New way of efficient construction of analysis datasets for analysis and presentation when basing the safety analysis on time to event

Presented by Mikael Staf, Katarina Hedman, Sharmila Agarwal and Johan Stockenberg, for the AstraZeneca statistical safety working group Cardiovascular, Renal and Metabolic therapeutic area

Meet the Speakers

Mikael Staf

Title: Statistical Programming Associate Director

Organization: AstraZeneca Gothenburg, Sweden

9 years' experience as a statistical programmer at AstraZeneca. Project leader and data automation lead within the cardiovascular, renal and metabolic therapeutic area.

Katarina Hedman, PhD

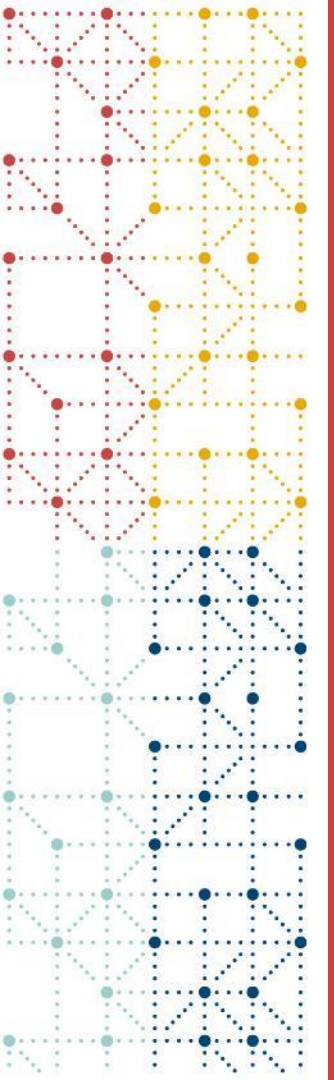
Title: Statistical Science Director

Organization: AstraZeneca Gothenburg, Sweden

+20 years in life science industry including 10 years at AstraZeneca. Leader of the AstraZeneca statistical safety working group for the cardiovascular, renal and metabolic therapeutic area.

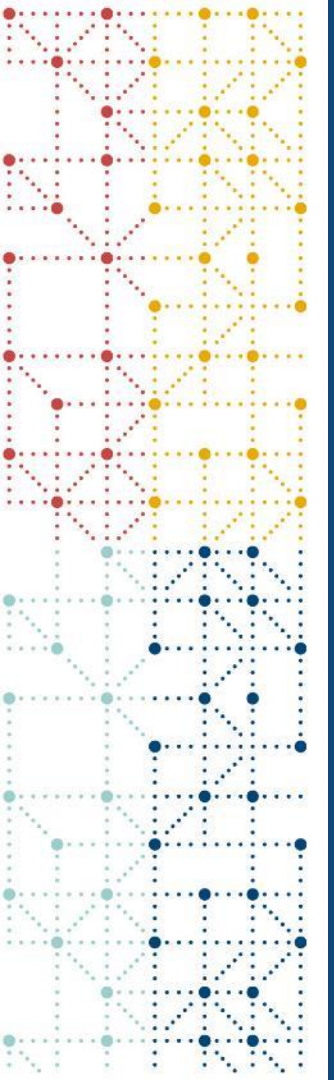
Disclaimer and Disclosures

- *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.*
- *The presenters are employees of AstraZeneca and have stock ownership or options in AstraZeneca.*



Agenda

1. The background - Moving from describing the safety data to parameter estimation
2. The programming package - ADaM basic data structure for time-to-event analyses and efficient coding to deliver the new safety analysis package



