FDA Toxicity Grading Scale for Healthy Volunteers During ADLB Implementation

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Meet the Speakers

Qianyuan Zhang

Title: Experienced I Stat Programmer

Organization: Clinical & Statistical Programming, Johnson & Johnson

Qianyuan joined Johnson & Johnson as a Statistical Programmer Analyst after graduated from China Pharmaceutical University in 2018. She has accumulated extensive experience across various projects in Infectious Diseases & Vaccine, Immunology, and Clinical Pharmacology. Since last year, she has dedicated herself to Clinical Pharmacology studies, applying the latest standards, and actively participating in internal process development efforts.

Jiaqi Song

Title: Principal I Stat Prog Lead

Organization: Clinical & Statistical Programming, Johnson & Johnson

Jiaqi holds a PhD in Biostatistics and has seven years of industry experience as a statistical programmer supporting end-to-end drug development, with expertise in hematological malignancy and clinical pharmacology. He recently led his team's successful support of the global BLA submission for Daratumumab and has spearheaded key initiatives including implementing R programming across teams and developing R Shiny applications to enhance operational efficiency. As Co-Chair of the Johnson & Johnson China HOCO Digital Club, he explores advanced AI technologies and their potential applications in statistical programming. Jiaqi is committed to applying cutting-edge technologies to maximize efficiency and quality in statistical programming workflows.

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- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of Johnson & Johnson.*

- *The author(s) have no real or apparent conflicts of interest to report.*

- *The data analysis in this presentation is based on dummy data, with no real data involved. The results are for illustrative purposes only and have no practical significance.*

Agenda

1. What’s FDA Toxicity Grading Scale
2. How to perform Toxicity Grade Analysis

What’s FDA Toxicity Grading Scale

Lab Data

Chemistry

- General Chemistry
- Liver biochemistry
- Kidney function
- Lipid

Hematology

- Completed Blood Count
- White Blood Cell Differential
- Coagulation Studies

Urinalysis

- Data Categories -

Result Scale

- *QUANTITATIVE*
- *SEMI-QUANTITATIVE*
- *ORDINAL*
- *…*

Data collection

Central lab Local lab

In March 2024, the FDA revised TCG to require sponsors to submit two distinct domains for lab results.

- **Structured Data Domains**: LB domain for SI units and LC domain for conventional units.
- **Analysis-Driven Creation**: ADaM recommends creating ADLB or ADLC based on analysis requirements.

FDA (2007) Toxicity Grading Scale

Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Food and Drug Administration (FDA, 2007)).

It contains 2 tables: 1) for Clinical Abnormalities and 2) for Laboratory Abnormalities.

It categorizes toxicity into four grades for both clinical and laboratory abnormalities: Grade 1 (**mild**), Grade 2 (**moderate**), Grade 3 (**severe**), and Grade 4 (potentially life-threatening).

NCI's Common Toxicity Criteria and the AIDS Division's Grading Scale, are designed for patients with existing conditions and **may not be suitable for healthy volunteers** (potentially leading to missed adverse events).

FDA (2007) is extended for other clinical trials for healthy adult and adolescent volunteers.

Other criteria: National and Regional Standards (such as FCPI, NMPA).

FDA (2007) Toxicity Grading Scale

	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE Term				
Category: Metabolism and nutrition disorders				
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium **>150 - 155 mmol/L**; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*

Key: ULN=Upper Limit of Normal
Text in gray italic in the table is present in the grading scale but is not applied when grading lab data.
Resource: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
FDA (2007) Laboratory Test / Toxicity Term				
Category: Chemistry				
Sodium - Hypernatremia	Sodium 144 – 145 mmol/L	Sodium **146 – 147 mmol/L**	Sodium 148 – 150 mmol/L	Sodium > 150 mmol/L

Resource: https://www.fda.gov/media/73679/download

What outputs will be performed

TSFLAB03b: Subjects With ≥1 Laboratory Values With Elevated or Low Values Based on Worst On-treatment Value Based on FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers – [Part 1]: Safety Analysis Set (Study xxx)

