Setup of ADAE and ADTTE for Exposure-Adjusted Incidence Rate Reporting in an Integrated Summary of Safety (ISS) Submission

Mitchikou Tseng, Senior Statistical Programmer, OCS Life Sciences

Meet the Speaker

Mitchikou Tseng

Title: Senior Statistical Programmer

Organization: OCS Life Sciences

Mitch is a Senior Statistical Programmer from OCS Life Sciences and has been working as a SAS programmer in the pharmaceutical research industry for more than 8 years. Her initial five years of experience were primarily in Phase 2 and 3 studies, while in recent years, she has expanded her experience to early development stage/Phase 1, pharmacokinetic analyses, nutrition research and integration studies.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Agenda

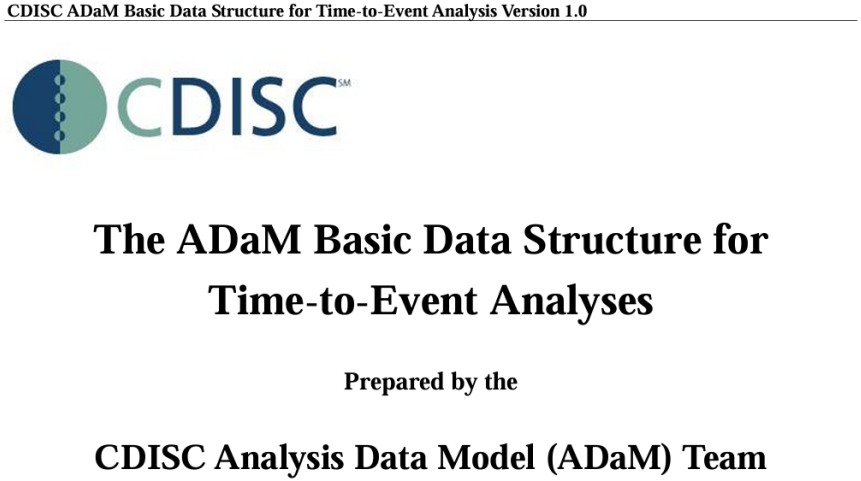
1. Time to Event
2. Exposure-Adjusted Incidence Rate (EAIR)
3. Implementation in ADAE and ADTTE
4. Challenges and Solutions
5. Conclusion

Time to Event

Time to Event

- **Length of time elapsing before an event is experienced**
- **Two components**
  - a length of time during which no event was observed
  - an indicator of whether the end of that period corresponds to an event or just the end of observation
- **Clinical application**
  - Starting time - time of diagnosis or time of treatment randomization
  - Events of interest - achieving complete remission, recurrence of a disease, death or discharge from hospital
- **Censored participants - does not end in an event**

Time to Event Analysis Dataset



- ADaM BDS
- ADTTE
- Examples
  - Time to Death
  - Progression Free Survival
  - Time to Hepatitis B e Antigen Seroconversion

ADTTE Important Variables

Variable Name	Variable Label	Notes
PARAM	Parameter	The description of the analysis parameter.
AVAL	Analysis Value	AVAL is the elapsed time to the event of interest from the origin. For example, if AVAL is measured in days, AVAL would be ADT – STARTDT or ADT – STARTDT + 1.
STARTDT	Time to Event Origin Date for Subject	The original date of risk for the time-to-event analysis.
ADT	Analysis Date	Analysis date of event or censoring associated with AVAL in numeric format.
CNSR	Censor	CNSR = 0 for event and CNSR > 0 for censored records.
EVNTDESC	Event or Censoring Description	Describe the event of interest or an event that warrants censoring.