The Background

Moving from describing the safety data to parameter estimation

Acknowledgement

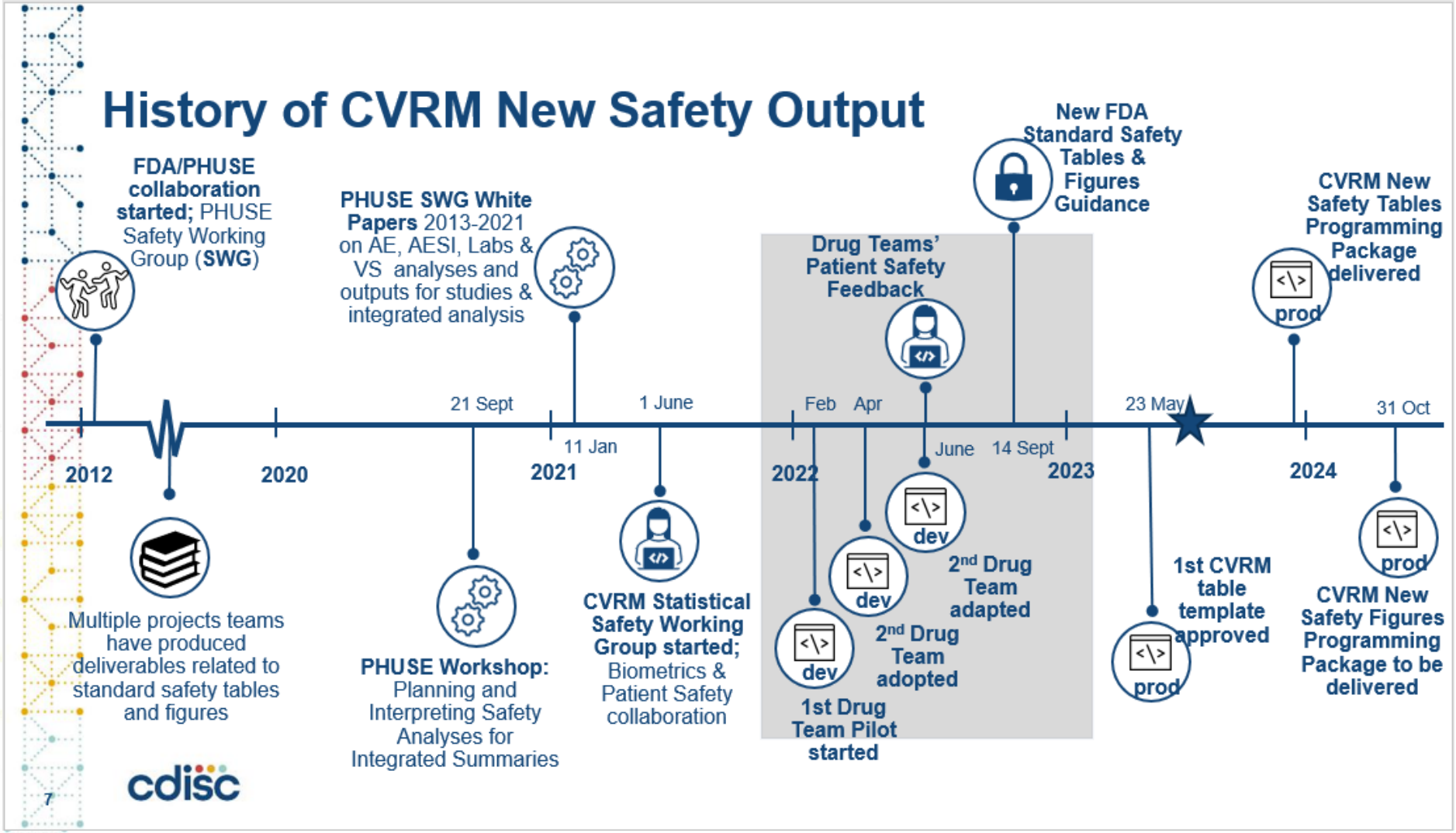
AstraZeneca Statistical Safety Working Group for the Cardiovascular, Renal and Metabolic (CVRM) Therapeutic Area

- Sponsors Hongjian Li & Per Nyström, leader Katarina Hedman, contributors Vera Lisovskaja, Vijay Vaidya, George Kordzakhia, Parag Wani, Simon Lundberg, Nishanth Chinthala, Sharmila Agarwal, Likith Gopikumar, Mikael Staf, Johan Stockenberg, Tomasz Kotecki, Sherrie Gallas, Kristina Johnsson, Syed (Asif) Haque, Francisco Hernandorena, Annika Yeiter

AstraZeneca CVRM Safety Package Programming Working Team

- Leader Vijay Vaidya, contributors Sharmila Agarwal, Johan Stockenberg, Mikael Staf, Nishanth Chinthala, Likith Gopikumar, Tomasz Kotecki

History of CVRM New Safety Output



Defining a Safety Estimand for the Global Safety Objective in a Clinical Trial

A. **Clinical question:** What is the magnitude of the ***increase in risk*** of experiencing a safety event if the treatment is taken for a specific period?

B. **Clinical context:** Long-term regular treatment in ***progressive disease***, where a difference in patients' follow-up in the studies is common and ***mortality is relatively low***.

