parameter Category 2 (N)		Numeric equivalent of PARCAT2
PARCAT3	Parameter Category 3	RANDDT, TRTSDT,	Derived for study period categorization
		TRTEDT,	
PARCAT3N	Parameter Category 3 (N)	EOSDT	Numeric equivalent of PARCAT3
PARCAT4	Parameter Category 4	AETERM, AESER, AEOUT, AEACN, AEREL, AESEV	Sub-setting variable used to subset subcategory of AE for safety reports.
PARAM	Parameter	PARCAT1,	Combination of all the parameter category and the coded variables
		PARCAT2,	
		PARCAT3,	
		PARCAT4,	
		AESOC,	
		AEHLGT,	
		AEHLT,	
PARAMCD	Parameter Code	AEDECOD	Compressed character equivalent of PARAM

Well defined purpose of each derived variable for sub setting: Variable used in time to event analysis.

Derived Variables	Variable Description	Source	Purpose
AVAL	Analysis Value.	ADT, STARTDT	Analysis value is the elapsed time to the event of interest from the origin.
STARTDT	Time-to-Event Origin Date for Subject	TRTSDT, RANDDT	Used in derivation of censor variable
STOPDT	Stop Date for Subject Event Selection	EOST, TRTEDT	Used in derivation of censor variable
ADT	Event date	ASTDT, EOST, TRTEDT	Used in derivation of censor variable and AVAL
CNSR	Censor variable CNSR = 0 for event and CNSR =1 for censored records.		Used in TTE analysis to represent the event as 0 and the censor as 1
EVNTDESC	Event or Censoring Description		Description of Event
CNSDTDSC	Censor Date Description		Description of Censor

ADAE to ADTTEAEx Transformation record count Branched Structure for subgroup analysis

ADAE

- ADAE dataset has 187 Adverse events for 157
- Unique PT (109), unique HTL (86) and unique HLGT (56) under a unique SOC (18) across subjects
- **Total number of records - 187**

Analyses Categories

- Summary of main category of adverse event under PARCAT1 (8 sub-categories)
- Summary by Overall, by SOC, by HLGT, by HLT and PT under PARCAT2 (5 sub-categories)
- Summary by period On-study, On-treatment and Planned treatment under PARCAT3 (3 sub-categories)
- Summary of subcategory of adverse event under PARCAT4 (8 sub-categories)
- **Total categories - 960**

ADTTEAEx

- Overall summary per subject per main category of adverse event (24 records)
- Summary by SOC per subject per main category of adverse event (54 records)
- Summary by HLGT per subjectper main category of adverse event (168 records)
- Summary by HLT per subject per main category of adverse event (327 records)
- Summary by PT per subjectper main category of adverse event (258 records)
- **Total records per subject per main category of adverse event - 831 records**
- **Total records per subject - 6648 records**
- **Total records in ADTTEAE - 1043736 records**

Final data - Overall

PARCAT1	PARCAT2	PARCAT3	PARAM	PARAMCD	AVAL	CNSR
All AEs	Overall	On-study period	A1A: All AEs: Any AE	A1A00001	2	0
All AEs	Overall	On-study period	A1A: All AEs: Any SAE	A1A00002	279	1
All AEs	Overall	On-study period	A1A: All AEs: Any SAE with outcome death	A1A00003	279	1
All AEs	Overall	On-study period	A1A: All AEs: Any AE leading to discontinuation of IP	A1A00004	41	1
All AEs	Overall	On-study period	A1A: All AEs: Any AE leading to interruption of IP	A1A00005	41	1
All AEs	Overall	On-study period	A1A: All AEs: Any AE leading to interruption of IP and subsequently leading to discontinuation of IP	A1A00006	41	1
All AEs	Overall	On-study period	A1A: All AEs: Any possibly related AE	A1A00007	279	1
All AEs	Overall	On-study period	A1A: All AEs: Any AE reflecting hypersensitivity	A1A00008	2	0
All AEs	Overall	On-treatment period	A2A: All AEs: Any AE	A2A00001	2	0
All AEs	Overall	On-treatment period	A2A: All AEs: Any SAE	A2A00002	72	1
All AEs	Overall	On-treatment period	A2A: All AEs: Any SAE with outcome death	A2A00003	72	1
All AEs	Overall	On-treatment period	A2A: All AEs: Any AE leading to discontinuation of IP	A2A00004	41	1
All AEs	Overall	On-treatment period	A2A: All AEs: Any AE leading to interruption of IP	A2A00005	41	1
All AEs	Overall	On-treatment period	A2A: All AEs: Any AE leading to interruption of IP and subsequently leading to discontinuation of IP	A2A00006	41	1
All AEs	Overall	On-treatment period	A2A: All AEs: Any possibly related AE	A2A00007	72	1
All AEs	Overall	On-treatment period	A2A: All AEs: Any AE reflecting hypersensitivity	A2A00008	2	0