Exposure-Adjusted Incidence Rate (EAIR)

Integrated Summary of Safety

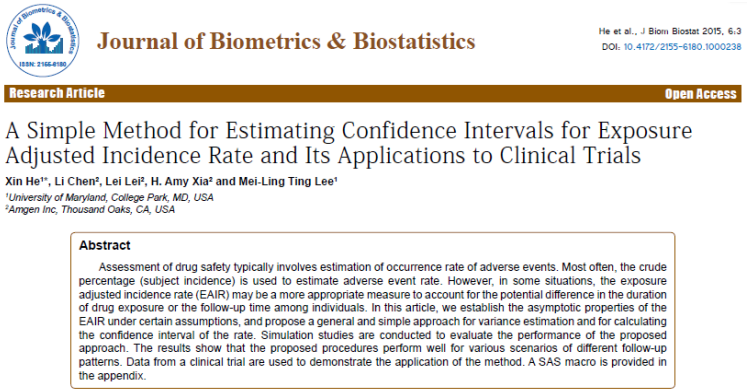
Exposure-Adjusted Incidence Rate (EAIR)

- **Safety profiles of investigational drugs**
  - Safety event incidences
  - Crude percentages = $\frac{n}{N}$
    - Individuals are treated and followed up for the same period of time

- **Integrated Summary of Safety**
  - Different drug exposure times or follow up times

- **EAIR = Adjusts for potential differences on duration of drug exposure**

- **Incidence Density**



Journal of Biometrics & Biostatistics

He et al., J Biom Biostat 2015, 6:3
DOI: 10.4172/2155-6180.1000238

Research Article | Open Access

A Simple Method for Estimating Confidence Intervals for Exposure Adjusted Incidence Rate and Its Applications to Clinical Trials

Xin He[1*], Li Chen[2], Lei Lei[2], H. Amy Xia[2] and Mei-Ling Ting Lee[1]

[1]University of Maryland, College Park, MD, USA
[2]Amgen Inc, Thousand Oaks, CA, USA

Abstract

Assessment of drug safety typically involves estimation of occurrence rate of adverse events. Most often, the crude percentage (subject incidence) is used to estimate adverse event rate. However, in some situations, the exposure adjusted incidence rate (EAIR) may be a more appropriate measure to account for the potential difference in the duration of drug exposure or the follow-up time among individuals. In this article, we establish the asymptotic properties of the EAIR under certain assumptions, and propose a general and simple approach for variance estimation and for calculating the confidence interval of the rate. Simulation studies are conducted to evaluate the performance of the proposed approach. The results show that the proposed procedures perform well for various scenarios of different follow-up patterns. Data from a clinical trial are used to demonstrate the application of the method. A SAS macro is provided in the appendix.

Exposure-Adjusted Incidence Rate (EAIR)

- **A measure of average events per unit time of exposure or follow-up**

- $$\frac{\textbf{number of subjects exposed to the drug and experiencing a certain event}}{\textbf{total exposure time of all subjects who are at risk for the event}} = \frac{n}{\textbf{Exp.yrs}}$$

  - for **subjects with no event**, the exposure time is the time from the first drug intake to **a decided reference end date**;
  - for **subjects with at least one event**, the exposure time is the time from the first drug intake to **first event**.

EAIR in an Overview Adverse Event table

Table 1: Overview of treatment-emergent adverse events (TEAEs): number of patients and events

	Treatment X (N=XXX)		Placebo (N=XXX)		EAIR diff. est.
	n (%) [m]	Exp. yrs. EAIR	n (%) [m]	Exp. yrs. EAIR	EAIR diff. (95% CI)
TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TEAEs by severity					
Mild	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Moderate	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Severe	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TEAEs related to study treatment	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TE AESIs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Serious TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Serious TEAEs related to study treatment	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TEAEs leading to study treatment discontinuation	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)

