

Making visualizations work

TIMOTHY KROPP

ASSOCIATE DIRECTOR FOR INNOVATION

OFFICE OF COMPUTATIONAL SCIENCE, OTS/CDER/FDA

Why

To protect and promote the public health.



Right drugs, for the right indication, at the right dose, at the right time.

We've made great strides

...but



On to the next step?



Just out of reach



Because tools are trying to replicate the outputs that humans created manually

Why? Because we're difficult.

Unique context.

Shifting context.

A group is not a group

Humans make a lot of assumptions without realizing it.

Humans make a lot of interpretations without realizing it.

Humans make *mistakes* in assumption and interpretation without realizing it.

Unique Context -- Adverse Events



Identify possible safety signals by looking at risk differences and relative risks at the PT and SOC levels



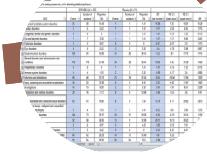
Drill down from the SOC level to see what PTs are driving each SOC and check to see if baseline characteristics have an effect on risk estimators



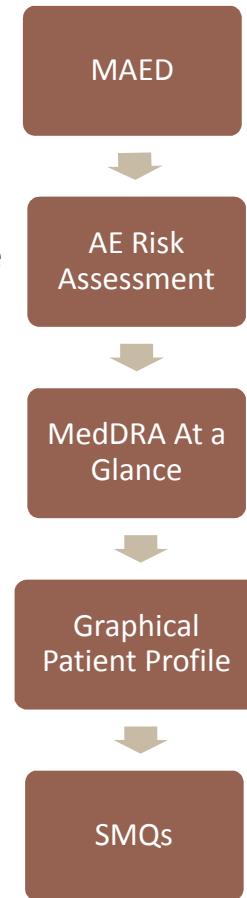
Easily follow a potential signal across multiple levels of the hierarchy in this combined view. Identify any DMEs that occurred in the study



Drill down to the specific patients for which a signal exists and determine if an AE coincides with any other events/exposures



Determine if similar AEs have been split across SOCs to identify specific medical conditions or areas of interest



Adverse Event Exploration Flow

Review Questions:

What are the most frequently occurring AEs?

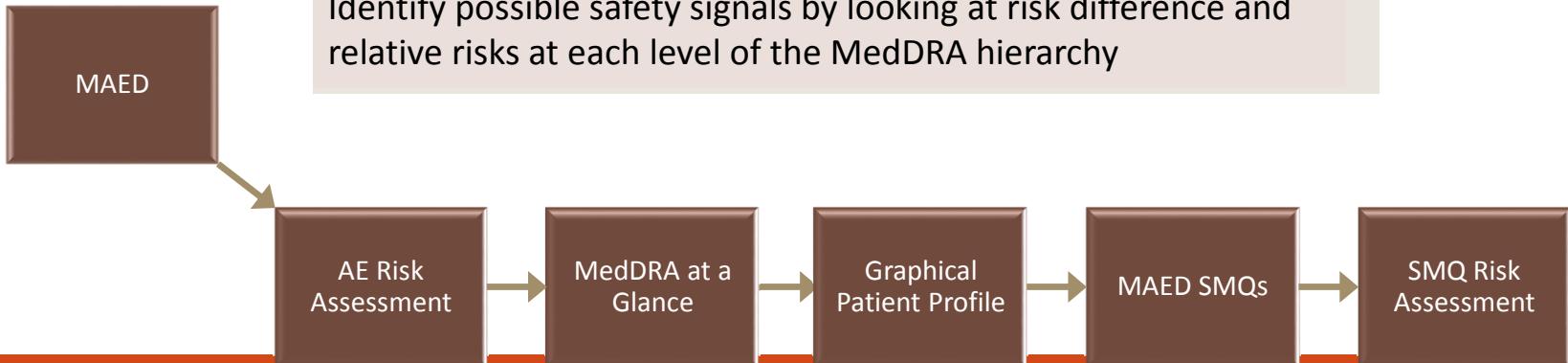
Which AEs occur more often in the treatment in relation to the comparator?