C. **Key intercurrent events** (ICEs) and their strategies:
   - Treatment policy for changes in concomitant medications, and Hypothetical for death
   - Hypothetical for treatment discontinuation, implemented via two complementary assumptions
     1. On-study analysis period applicable (requiring data collection continues after this ICE) = Treatment policy
     2. On-treatment analysis period applicable

Hedman K, Lisovskaja V and Nyström P. A safety estimand for late phase clinical trials where the analysis period varies over the subjects. Clinical Trials 2024. DOI: 10.1177/17407745241230933

The New CVRM Safety Table Structure

Overall summary of adverse events - <<Period>> (<<Population>>)

	Drug A N=109		Drug B N=112		Drug C N=120		Absolute comparison at 360 days Diff in KM% (95% CI)	Relative comparison HR (95% CI)
	n (%)	KM% (95% CI) at 90 days 360 days	n (%)	KM% (95% CI) at 90 days 360 days	n (%)	KM% (95% CI) at 90 days 360 days	Drug A vs Drug C Drug B vs Drug C	Drug A vs Drug C Drug B vs Drug C
Any SAE	15 (13.8)	10.6 (6.04, 18.41) 14.8 (9.16, 23.30)	16 (14.3)	12.0 (7.16, 19.80) 14.9 (9.39, 23.15)	24 (20.0)	11.1 (6.58, 18.30) 24.9 (15.75, 38.01)	-10.1 (-23.2, 2.9) -10.0 (-22.9, 2.9)	0.67 (0.35, 1.28) 0.69 (0.37, 1.31)
Any SAE with outcome death	2 (1.8)	0.9 (0.13, 6.45) 2.0 (0.49, 7.65)	2 (1.8)	0.9 (0.13, 6.28) 1.9 (0.47, 7.24)	3 (2.5)	0.8 (0.12, 5.86) 2.7 (0.86, 8.02)	-0.7 (-4.7, 3.3) -0.8 (-4.7, 3.1)	0.74 (0.12, 4.43) 0.70 (0.12, 4.21)
Any AE	52 (47.7)	35.1 (26.95, 44.93) 48.8 (39.78, 58.75)	45 (40.2)	33.9 (25.87, 43.65) 49.0 (34.59, 65.69)	55 (45.8)	32.7 (25.10, 41.95) 56.0 (41.39, 71.75)	-7.2 (-25.5, 11.1) -7.0 (-29.2, 15.2)	1.06 (0.73, 1.55) 0.88 (0.60, 1.31)
Any AE leading to discontinuation of IP	4 (3.7)	3.7 (1.41, 9.57) 3.7 (1.41, 9.57)	1 (0.9)	0.9 (0.13, 6.33) 0.9 (0.13, 6.33)	7 (5.8)	4.2 (1.76, 9.74) 5.9 (2.88, 12.08)	-2.2 (-7.8, 3.3) -5.0 (-9.7, -0.4)	0.63 (0.18, 2.16) 0.15 (0.02, 1.24)
Any AE possibly related	0	0 (NC) 0 (NC)	0	0 (NC) 0 (NC)	0	0 (NC) 0 (NC)	0 (NC) 0 (NC)	1 (NC) 1 (NC)
Any intensity	52 (47.7)	35.1 (26.95, 44.93) 48.8 (39.78, 58.75)	45 (40.2)	33.9 (25.87, 43.65) 49.0 (34.59, 65.69)	55 (45.8)	32.7 (25.10, 41.95) 56.0 (41.39, 71.75)	-7.2 (-25.5, 11.1) -7.0 (-29.2, 15.2)	1.06 (0.73, 1.55) 0.88 (0.60, 1.31)
Moderate or severe	29 (26.6)	20.7 (14.12, 29.67) 27.5 (20.00, 37.14)	31 (27.7)	23.2 (16.30, 32.35) 45.9 (21.37, 79.28)	36 (30.0)	17.9 (12.08, 26.16) 35.1 (24.94, 47.84)	-7.6 (-21.9, 6.7) 10.9 (-22.4, 44.1)	0.88 (0.54, 1.44) 0.91 (0.56, 1.48)
Severe	7 (6.4)	4.8 (2.04, 11.23) 6.9 (3.35, 13.95)	11 (9.8)	6.5 (3.13, 13.06) 27.5 (7.77, 72.03)	13 (10.8)	5.1 (2.34, 11.10) 15.2 (7.83, 28.46)	-8.3 (-19.4, 2.7) 12.2 (-21.4, 45.8)	0.59 (0.23, 1.47) 0.85 (0.38, 1.90)
Missing intensity	0		0		0			

AstraZeneca synthetic clinical data D-code D0000C00222
description in supplement DOI: 10.1177/17407745241230933