$$EAIR = \frac{n}{Exp.yrs}$$

EAIR in an Overview Adverse Event table

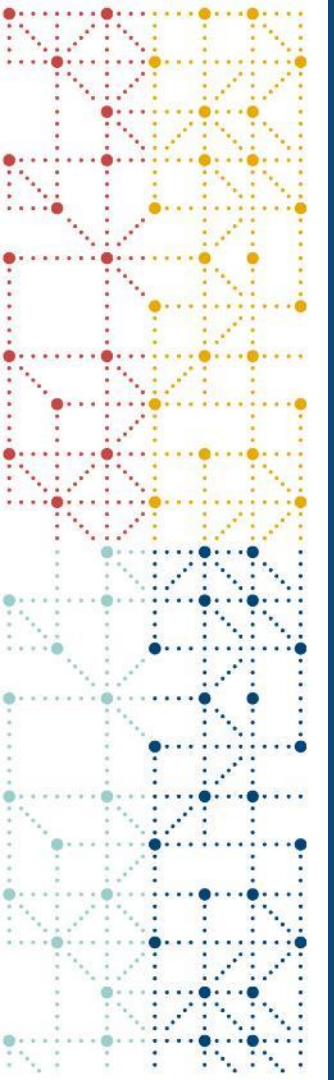
Table 1: Overview of treatment-emergent adverse events (TEAEs): number of patients and events

	Treatment X (N=XXX)		Placebo (N=XXX)		EAIR diff. est.
	n (%) [m]	Exp. yrs. EAIR	n (%) [m]	Exp. yrs. EAIR	EAIR diff. (95% CI)
TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)

$$EAIR = \frac{n}{Exp.yrs}$$

SUBJECT	TRTSDT	TRTEDT	AE	Emergent	Serious	Date of AE	Exposure Year *
001	01JAN2023	15JUN2023	NO AE				Time in between TRTSDT and TRTEDT + 30
002 ✓	01JAN2023	15JUN2023	Dizziness	Y		03FEB2023	Time in between TRTSDT and date of earliest treatment emergent AE
002 ✗	01JAN2023	15JUN2023	Headache	Y	Y	07FEB2023	

*** Project specific derivation**



Implementation in ADAE and ADTTE

Implementation in ADAE and ADTTE

- Applicability
- Ensure traceability
- Easy QC process
- Faster creation of subgroup analyses or repeat TLFs

ADTTE Application – AE Overall Table

Variable Name
PARAM
AVAL
STARTDT
ADT
CNSR
EVNTDESC

Table 1: Overview of treatment-emergent adverse events (TEAEs): number of patients and events

	Treatment X (N=XXX)		Placebo (N=XXX)		EAIR diff. est.
	n (%) [m]	Exp. yrs. EAIR	n (%) [m]	Exp. yrs. EAIR	EAIR diff. (95% CI)
TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)

SUBJECT	TRTSDT	TRTEDT	AE	Emergent	Serious	Date of AE	Exposure Year *
001	01JAN2023	15JUN2023	NO AE CNSR=1				Time in between TRTSDT and TRTEDT + 30
002	01JAN2023	15JUN2023	Dizziness	Y CNSR=0		03FEB2023	Time in between TRTSDT and date of earliest treatment emergent AE
002	01JAN2023	15JUN2023	Headache	Y	Y	07FEB2023	

* **Project specific derivation**

ADTTE Application – AE SOC and PT Table

Variable Name
PARAM
AVAL
STARTDT
ADT
CNSR
EVNTDESC

Table 2: Treatment-emergent adverse events (TEAEs) by system organ class and preferred term

System Organ Class Preferred Term	Treatment X (N=XXX) n (%) [m]	 Exp. yrs. EAIR	Placebo (N=XXX) n (%) [m]	 Exp. yrs. EAIR	EAIR diff. est. EAIR diff. (95% CI)
TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
System organ class 1	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Preferred term 1	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)

SUBJECT	TRTSDT	TRTEDT	AE	Emergent	Serious	Date of AE	Exposure Year *
001	01JAN2023	15JUN2023	NO AE				Time in between TRTSDT and TRTEDT + 30
002	01JAN2023	15JUN2023	Dizziness	Y		03FEB2023	Time in between TRTSDT and date of earliest treatment emergent AE
002	01JAN2023	15JUN2023	Headache	Y	Y	07FEB2023	