Which AEs have the largest risk difference and/or relative risks?

SOC	Events	Subjects (%)	Number of Events (%)	Events	Subjects (%)	Number of Events (%)	Events	Subjects (%)	Group (N = 140)	Proportion	RD (per hundred)	RD (per hour)	
WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!													
Secondary preferred terms excluded													
P-values should be used for ranking purposes only, not for determining statistical significance.													
6													
Vedolizumab for Every 4 Weeks During													
7	Blood and lymphatic system disorders	55	47	10.36	9	8	6.96	14	9	9.4	0.96	-4.5	
8	Cardiac disorders	14	13	2.86	10	5	4.1	2	2	1.34	1.52	-0.88	
9	Congenital, familial and genetic disorders	1	1	0.22	1	1	0.82	0	0	0	0.22	-0.21	
10	Eye and labyrinth disorders	19	16	3.53	2	2	2.46	3	3	2.14	1.53	-1.31	
11	Executive function disorders	8	8	1.76	2	2	1.64	1	1	0.67	1.09	-0.69	
12	Eye disorders	43	31	6.83	17	16	13.11	9	6	4.03	2.8	-1.12	
13	Gastrointestinal disorders	330	168	37	70	43	35.25	106	54	36.24	0.76	-8.14	
General disorders and administration site conditions													
14	Hepatobiliary disorders	135	88	19.38	22	20	16.39	26	19	12.75	6.03	0.16	
15	Hepatopathy disorders	4	4	0.88	1	1	0.82	4	2	1.34	0.46	-3.3	
16	Immune system disorders	3	3	0.66	1	1	0.82	1	1	0.67	-0.01	-1.52	
17	Infectious and infiltrations	364	193	42.51	99	62	59.82	74	46	30.87	11.64	2.9	
18	Injury, poisoning and procedural complications	53	35	7.71	11	9	7.38	3	3	2.01	5.7	2.36	
19	Investigations	86	50	11.01	24	15	12.3	61	25	16.73	5.77	-12.42	
20	Metabolism and nutrition disorders	43	32	7.05	2	2	1.64	11	9	6.16	1.01	-3.48	
21	Musculoskeletal and connective tissue disorders	166	101	22.25	47	28	22.95	30	22	14.77	7.48	0.62	
22	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	4	0.88	4	4	3.20	2	1	0.67	0.21	-1.36	
23	Nervous system disorders	204	97	21.37	44	29	22.95	59	28	16.79	2.57	-4.74	
24	Pregnancy, puerperium and perinatal conditions	1	1	0.22	0	0	0	0	0	0	0.22	-0.21	
25	Psychiatric disorders	47	36	7.91	10	10	4.21	6	6	4.24	1.34	-1.11	
26	Reproductive system disorders	14	11	2.42	7	7	2.46	2	2	1.34	1.08	-1.25	
27	Reproductive system and breast disorders	11	10	2.2	6	5	4.1	2	2	1.34	0.96	-1.43	
28	Respiratory, thoracic and mediastinal disorders	99	61	13.44	30	21	17.21	23	15	10.07	3.37	-2.39	
29	Skin and subcutaneous tissue disorders	137	97	21.37	31	21	13.93	30	19	12.75	8.61	2.06	

Analysis enables you to...

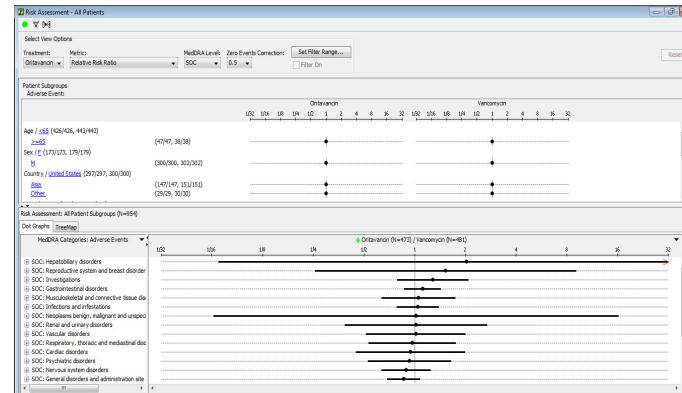
Identify possible safety signals by looking at risk difference and relative risks at each level of the MedDRA hierarchy



Adverse Event Exploration Flow

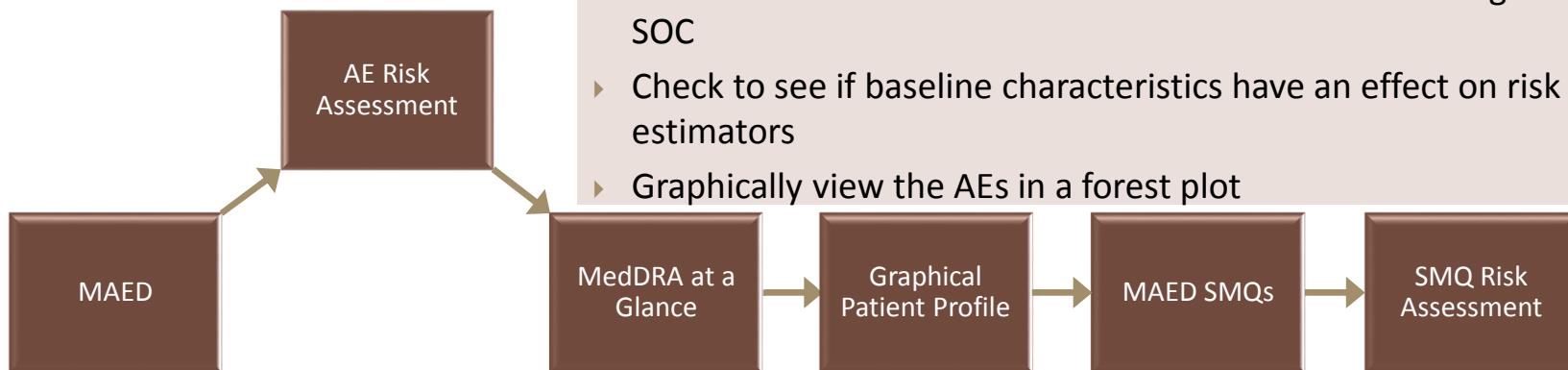
Review Questions:

- ▶ Which PTs are driving the risk differences and/or relative risks seen at the SOC level?
- ▶ Do different baseline or demographic characteristics have an effect on the risk estimators?



Analysis enables you to...

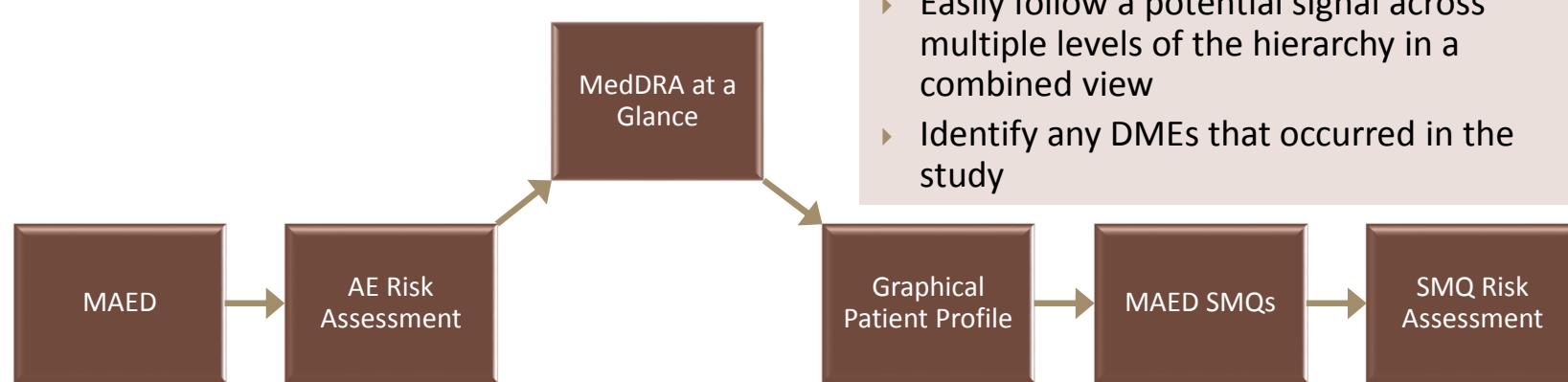
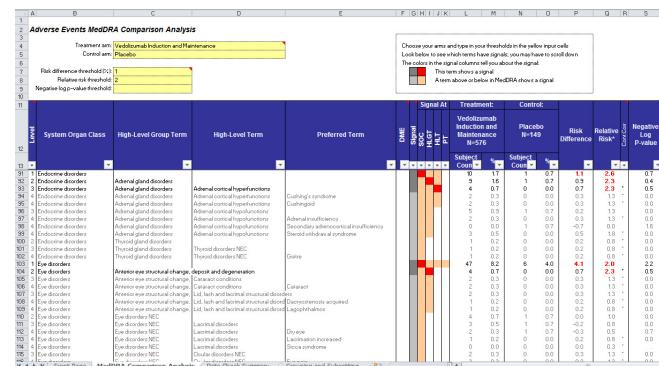
- ▶ Drill down from the SOC level to see what PTs are driving each SOC
- ▶ Check to see if baseline characteristics have an effect on risk estimators
- ▶ Graphically view the AEs in a forest plot



Adverse Event Exploration Flow

Review Questions:

- ▶ Which level of the MedDRA hierarchy best characterizes a safety signal of interest?
- ▶ Are there worrisome AEs or Designated Medical Events (DMEs)?



Analysis enables you to...

- ▶ Easily follow a potential signal across multiple levels of the hierarchy in a combined view
- ▶ Identify any DMEs that occurred in the study

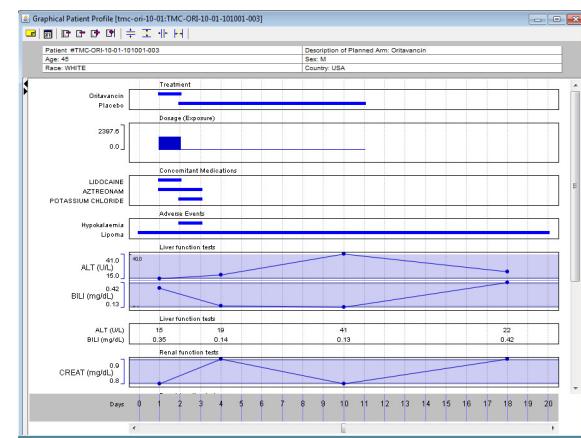
Adverse Event Exploration Flow

Review Questions:

What day does an AE begin for a particular subject?

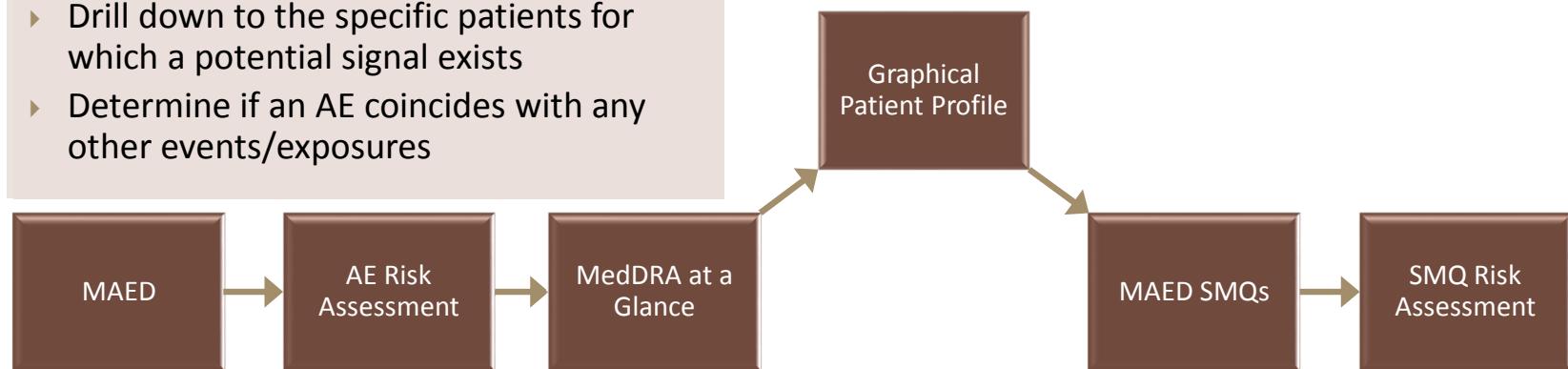
Did a subject take any concomitant medications as a result of the AE?

Did any other events occur around the same time as the AE of interest?



Analysis enables you to...

- ▶ Drill down to the specific patients for which a potential signal exists
- ▶ Determine if an AE coincides with any other events/exposures



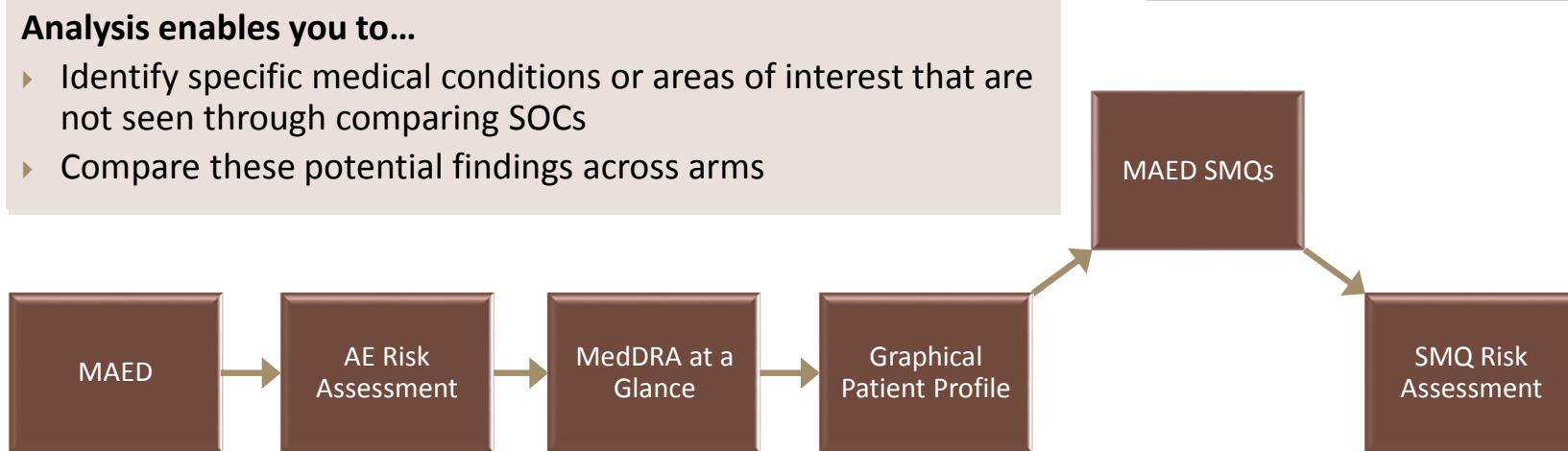
Adverse Event Exploration Flow

Review Questions:

Are there any similar AE signals split across different SOCs?

Analysis enables you to...

- Identify specific medical conditions or areas of interest that are not seen through comparing SOCs
- Compare these potential findings across arms



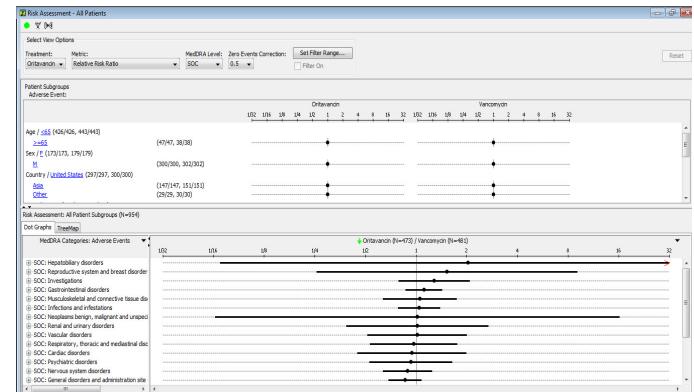
SOC	Vedolizumab for Every 4 Weeks During			Vedolizumab for Every 8 Weeks During			Group 0 (N = 449)			RD C.I.	VE
	Events	Number of subjects	Proportion	Events	Number of subjects	Proportion	Events	Number of subjects	Proportion		
7. Blood and lymphatic system disorders	59	103	0.57	9	5	0.16	14	1	9.4	0.96	4.5
8. Cardiac disorders	14	13	2.86	10	5	4.1	2	2	1.34	1.52	-0.88
9. Congenital, familial and genetic disorders	1	1	0.22	1	1	0.82	0	0	0	0.22	-0.21
10. Ear and labyrinth disorders	10	16	3.52	4	3	2.46	3	3	2.01	1.51	-1.31
11. Endocrine disorders	6	—	1.76	2	2	1.64	1	1	0.67	1.09	-0.69
12. Eye disorders	4	21	6.83	17	16	15.11	9	6	4.53	2.3	-1.12
13. Gastrointestinal disorders	330	168	37	78	43	35.25	108	54	38.24	0.76	-0.14
General disorders and administration site conditions	130	88	19.38	22	20	16.30	26	19	12.75	6.63	0.16
15. Hepatobiliary disorders	4	4	0.88	1	1	0.82	4	2	1.44	0.48	-1.36
16. Immune system disorders	3	—	0.56	1	1	0.82	1	1	0.67	0.51	-1.02
17. Infections and infestations	164	193	42.51	99	62	50.62	74	46	30.87	11.54	2.94
18. Injury, poisoning and procedural complications	53	35	7.71	11	9	7.38	3	3	2.06	5.7	2.36
19. Investigations	86	50	11.01	24	15	12.3	61	25	16.78	-5.77	-12.42
20. Metabolism and nutrition disorders	43	32	7.05	2	2	1.64	11	9	6.04	1.01	-3.48
Musculoskeletal and connective tissue disorders	166	101	22.25	47	28	22.95	30	22	14.77	7.48	0.62
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	4	0.88	4	4	3.28	2	1	0.67	0.21	-1.36
23. Nervous system disorders	204	97	21.37	44	28	22.95	59	29	18.79	2.57	-4.74
24. Pregnancy, puerperium and perinatal conditions	1	1	0.22	0	0	0	0	0	0	0.22	-0.21
Psychiatric disorders	47	36	7.93	10	10	8.2	8	6	4.03	3.9	-0.11
Renal and urinary disorders	14	11	2.42	3	3	2.65	2	2	1.08	1.08	-1.43
27. Reproductive system and breast disorders	11	40	2.7	6	5	4.1	2	2	1.34	0.98	-0.37
28. Respiratory, thoracic and mediastinal disorders	99	61	13.44	38	21	17.21	23	15	10.07	3.37	-2.39
Skin and subcutaneous tissue disorders	137	97	21.37	31	17	13.83	30	19	12.75	8.61	2.05

Adverse Event Exploration Flow

Review Questions:

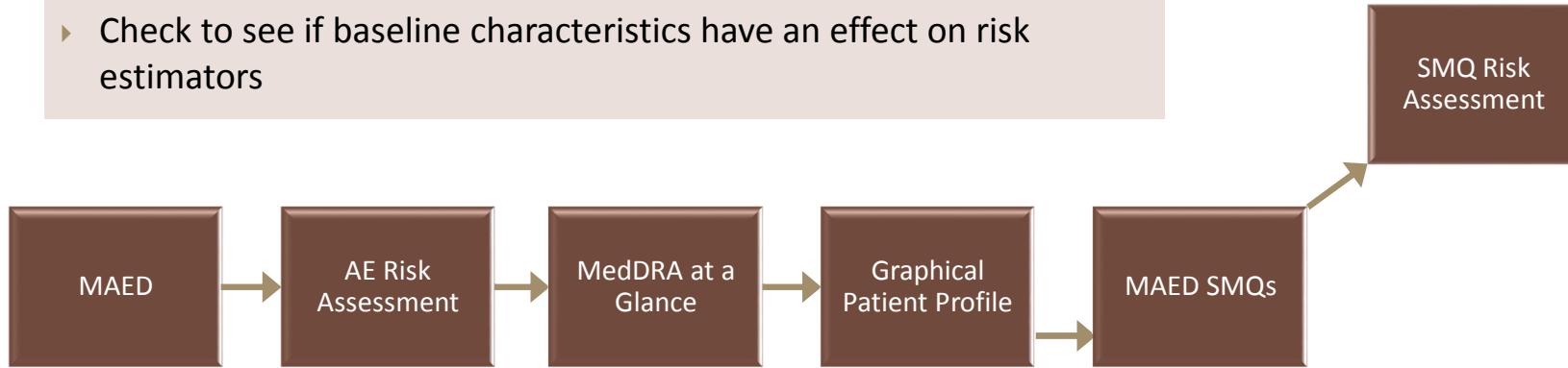
What PTs are driving particular SMQs?

Are there significant differences between patient subgroups?



Analysis enables you to...

- ▶ Determine the PTs that are driving each SMQ
- ▶ Check to see if baseline characteristics have an effect on risk estimators



Unique Context -- Histopathology

Treatment-Related Microscopic Findings		No. of animals affected							
		Males				Females			
Dose (mg/kg/day)		0	0.05	0.10	1.0	0	0.05	0.10	1.0
Number of animals examined		0/4/2	0/4/2	0/4/2	3*/2/2	0/4/2	0/4/2	0/4/2	4*/2/1
Organ	Finding								
Spinal cord, lumbar	Acute inflammation in meninges	Marked	-	-	-	1*/0/0	-	-	-
	Necrosis	Marked	-	-	-	1*/0/0	-	-	-
Spinal cord, thoracic	Acute inflammation in meninges	Mild	-	-	-	1*/0/0	-	-	-
	Lymphoid depletion of germinal center	Total	-	0/1/0	-	3*/1/0	-	0/1/0	0/1/0
Spleen		Minimal	-	-	-	0/1/0	-	0/1/0	0/1/0
		Mild	-	0/1/0	-	1*/0/0	-	-	1*/0/0
		Moderate	-	-	-	1*/0/0	-	-	-
		Marked	-	-	-	1*/0/0	-	-	1*/0/0
		Severity not listed	-	-	-	-	-	-	1*/0/0
		Total	0/1/1	0/4/0	0/2/0	3*/2/1	0/3/2	0/3/2	0/4/2
Thymus	Lymphoid depletion of cortex/medulla	Minimal	-	0/2/0	-	0/0/1	-	0/0/2	0/0/1
		Mild	0/1/1	0/1/0	0/1/0	-	0/2/2	0/2/0	0/2/1
		Moderate	-	0/1/0	0/1/0	-	0/1/0	0/1/0	0/2/0
		Marked	-	-	-	3*/2/0	-	-	2*/2/0

We've got other challenges too

Machine learning alone doesn't hack it for regulatory work - close enough is no cigar

Review clocks down to 30 days for some types of review mean more customizations are necessary.

Solution 1 (partial) - Integrated views



Solution 2

Collaboration and
Conversation

Summary

We have made tremendous strides in getting data in, setting up systems, and developing and delivering tools to transform and modernize review *AND* we still have miles to go before we rest.