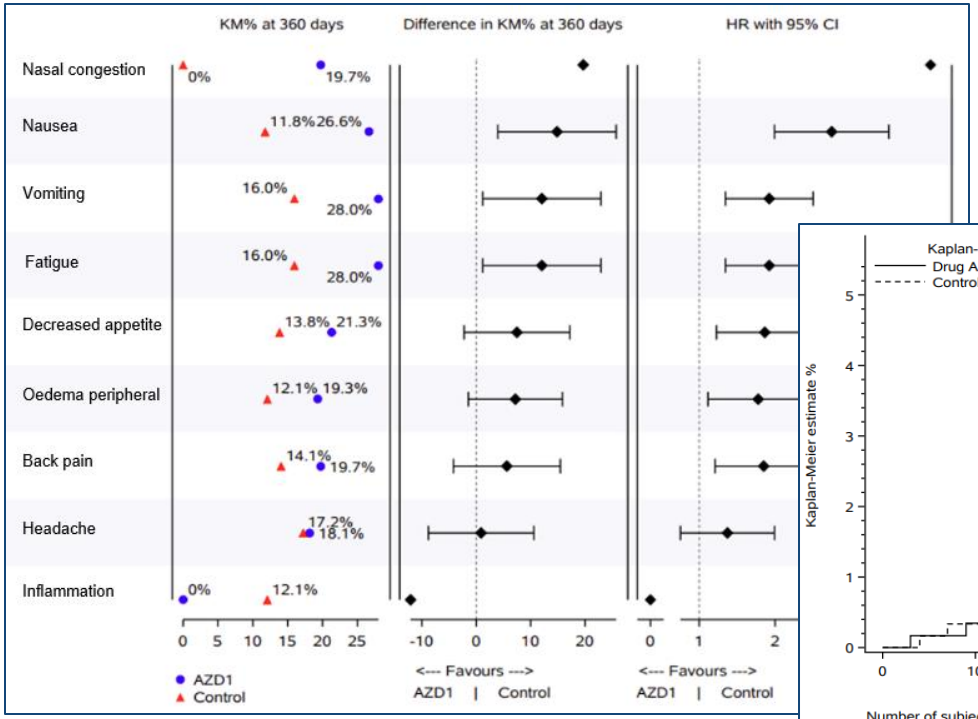
The New CVRM Safety Table Structure

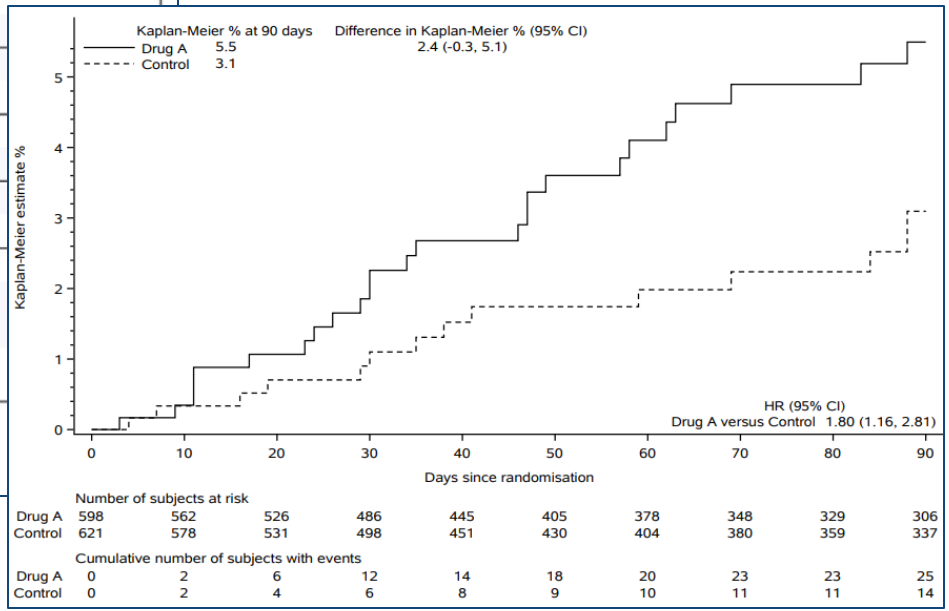
Lab treatment emergent abnormalities by predefined criteria - <<Period>> (<<Population>>)