Laboratory Category Laboratory Test Grade, n (%)	[Active Study Agent] [Treatment Group A] N=XXX	[Treatment Group B] N=XXX	[Placebo] N=XXX	Total N=XXX
Chemistry				
Sodium – Hyponatremia				
N	N	N	N	N
Grade 1	n (%)	n (%)	n (%)	n (%)
Grade 2	n (%)	n (%)	n (%)	n (%)
Grade 3	n (%)	n (%)	n (%)	n (%)
Grade 4	n (%)	n (%)	n (%)	n (%)
Sodium – Hypernatremia				
N	N	N	N	N
Grade 1	n (%)	n (%)	n (%)	n (%)
Grade 2	n (%)	n (%)	n (%)	n (%)
Grade 3	n (%)	n (%)	n (%)	n (%)
Grade 4	n (%)	n (%)	n (%)	n (%)
Potassium – Hypokalemia				
N	N	N	N	N
Grade 1	n (%)	n (%)	n (%)	n (%)
Grade 2	n (%)	n (%)	n (%)	n (%)
Grade 3	n (%)	n (%)	n (%)	n (%)
Grade 4	n (%)	n (%)	n (%)	n (%)
Potassium – Hyperkalemia				
N	N	N	N	N
Grade 1	n (%)	n (%)	n (%)	n (%)
Grade 2	n (%)	n (%)	n (%)	n (%)
Grade 3	n (%)	n (%)	n (%)	n (%)
Grade 4	n (%)	n (%)	n (%)	n (%)

What outputs will be performed

TSFLAB05b: Shift in Laboratory Values From Baseline to Worst Grade [During Time Period] Based on FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers – [Part 1]: Safety Analysis Set (Study xxx)

Laboratory Category / Laboratory Test	N	Baseline Toxicity Grade					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
[Treatment Group A]	N						
[Treatment Group B]	N						
[Placebo]	N						
Chemistry							
Laboratory test							
[Treatment Group A]	N						
Worst toxicity grade, n							
Grade 0		n	n	n	n	n	n
Grade 1		n	n	n	n	n	n
Grade 2		n	n	n	n	n	n
Grade 3		n	n	n	n	n	n
Grade 4		n	n	n	n	n	n
Total		n	n	n	n	n	n
[Treatment Group B]	N						
Worst toxicity grade, n							
Grade 0		n	n	n	n	n	n
Grade 1		n	n	n	n	n	n
Grade 2		n	n	n	n	n	n
Grade 3		n	n	n	n	n	n
Grade 4		n	n	n	n	n	n
Total		n	n	n	n	n	n

What outputs will be performed

LSFLAB01: Listing of Laboratory Values - [Part 1]; Safety Analysis Set (Study xxx)

Treatment Group/Treatment Sequence	Subject ID	Age (years) /Sex/Race	Laboratory Test (unit)	Assessment Date/Time (Study Day[a])	Visit	Time Point	Result	[Criteria Flag]	Change From Baseline	Reference Range

Key: [CS=clinically significant]
[a] Study day is relative to [the start of [study treatment]].

For Toxicity Grade column: retain the toxicity term for parameters with two directions and grade >= 1 (for example, Hypernatremia: grade 1).

How to perform Toxicity Grade Analysis

1. CDISC Requirements
2. Workflow

CDISC Requirement

ADLB (ADaMIG 1.1) and ADLBTOX (company standard)

USUBJID	AVISIT	PARAMCD	PARAM	AVAL	BASE	ABLFL	ATOXGR	BTOXGR	ATOX	BTOX	ANL05FL - Worst Tox Grade
001-0001	Screening	SODIUM	Sodium (mmol/L)	136	136	Y	0	0	Sodium - Hypernatremia, Sodium - Hyponatremia	Sodium - Hypernatremia, Sodium - Hyponatremia	
001-0001	Day 1	SODIUM	Sodium (mmol/L)	135	136		0	0	Sodium - Hypernatremia, Sodium - Hyponatremia	Sodium - Hypernatremia, Sodium - Hyponatremia	
001-0001	Day 3	SODIUM	Sodium (mmol/L)	132	136		1	0	Sodium - Hyponatremia	Sodium - Hypernatremia, Sodium - Hyponatremia	Y
001-0001	Day 5	SODIUM	Sodium (mmol/L)	140	136		0	0	Sodium - Hypernatremia, Sodium - Hyponatremia	Sodium - Hypernatremia, Sodium - Hyponatremia	
001-0001	Day 9	SODIUM	Sodium (mmol/L)	145	136		1	0	Sodium - Hypernatremia	Sodium - Hypernatremia, Sodium - Hyponatremia	Y
001-0001	EOS	SODIUM	Sodium (mmol/L)	137	136		0	0	Sodium - Hypernatremia, Sodium - Hyponatremia	Sodium - Hypernatremia, Sodium - Hyponatremia	