* Project specific derivation

ADTTE Result

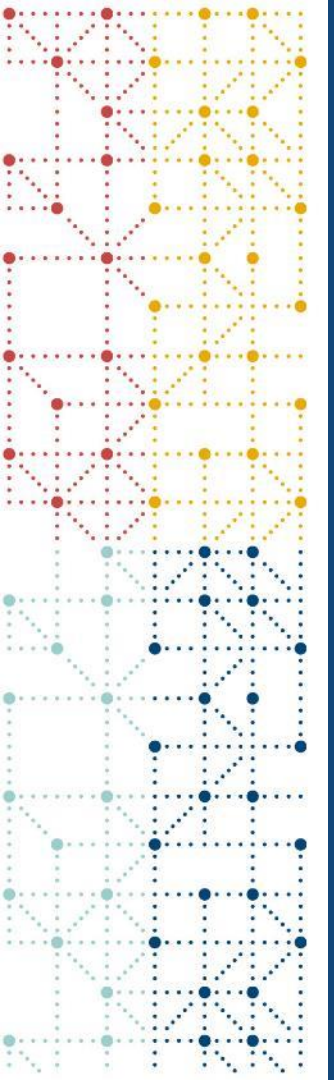
SUBJECT	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVENTDSC
001	TEAEs	TEAE	0.536619	01JAN2023	15JUN2023	1	NO TEAEs
001	Dizziness	DIZZ	0.536619	01JAN2023	15JUN2023	1	NO Dizziness
001	Headache	HEAD	0.536619	01JAN2023	15JUN2023	1	NO Headache
002	TEAEs	TEAE	0.093087	01JAN2023	03FEB2023	0	TEAEs
002	Dizziness	DIZZ	0.093087	01JAN2023	03FEB2023	0	Dizziness
002	Headache	HEAD	0.104038	01JAN2023	07FEB2023	0	Headache

ADAE - Flag Variables

Table 1: Overview of treatment-emergent adverse events (TEAEs): number of patients and events

	Treatment X (N=XXX)		Placebo (N=XXX)		EAIR diff. est.
	n (%) [m]	Exp. yrs. EAIR	n (%) [m]	Exp. yrs. EAIR	EAIR diff. (95% CI)
TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TEAEs by severity					
Mild	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Moderate	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Severe	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TEAEs related to study treatment	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TE AESIs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Serious TEAEs	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
Serious TEAEs related to study treatment	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)
TEAEs leading to study treatment discontinuation	xx (xx.x) [xx]	xx xx.x	xx (xx.x) [xx]	xx xx.x	x.xx (x.xx;x.xx)

AOCCzzFL	1st Occurrence of ...	Char	Y		Perm	Perm	Additional flag variables as needed for analysis. Derivation rules for these flags need to be described in the metadata.



Challenges and Solutions

ISS ADAE Specific Challenges

- **No ISS SAP**
- **Defining the integrated Treatment Emergent AE derivation**
  - Accounting incomplete dates in the derivation
  - Accounting run-in or washout period
- **Defining the unique AE**
  - Upgrade MedDRA coding
- **Differences against previous CSR results**

ISS ADAE Lessons Learned

- Creation of an ISS SAP
- Align expectations on the previous CSR results investigations of differences
- Request a copy of the CSR, programs, mapping specifications and datasets of studies being integrated
- Prepare investigative skills and lots of patience

Big Data

- **Lots of flags in ADAE to identify the first occurrence of an AE category**

- **Millions of records in ADTTE**
  - Huge number of parameters per subject
    - AE Overall Categories
      - First TEAE
      - First Serious
      - First Mild
      - etc
    - AE System Organ Class and Preferred Term
      - First Nervous system disorders
      - First Dizziness
      - etc
  - Huge number of subjects because of integrated studies