	Drug A N=109		Drug B N=112		Drug C N=120		Absolute comparison at 90 days Diff in KM% (95% CI)	Relative comparison HR (95% CI)
	n/Nb (%)	KM% (95% CI) at 90 days	n/Nb (%)	KM% (95% CI) at 90 days	n/Nb (%)	KM% (95% CI) at 90 days	Drug A vs Drug C Drug B vs Drug C	Drug A vs Drug C Drug B vs Drug C
Alkaline Phosphatase (ukat/L)								
Alkaline Phosphatase > 3X ULN	0/ 109 (0.0)	0 (NC)	1/ 112 (0.9)	0.9 (0.13, 6.51)	2/ 120 (1.7)	0.9 (0.13, 6.28)	-0.9 (NC) 0.0 (-2.5, 2.6)	0 (NC) 0.55 (0.05, 6.07)
Alanine Aminotransferase (ukat/L)								
Alanine Aminotransferase > 3X ULN	1/ 108 (0.9)	0.9 (0.13, 6.39)	1/ 112 (0.9)	0.9 (0.13, 6.51)	1/ 118 (0.8)	0 (NC)	0.9 (NC) 0.9 (NC)	1.10 (0.07, 17.57) 1.04 (0.06, 16.60)
Alanine Aminotransferase > 5X ULN	0/ 109 (0.0)	0 (NC)	1/ 112 (0.9)	0.9 (0.13, 6.51)	1/ 119 (0.8)	0 (NC)	0 (NC) 0.9 (NC)	0 (NC) 1.04 (0.06, 16.60)
Aspartate Aminotransferase (ukat/L)								
Aspartate Aminotransferase > 3X ULN	1/ 109 (0.9)	0.9 (0.13, 6.39)	1/ 112 (0.9)	0.9 (0.13, 6.51)	0/ 119 (0.0)	0 (NC)	0.9 (NC) 0.9 (NC)	Inf (NC) Inf (NC)
Creatine Kinase (ukat/L)								
Creatine Kinase > 5X ULN	0/ 109 (0.0)	0 (NC)	0/ 112 (0.0)	0 (NC)	1/ 120 (0.8)	0.9 (0.13, 6.28)	-0.9 (NC)	0 (NC)

AstraZeneca synthetic clinical data D-code D0000C00222
description in supplement DOI: 10.1177/17407745241230933

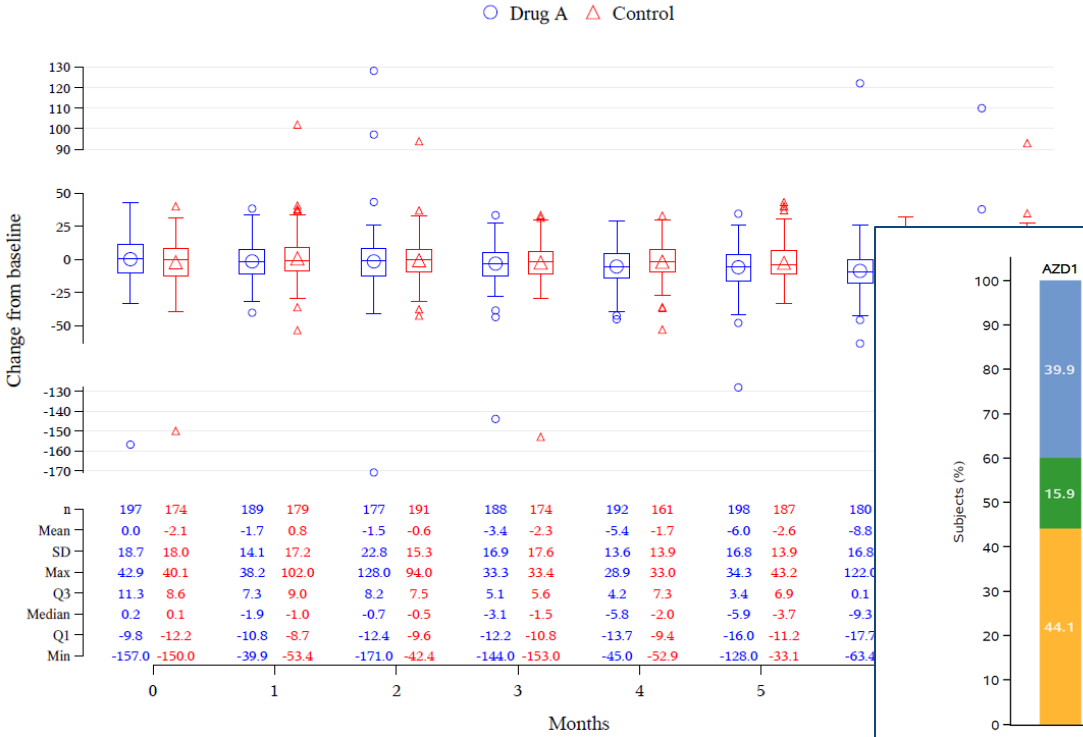
The New CVRM Safety Figures - a selection



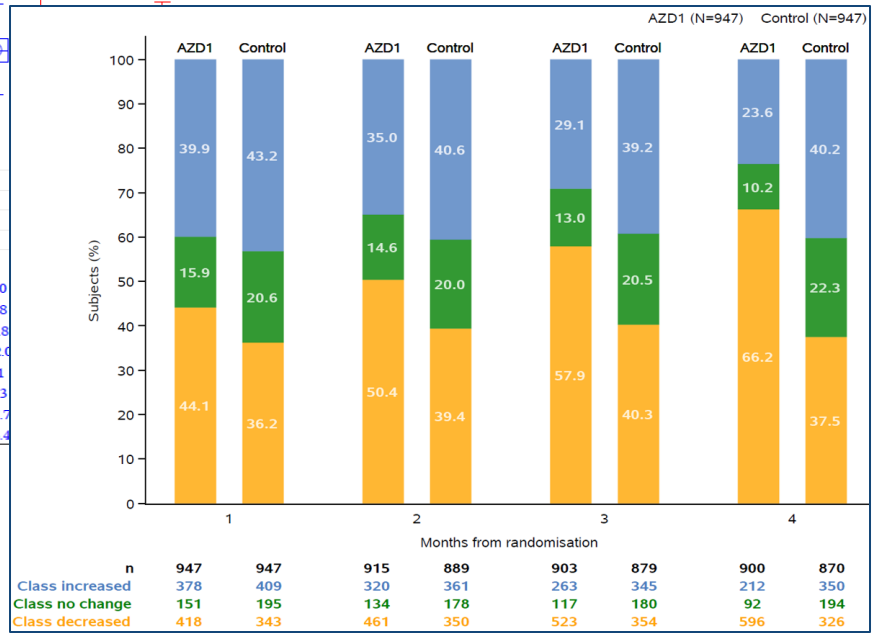


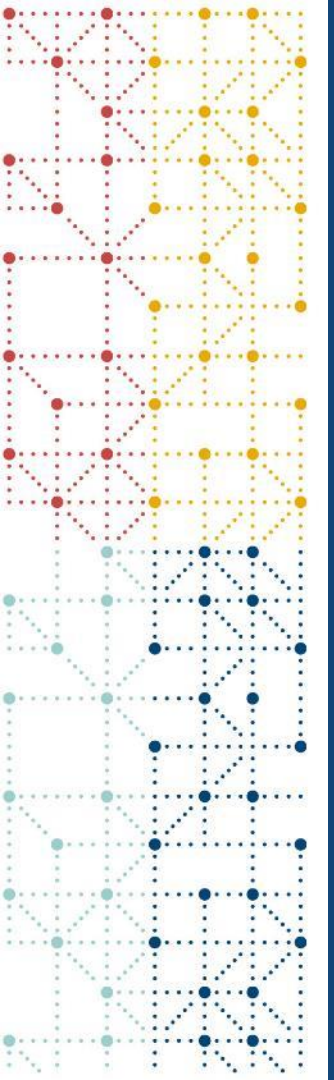
Simulated data

The New CVRM Safety Figures - a selection



Simulated data



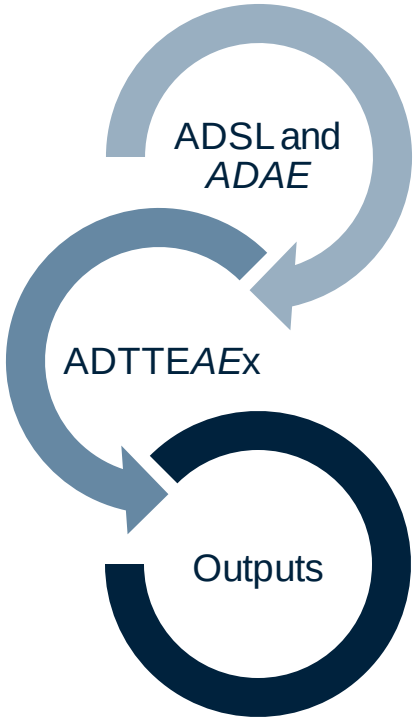


ADaM ADTTEx

Designing the TTE dataset

Process flow

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



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

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

PARAMCD & PARAM – structure

1. Use a letter for Overall (A), SOC (S), HLGT (G), HLT (H), PT (P) as the first character in the PARAMCD
2. Use 1 or 2 for On study or On treatment, resp., as the second character in the PARAMCD
3. Use a letter for the third character in the PARAMCD, so if it is:
    1. All AEs (A)
    2. SAEs (B)
    3. SAEs with outcome death (C)
    4. AEs leading to discontinuation of IP (D)
    5. …
4. a) For SOC (S), HLGT (G), HLT (H), PT (P), use the last 5 numbers in the AESOCCD, AEHLGTCD, AEHLTCD, AEPTCD, as fourth to eighth symbol in the PARAMCD.

   b) For Overall (A) use 00001-00008 for the fourth to eighth symbols in the PARAMCD, so if it is:
    1. Any AE (00001)
    2. Any SAE (00002)
    3. Any SAE with outcome death (00003)…

PARAM & PARAMCD – ADAE variables

AETERM	AELLT	AELLTCD	AEDECOD
Headache	Headache	10019211	Headache
AEPTCD	**AEHLT**	**AEHLTCD**	**AEHLGT**
10019211	Headaches NEC	10019233	Headaches
AEHLGTCD	**AESOC**	**AESOCCD**	**SOCINT**
10019231	Nervous system disorders	10029205	8

PARAM & PARAMCD – First character

PARCAT1	PARCAT1N	PARCAT2	PARCAT2N	PARCAT3	PARCAT3N	PARAM	PARAMCD
1.Use a letter for Overall (A), SOC (S), HLGT (G), HLT (H), PT (P) as the first symbol in the PARAMCD		Overall	1			**A**1A: All AEs: Any AE	**A**1A00001
		By SOC	2			**S**1A: Nervous system disorders	**S**1A29205
		By HLGT	3			**G**1A: Headaches	**G**1A19231
		By HLT	4			**H**1A: Headaches NEC	**H**1A19233
		By PT	5			**P**1A: Headache	**P**1A19211

PARAM & PARAMCD – Second character

PARCAT1	PARCAT1N	PARCAT2	PARCAT2N	PARCAT3	PARCAT3N	PARAM	PARAMCD
Use 1 or 2 for On study or On treatment, resp., as the second symbol in the PARAMCD		Overall	1	On-study	1	A**1**A: All AEs: Any AE	A**1**A00001
		By SOC	2	On-study	1	S**1**A: Nervous system disorders	S**1**A29205
		By HLGT	3	On-study	1	G**1**A: Headaches	G**1**A19231
		By HLT	4	On-study	1	H**1**A: Headaches NEC	H**1**A19233
		By PT	5	On-study	1	P**1**A: Headache	P**1**A19211

PARAM & PARAMCD – Third character

PARCAT1	PARCAT1N	PARCAT2	PARCAT2N	PARCAT3	PARCAT3N	PARAM	PARAMCD
All AEs	1					A1**A**: All AEs: Any AE	A1**A**00001
All AEs	1					S1**A**: Nervous system disorders	S1**A**29205
All AEs	1					G1**A**: Headaches	G1**A**19231
All AEs	1					H1**A**: Headaches NEC	H1**A**19233
All AEs	1					P1**A**: Headache	P1**A**19211

1. Use a letter for the third symbol in the PARAMCD, so if it is:
    1. All AEs (A)
    2. SAEs (B)
    3. SAEs with outcome death (C)
    4. AEs leading to discontinuation of IP (D)

PARAM & PARAMCD – Last characters – Any AE

PARCAT2	*ASSIGNED*	*ASSIGNED*	PARAM	PARAMCD
Overall	**00001**	**Any AE**	A1A: All AEs: **Any AE**	A1A**00001**
By SOC			S1A: Nervous system disorders	S1A29205
By HLGT			G1A: Headaches	G1A19231
By HLT			H1A: Headaches NEC	H1A19233
By PT			P1A: Headache	P1A19211

For SOC (S), HLGT (G), HLT (H), PT (P), use the last 5 numbers in the AESOCCD, AEHLGTCD, AEHLTCD, AEPTCD, as fourth to eighth symbol in the PARAMCD. For Overall (A) use 00001-00008 for the fourth to eighth symbols in the PARAMCD, so if it is:

1. Any AE (00001)
2. Any SAE (00002)
3. ...

PARAM & PARAMCD – Last characters – SOC

PARCAT2	AESOCCD	AESOC	PARAM	PARAMCD
Overall			A1A: All AEs: Any AE	A1A00001
By SOC	100**29205**	**Nervous system disorders**	S1A: **Nervous system disorders**	S1A**29205**
By HLGT	10029205	Nervous system disorders	G1A: Headaches	G1A19231
By HLT	10029205	Nervous system disorders	H1A: Headaches NEC	H1A19233
By PT	10029205	Nervous system disorders	P1A: Headache	P1A19211

For SOC (S), HLGT (G), HLT (H), PT (P), use the last 5 numbers in the AESOCCD, AEHLGTCD, AEHLTCD, AEPTCD, as fourth to eighth symbol in the PARAMCD. For Overall (A) use 00001-00007 for the fourth to eighth symbols in the PARAMCD, so if it is:

1. Any AE (00001)
2. Any SAE (00002)
3. …

PARAM & PARAMCD – Last characters – HLGT

PARCAT2	AEHLGTCD	AEHLGT	PARAM	PARAMCD
Overall			A1A: All AEs: Any AE	A1A00001
By SOC	10019231	Headaches	S1A: Nervous system disorders	S1A29205
By HLGT	100**19231**	**Headaches**	G1A: **Headaches**	G1A**19231**
By HLT	10019231	Headaches	H1A: Headaches NEC	H1A19233
By PT	10019231	Headaches	P1A: Headache	P1A19211

For SOC (S), HLGT (G), HLT (H), PT (P), use the last 5 numbers in the AESOCCD, AEHLGTCD, AEHLTCD, AEPTCD, as fourth to eighth symbol in the PARAMCD. For Overall (A) use 00001-00007 for the fourth to eighth symbols in the PARAMCD, so if it is:

1. Any AE (00001)
2. Any SAE (00002)
3. ...

PARAM & PARAMCD – Last characters – HLT

PARCAT2	AEHLTCD	AEHLT	PARAM	PARAMCD
Overall			A1A: All AEs: Any AE	A1A00001
By SOC	10019231	Headaches NEC	S1A: Nervous system disorders	S1A29205
By HLGT	10019231	Headaches NEC	G1A: Headaches	G1A19231
By HLT	100**19233**	**Headaches NEC**	H1A: **Headaches NEC**	H1A**19233**
By PT	10019231	Headaches NEC	P1A: Headache	P1A19211

For SOC (S), HLGT (G), HLT (H), PT (P), use the last 5 numbers in the AESOCCD, AEHLGTCD, AEHLTCD, AEPTCD, as fourth to eighth symbol in the PARAMCD. For Overall (A) use 00001-00007 for the fourth to eighth symbols in the PARAMCD, so if it is:

1. Any AE (00001)
2. Any SAE (00002)
3. ...

PARAM & PARAMCD – Last characters – PT

PARCAT2	AEPTCD	AEDECOD	PARAM	PARAMCD
Overall			A1A: All AEs: Any AE	A1A00001
By SOC	10019231	Headache	S1A: Nervous system disorders	S1A29205
By HLGT	10019231	Headache	G1A: Headaches	G1A19231
By HLT	10019233	Headache	H1A: Headaches NEC	H1A19233
By PT	100**19211**	**Headache**	P1A: **Headache**	P1A**19211**

For SOC (S), HLGT (G), HLT (H), PT (P), use the last 5 numbers in the AESOCCD, AEHLGTCD, AEHLTCD, AEPTCD, as fourth to eighth symbol in the PARAMCD. For Overall (A) use 00001-00007 for the fourth to eighth symbols in the PARAMCD, so if it is:

1. Any AE (00001)
2. Any SAE (00002)
3. ...

PARAM & PARAMCD – Final

PARCAT1	PARCAT1N	PARCAT2	PARCAT2N	PARCAT3	PARCAT3N	PARAM	PARAMCD
All AEs	1	Overall	1	On-study	1	A1A: All AEs: Any AE	A1A00001
All AEs	1	By SOC	2	On-study	1	S1A: Nervous system disorders	S1A29205
All AEs	1	By HLGT	3	On-study	1	G1A: Headaches	G1A19231
All AEs	1	By HLT	4	On-study	1	H1A: Headaches NEC	H1A19233
All AEs	1	By PT	5	On-study	1	P1A: Headache	P1A19211

PARAM & PARAMCD – Overall

PARCAT1	PARCAT1N	PARCAT2	PARCAT2N	PARCAT3	PARCAT3N	PARAM	PARAMCD
All AEs	1	Overall	1	On-study	1	A1A: All AEs: Any AE	A1A00001
SAE	2	Overall	1	On-treatment	2	A2B: SAEs: Any SAE with outcome death	A2B00003

3.Use a letter for the third symbol in the PARAMCD, so if it is: 1.All AEs (A) 2.SAEs (B) 3…. (x)	1.Use a letter for Overall (A), SOC (S), HLGT (G), HLT (H), PT (P) as the first symbol in the PARAMCD	2. Use 1 or 2 for On study or On treatment, resp., as the second symbol in the PARAMCD	4. For Overall (A) use 00001-00007 for the fourth to eighth symbols in the PARAMCD, so if it is: Any AE (00001) Any SAE (00002) Any SAE with outcome death (00003)

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

Thank You!