Final data - By PT

PARCAT1	PARCAT2	PARCAT3	PARAM	PARAMCD	AVAL	CNSR
All AEs	By PT	On-study period	P1A: Haemoglobin decreased	P1A18884	279	1
All AEs	By PT	On-study period	P1A: Haemorrhoids	P1A19022	279	1
All AEs	By PT	On-study period	P1A: Haemothorax	P1A19027	279	1
All AEs	By PT	On-study period	P1A: Head injury	P1A19196	279	1
All AEs	By PT	On-study period	P1A: Headache	P1A19211	2	0
All AEs	By PT	On-study period	P1A: Hepatic steatosis	P1A19708	279	1
All AEs	By PT	On-study period	P1A: Herpes zoster	P1A19974	279	1
All AEs	By PT	On-study period	P1A: Hordeolum	P1A20377	279	1
All AEs	By PT	On-study period	P1A: Hyperglycaemia	P1A20635	279	1
All AEs	By PT	On-study period	P1A: Hyperkalaemia	P1A20646	279	1
All AEs	By PT	On-study period	P1A: Hyperkeratosis	P1A20649	279	1
All AEs	By PT	On-study period	P1A: Hypertension	P1A20772	279	1
All AEs	By PT	On-study period	P1A: Hyperuricaemia	P1A20903	279	1
All AEs	By PT	On-study period	P1A: Hypervolaemia	P1A20919	279	1

TTE Dataset - split

- Due to size limit, we created multiple TTE datasets with a logical split
  - ADTTEAEA with all AEs (PARCAT1= 'All AEs')
  - ADTTEAEB with all SAEs (PARCAT1 = 'SAEs')
  - ADTTEAEC with all SAEs resulting in death (PARCAT1 = 'SAEs with outcome death')
  - …
- Depending on the number of AEs, you can split in several ways

Lessons learned

- How big will it be? Impossible to say before the study closes.
  - ≈ 400 subjects with >800 adverse event (≈ 300 unique) (ADAE)
  - 21 different SOC
  - ≈ 200 unique High Level Term
  - ≈ 110 unique High Level Group Term
  - ≈ 16 different AE categories
  - ≈ 5 000 000 observarions across 16 datasets
- Code optimization and run time of ADaM datasets
  - 100 minutes vs 7 minutes
- Worth spending time on automation
  - Makes sure you are consistent and have to create a standard
  - Can be re-used – saves time
  - Easy to add extra features
    - Lab, VS, FMQ, SMQ

Conclusion

The standard safety analyses is evolving by moving away from merely describing safety data by treatment to estimating population parameters and comparing them between treatments, in order **to aid the evaluation of safety and tolerability of our drugs.**

Hence, the main purpose of the new safety analysis is to **implement a more systematic quantitative approach for detecting safety signals** to enhance the interpretability and make the evaluation less sensitive to subjectivity.

The Global Healthcare Data Science Community

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