ADLBTOX

USUBJID	PARAMCD	PARAM	AVAL	BASE
001-0001	SODIUML	Sodium - Hyponatremia	1	0
001-0001	SODIUMH	Sodium - Hypernatremia	1	0

ADLB (ADaMIG 1.3)

USUBJID	AVISIT	PARAMCD	PARAM	AVAL	BASE	ABLFL	ATOXGR	BTOXGR	ATOXDSCL	ATOXGRL	BTOXGRL	ATOXDSCH	ATOXGRH	BTOXGRH	ANL04FL - Worst Tox Grade low	ANL05FL - Worst Tox Grade High
001-0001	Screening	SODIUM	Sodium (mmol/L)	136	136	Y	0	0	Sodium - Hyponatremia	0	0	Sodium - Hypernatremia	0	0		
001-0001	Day 1	SODIUM	Sodium (mmol/L)	135	136		0	0	Sodium - Hyponatremia	0	0	Sodium - Hypernatremia	0	0		
001-0001	Day 3	SODIUM	Sodium (mmol/L)	132	136		1	0	Sodium - Hyponatremia	1	0	Sodium - Hypernatremia	0	0	Y	
001-0001	Day 5	SODIUM	Sodium (mmol/L)	140	136		0	0	Sodium - Hyponatremia	0	0	Sodium - Hypernatremia	0	0		
001-0001	Day 9	SODIUM	Sodium (mmol/L)	145	136		1	0	Sodium - Hyponatremia	0	0	Sodium - Hypernatremia	1	0		Y
001-0001	EOS	SODIUM	Sodium (mmol/L)	137	136		0	0	Sodium - Hyponatremia	0	0	Sodium - Hypernatremia	0	0		

CDISC Requirement

ADaMIG 1.3

USUBJID	SEX	AVISIT	PARAMCD	PARAM	AVAL
Unique Subject Identifier	Sex	Analysis Visit	Parameter Code	Parameter	Analysis Value
002-001	F	Screening	Sodium	Sodium (mmol/L)	115
002-001	F	Cycle 04	Sodium	Sodium (mmol/L)	132
002-001	F	Cycle 05	Sodium	Sodium (mmol/L)	144

ATOXDSCL	ATOXGRL
Analysis Toxicity Description Low	Analysis Toxicity Grade Low
Sodium - Hyponatremia	0
Sodium - Hyponatremia	1
Sodium - Hyponatremia	0

Grade 1: 132 – 134 mmol/L

ATOXDSCH	ATOXGRH
Analysis Toxicity Description High	Analysis Toxicity Grade High
Sodium - Hypernatremia	0
Sodium - Hypernatremia	0
Sodium - Hypernatremia	1

Grade 0: <144 mmol/L

Max(ATOXGRL, ATOXGRH)

ATOXGR
Analysis Toxicity Grade
0
1
1

Workflow

SAP Appendix

Lab Toxicity Spreadsheet

Core Macros

Workflow

SAP Appendix

Each term and grade are described based on the grading scale.