Big Data = Performance Issues

- **Memory**
- **Processing time**
  - Loops and Macros
- **Input/Output time**
  - ADaM finalization macro takes longer time
  - Double programming's PROC COMPARE takes longer

Solution = Efficient Programming

- **Identifying which process consumes huge time**

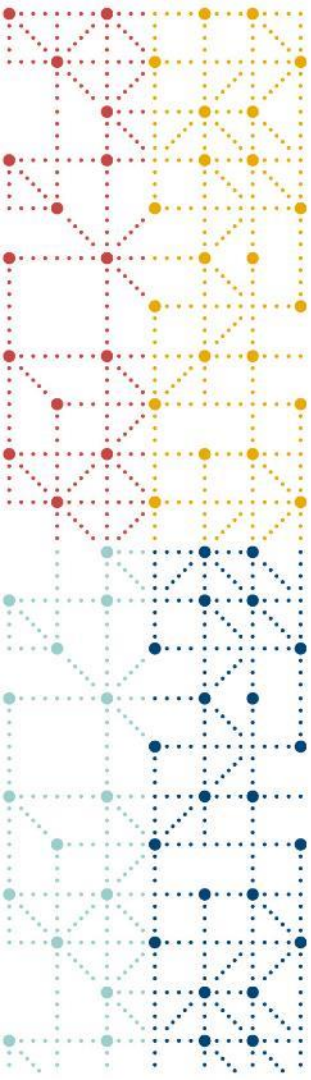
```
3978  NOTE: Compressing data set WORK.ADAM_TTE_FINALIZE decreased size by 90.97 percent.
3979        Compressed is 15165 pages; un-compressed would require 168027 pages.
3980  NOTE: Table WORK.ADAM_TTE_FINALIZE created, with 6889091 rows and 18 columns.
3981
3982  555         quit;
3983  NOTE: PROCEDURE SQL used (Total process time):
3984        real time               7:21.40
3985        cpu time                1:30.56
3986
3987
```

results - (303 hits)

```
Line 3796:      real time          0.03 seconds
Line 3830:      real time          0.00 seconds
Line 3843:      real time          0.00 seconds
Line 3921:      real time          19.07 seconds
Line 3939:      real time          2:01.61
Line 3958:      real time          20.44 seconds
Line 3984:      real time          7:21.40
Line 4111:      real time          0.45 seconds
Line 4156:      real time          19.16 seconds
```

Solution = Efficient Programming

- **Identifying which process consumes huge time**
- **Only including variables that are necessary**
- **Only including records that are necessary**
  - Do not create records for System Organ Classes/Preferred Terms that were not identified as Treatment Emergent for at least one subject
- **PROC IML with UNIQUEBY function was mainly used in computing the EAIR, the EAIR difference estimate and its confidence intervals**
- **Subset PROC COMPARE**



Conclusion

Conclusion

- ISS ADAE can be challenging
- EAIR analysis can be supported by ADTTE
- Exposure years of a subject in a certain AE or AE category is stored
- Performance issues can be encountered but can be solved by efficient programming
- Explore alternative options

Resources

- ADaM Structure for Occurrence Data (OCCDS) Implementation Guide, Version 1.1 (Final), February 16, 2016
- Chen H.L, and Wang H. (2012) Multiple Applications of ADaM Time-to-Event Datasets, PharmaSUG 2012, DS19.
- He X et al. (2015) A Simple Method for Estimating Confidence Intervals for Exposure Adjusted Incidence Rate and Its Applications to Clinical Trials, Journal of Biometrics and Biostatistics 2015, 6:3.
- The ADaM Basic Data Structure for Time-to-Event Analyses, Version 1.0, January 5, 2011

Thank You!

For further questions:

Contact me at mitchikou-tseng@ocs-consulting.com or

Visit the OCS Life Sciences booth

You can have a second look at the presentation: