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Effective Presentations of CTCAE Graded Laboratory Data

William Coar, Axio Research

Amber Randall, SCHARP Data Analytics Unit at Fred Hutch

- Motivation
- Treatment emergent laboratory abnormality
- NCI-CTCAE
- Vertical approach to summarization
- A challenge with CTCAE V5.0
- Q & A

- Lab data are:
 - ❖ Voluminous
 - ❖ Often require standardization
 - ❖ Usually challenging to work with
- Summary tables of many pages of continuous summary statistics
- Desire for more concise presentations
 - ❖ 2010 – ASA Webinar (Wittes & Downs)
 - ❖ 2016 – CTTI Recommendations on DMCs
 - ❖ 2018 – BASS XXVI – Kerr, Downs

- How do you find clinically concerning trends with concise presentation?
- Figures are good to show general trends
 - ❖ Extremes often wreak havoc on output
 - ❖ Extremes are often (but not always) the values of interest
- Consider defining treatment emergent abnormalities analogous to TEAE

Treatment Emergent Laboratory Abnormality

- Definition: clinically meaningful change in a laboratory parameter from a pre-treatment value.
- A slight change might be due simply to natural variation and NOT clinically meaningful or even related to the study drug
- Need to identify a clinically meaningful change
- Is the magnitude of a clinically meaningful change standard in practice?

Classification via Normal Ranges

- If normal ranges are provided, we can identify:
 - ❖ Normal
 - ❖ High
 - ❖ Low
- Shifts from baseline identify treatment emergent abnormalities
 - ❖ Normal-High
 - ❖ Normal-Low
 - ❖ Low-High
 - ❖ High-Low

Classification via Normal Ranges

Example

PARAMCD	AVISIT	AVAL	ANRLO	ANRHI	AVALCAT1	BASECAT1	SHIFT1
ALT	BASELINE	40	7	55	NORMAL	NORMAL	
ALT	WEEK4	80	7	55	HIGH	NORMAL	NORMAL-HIGH
ALT	WEEK8	50	7	55	NORMAL	NORMAL	NORMAL-NORMAL

Classification via Normal Ranges

Example

			Arm A			Arm B		
			Post Baseline			Post Baseline		
Parameter	Visit	Baseline	Low	Normal	High	Low	Normal	High
ALT	Week 4	Low	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)
		Normal	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)
		High	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)
	Week 8	Low	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)
		Normal	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)
		High	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)	xx(x.x%)
Etc								

Classification via Normal Ranges

Evaluation

- Doesn't require standardization of units
- Many rows/columns of 0s
- Not every treatment emergent low (or high) abnormality is of clinical interest
- Denominator isn't well defined
- No information on the magnitude of the change
- There could still be clinically concerning changes that are not identified (High-High, Low-Low)

- Focus on presentation of grades, not the actual grading (yet)
- Not all lab parameters are graded.
 - ❖ Some that are may not be of clinical interest
- Assignment of Grade 0 for convenience
 - ❖ Often values within normal range, but not always
- Shifts in grade identify treatment emergent abnormalities
- Examples include
 - ❖ Grade 0 – Grade 2 (high)
 - ❖ Grade 1 (high) – Grade 3 (high)
 - ❖ Grade 1 (low) – Grade 2 (high)

NCI-CTCAE Grading

Example

PARAMCD	AVISIT	AVAL	ATOXGR	BTOXGR	SHIFT1
ALT	BASELINE	40	GRADE 0	GRADE 0	
ALT	WEEK4	80	GRADE 1	GRADE 0	1 GRADE SHIFT
ALT	WEEK8	50	GRADE 0	GRADE 0	0 GRADE SHIFT

NCI-CTCAE Grading

Example

			Arm A					Arm A				
			Post Baseline					Post Baseline				
Parameter	Visit	Baseline	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4
ALT	Week 4	Grade 0	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)
		Grade 1	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)
		Grade 2	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)
		Grade 3	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)
		Grade 4	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)	Xx (x.x%)
	Etc											

NCI-CTCAE Grading

Evaluation

- Many more rows/columns of 0s
- May require a smaller font
- Magnitude of the shift represents the magnitude of the change
 - ❖ Grade 0-Grade 1 = 1 Grade Shift
 - ❖ Grade 1-Grade 4 = 3 Grade shift
- Denominator still isn't well defined
- Does not account for bi-directional grading

NCI-CTCAE Grading

Bi-directional grading

- Some labs such as sodium, calcium, and glucose have bi-directional grading
- Abnormal low and high are of clinical interest
- Data come with a single grade assignment
- Additional work is needed to know if it is abnormal low or high
- Update to previous table with trend column to know direction of the abnormality
 - ❖ Table becomes quite lengthy
 - ❖ Definition of the grade presented is not always clear

NCI-CTCAE Grading

Bi-directional grading

PARAMCD	AVISIT	AVAL	ATOXGR	ANRLO	ANRHI	BTOXGR	SHIFT1
SODIUM	BASELINE	131	GRADE 1	135	145		
SODIUM	WEEK4	153	GRADE 2	135	145		
SODIUM	WEEK8	148	GRADE 1	135	145		

- Cells in red depend on the trend you are summarizing

- Grading associates a lab parameter to a particular adverse event
- Grading in one direction (high or low) associated with one event
 - ❖ Abnormal high ALT -> *Alanine aminotransferase increased*
- Bi-directional grading associated with two events
 - ❖ Abnormal low sodium -> *hyponatremia*
 - ❖ Abnormal high sodium -> *hypernatremia*
- Grade 0 = event was Not Present

- Summarize by CTCAE term
 - ❖ Eliminates confusion with bi-directional grading
- Use a more vertical presentation
- Choose a *worst post baseline* value for summarization
- Identify clinically meaningful shifts to present
- Could consider also summarizing last observed value
 - ❖ May suggest if abnormality was transient

NCI-CTCAE Term

Proposal

CTCAE Term	Visit		Arm A	Arm B
Hyponatremia	Baseline	N	Xx	xx
		Not Present	Xx (x.x%)	Xx (x.x%)
		Grade 1	Xx (x.x%)	Xx (x.x%)
		Grade 2	Xx (x.x%)	Xx (x.x%)
		Grade 3	Xx (x.x%)	Xx (x.x%)
		Grade 4	Xx (x.x%)	Xx (x.x%)
	Worst Post-Baseline	N	Xx	xx
		Not Present	Xx (x.x%)	Xx (x.x%)
		Grade 1	Xx (x.x%)	Xx (x.x%)
		Grade 2	Xx (x.x%)	Xx (x.x%)
		Grade 3	Xx (x.x%)	Xx (x.x%)
		Grade 4	Xx (x.x%)	Xx (x.x%)
	Shift to Worst-Post Baseline	N	Xx	xx
		0 Grade Shift	Xx (x.x%)	Xx (x.x%)
		1 Grade Shift	Xx (x.x%)	Xx (x.x%)
		2 Grade Shift	Xx (x.x%)	Xx (x.x%)
		3 Grade Shift	Xx (x.x%)	Xx (x.x%)
		4 Grade Shift	Xx (x.x%)	Xx (x.x%)

- Combines both lab parameter and direction
- Grade 0 replaced by Not Present
- Requires some changes to analysis data structure
- Transitions from Low-high (or high-low) not identifiable, but the emergent event is summarized

NCI-CTCAE Term

Evaluation

PARAMCD	AVISIT	AVAL	ANRLO	ANRHI	ATOXGRL	BTOXGRL	ATOXGRH	BTOXGRH
SODIUM	BASELINE	131	135	145	GRADE 1	GRADE 1	GRADE 0	GRADE 0
SODIUM	WEEK4	153	135	145	GRADE 0	GRADE 1	GRADE 2	GRADE 0
SODIUM	WEEK8	148	135	145	GRADE 0	GRADE 1	GRADE 1	GRADE 0
SODIUM	WPB				GRADE 0	GRADE 1	GRADE 2	GRADE 0

SHIFTL	SHIFTH	ATOXDSCSCL	ATOXDSCSCL
		HYPONATREMIA	HYPERNATREMIA
-1 GRADE SHIFT	2 GRADE SHIFT	HYPONATREMIA	HYPERNATREMIA
-1 GRADE SHIFT	1 GRADE SHIFT	HYPONATREMIA	HYPERNATREMIA
-1 GRADE SHIFT	2 GRADE SHIFT	HYPONATREMIA	HYPERNATREMIA

NCI-CTCAE Term

Evaluation

PARAMCD	AVISIT	AVAL	ANRLO	ANRHI	ATOXGRL	BTOXGRL	ATOXGRH	BTOXGRH
SODIUM	BASELINE	131	135	145	GRADE 1	GRADE 1	GRADE 0	GRADE 0
SODIUM	WEEK4	153	135	145	GRADE 0	GRADE 1	GRADE 2	GRADE 0
SODIUM	WEEK8	148	135	145	GRADE 0	GRADE 1	GRADE 1	GRADE 0
SODIUM	WPB				GRADE 0	GRADE 1	GRADE 2	GRADE 0

SHIFTL	SHIFTH	ATOXDSCS	ATOXDSCH
		HYPONATREMIA	HYPERNATREMIA
-1 GRADE SHIFT	2 GRADE SHIFT	HYPONATREMIA	HYPERNATREMIA
-1 GRADE SHIFT	1 GRADE SHIFT	HYPONATREMIA	HYPERNATREMIA
-1 GRADE SHIFT	2 GRADE SHIFT	HYPONATREMIA	HYPERNATREMIA

CTCAE Version 5

Fundamental Changes

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransfe rase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransfer ase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

- V5.0 may depend on a baseline value
- Grade itself represents an emergent or worsening abnormality
- Shift in inherently part of grade
- May result in more challenges with presentation

CTCAE Version 5

Fundamental Changes

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransfe rase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransfer ase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

- V5.0 may depend on a baseline value
- Grade itself represents an emergent or worsening abnormality
- Shift in inherently part of grade
- May result in more challenges with presentation

- What is the definition of baseline when assigning a grade?
- Will assignment of grade be done at the analysis dataset stage rather than at a central lab?
- Will an algorithm in SAS programming represent clinical practice?

Concluding Thoughts

- A lot of information in traditional shift tables – too much
- Shift tables can be used to identify treatment emergent abnormalities (for now)
- Vertical structure + worst observed case greatly reduces the numbers of rows
- Fundamental change with CTCAE V5
- Interpretation requires a clear understanding of grading system
- Collaboration between statistics and clinical colleagues is essential

Axio

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