Laboratory Test / Toxicity Term	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)	Implementation Notes
Chemistry					
Sodium - Hyponatremia	Sodium 132 – 134 mEq/L 132 – 134 mmol/L	Sodium 130 – 131 mEq/L 130 – 131 mmol/L	Sodium 125 – 129 mEq/L 125 – 129 mmol/L	Sodium < 125 mEq/L < 125 mmol/L	Added ranges in SI unit (mmol/L).
Sodium - Hypernatremia	Sodium 144 – 145 mEq/L 144 – 145 mmol/L	Sodium 146 – 147 mEq/L 146 – 147 mmol/L	Sodium 148 – 150 mEq/L 148 – 150 mmol/L	Sodium > 150 mEq/L > 150 mmol/L	Added ranges in SI unit (mmol/L).
Potassium - Hyperkalemia	Potassium 5.1 – 5.2 mEq/L 5.1 – 5.2 mmol/L	Potassium 5.3 – 5.4 mEq/L 5.3 – 5.4 mmol/L	Potassium 5.5 – 5.6 mEq/L 5.5 – 5.6 mmol/L	Potassium > 5.6 mEq/L > 5.6 mmol/L	Added ranges in SI unit (mmol/L).
Potassium - Hypokalemia	Potassium 3.5 – 3.6 mEq/L 3.5 – 3.6 mmol/L	Potassium 3.3 – 3.4 mEq/L 3.3 – 3.4 mmol/L	Potassium 3.1 – 3.2 mEq/L 3.1 – 3.2 mmol/L	Potassium < 3.1 mEq/L < 3.1 mmol/L	Added ranges in SI unit (mmol/L).
Hematology					
Hemoglobin	Female 11.0 – 12.0 g/dL; 110 - 120 g/L Male 12.5 – 13.5 g/dL; 125 – 135 g/L	Female 9.5 – 10.9 g/dL; 95 - 109 g/L Male 10.5 – 12.4 g/dL; 105 - 124 g/L	Female 8.0 – 9.4 g/dL; 80 - 94 g/L Male 8.5 – 10.4 g/dL; 85 - 104 g/L	Female < 8.0 g/dL; < 80 g/L Male < 8.5 g/dL; < 85 g/L	Added ranges in SI unit (g/L).
Hemoglobin change from baseline value	Any decrease – 1.5 g/dL; Any decrease – 15 g/L	Decrease of 1.6 – 2.0 g/dL; 16 - 20 g/L	Decrease of 2.1 – 5.0 g/dL; 21 - 50 g/L	Decrease of > 5.0 g/dL; > 50 g/L	Added ranges in SI unit (g/L).

What about 131.5?

The above data is sourced from: https://www.fda.gov/media/73679/download

Workflow

Lab Toxicity Spreadsheet

- Excel preconfigured to align with the SAP appendix for these scales
- Used to generate toxicity grade variables (e.g., ATOXGR(H/L), ATOXGRL, ATOXGRH)
- CONDCHK displays grading criteria vertically

LBTESTCD	LBTEST	LBSPEC	LBMETHOD	TOXFAST	TOXSEX	TOXAGECAT	UNIT	INDICATR	TOXTERM	RESULTNM	TOXGRD	CONDCHK
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Potassium - Hyperkalemia	numeric	0	-999999 < result <= 5.1
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Potassium - Hyperkalemia	numeric	1	5.1 <= result <= 5.2
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Potassium - Hyperkalemia	numeric	2	5.2 < result <= 5.4
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Potassium - Hyperkalemia	numeric	3	5.4 < result <= 5.6
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Potassium - Hyperkalemia	numeric	4	5.6 < result <= 999999
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Potassium - Hypokalemia	numeric	0	3.6 < result < 999999
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Potassium - Hypokalemia	numeric	1	3.5 <= result <= 3.6
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Potassium - Hypokalemia	numeric	2	3.3 <= result < 3.5
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Potassium - Hypokalemia	numeric	3	3.1 <= result < 3.3
K	Potassium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Potassium - Hypokalemia	numeric	4	-999999 <= result < 3.1
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Sodium - Hypernatremia	numeric	0	-999999 < result < 144
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Sodium - Hypernatremia	numeric	1	144 <= result <= 145
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Sodium - Hypernatremia	numeric	2	145 < result <= 147
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Sodium - Hypernatremia	numeric	3	147 < result <= 150
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	HIGH	Sodium - Hypernatremia	numeric	4	150 < result <= 999999
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Sodium - Hyponatremia	numeric	0	134 < result <= 999999
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Sodium - Hyponatremia	numeric	1	132 <= result <= 134
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Sodium - Hyponatremia	numeric	2	130 <= result < 132
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Sodium - Hyponatremia	numeric	3	125 <= result < 130
SODIUM	Sodium	SERUM, PLASMA, SERUM OR PLASMA					mEq/L, mmol/L	LOW	Sodium - Hyponatremia	numeric	4	-999999 <= result < 125

131.5 belongs to Grade 2

Grade 0 is assigned to a lab assessment when the lab test is described in the SAP table, but the lab value is not assigned a grade 1 or higher.

Workflow

Core Macros

%adtoxgr: used to create ATOXGR, BTOXGR, ATOXDSCL, ATOXDSCH, ATOXGRL, ATOXGRLN, ATOXGRH, ATOXGRHN, BTOXGRL, BTOXGRLN, BTOXGRH, BTOXGRHN based on criteria in LBTOXGRADE spreadsheet.

Workflow

Core Macros

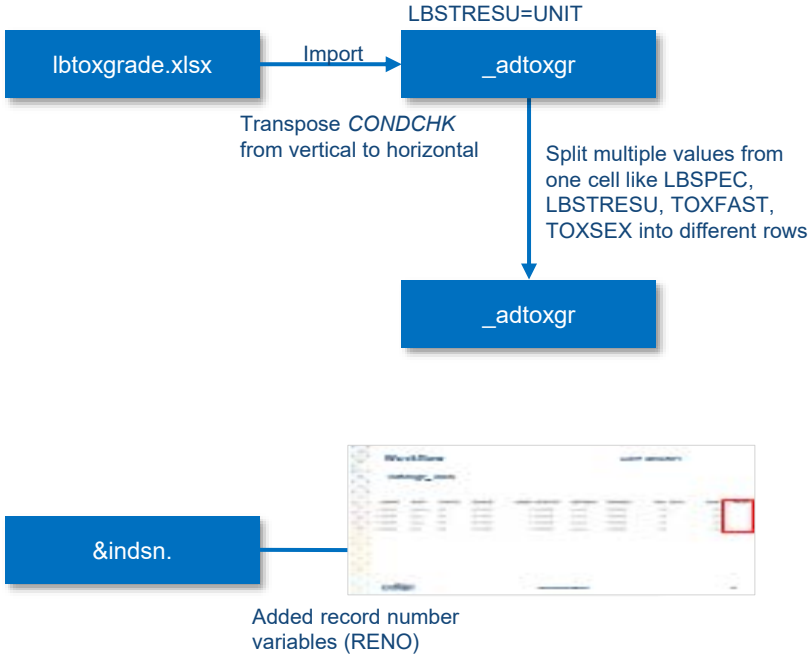
_adtoxgr

	LBTESTCD	LBSTRESU	LBSPEC	ATOX	RESULTNM	INDICATR	CONDCHK0	CONDCHK1	CONDCHK2	CONDCHK3	CONDCHK4
1	SODIUM	mEq/L	SERUM	Sodium - Hypernatremia	numeric	HIGH	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
2	SODIUM	mEq/L	PLASMA	Sodium - Hypernatremia	numeric	HIGH	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
3	SODIUM	mEq/L	SERUM OR PLASMA	Sodium - Hypernatremia	numeric	HIGH	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
4	SODIUM	mmol/L	SERUM	Sodium - Hypernatremia	numeric	HIGH	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
5	SODIUM	mmol/L	PLASMA	Sodium - Hypernatremia	numeric	HIGH	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
6	SODIUM	mmol/L	SERUM OR PLASMA	Sodium - Hypernatremia	numeric	HIGH	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
7	SODIUM	mEq/L	SERUM	Sodium - Hyponatremia	numeric	LOW	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
8	SODIUM	mEq/L	PLASMA	Sodium - Hyponatremia	numeric	LOW	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
9	SODIUM	mEq/L	SERUM OR PLASMA	Sodium - Hyponatremia	numeric	LOW	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
10	SODIUM	mmol/L	SERUM	Sodium - Hyponatremia	numeric	LOW	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
11	SODIUM	mmol/L	PLASMA	Sodium - Hyponatremia	numeric	LOW	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
12	SODIUM	mmol/L	SERUM OR PLASMA	Sodium - Hyponatremia	numeric	LOW	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125

Workflow

Core Macros

%adtoxgr



Workflow

Core Macros

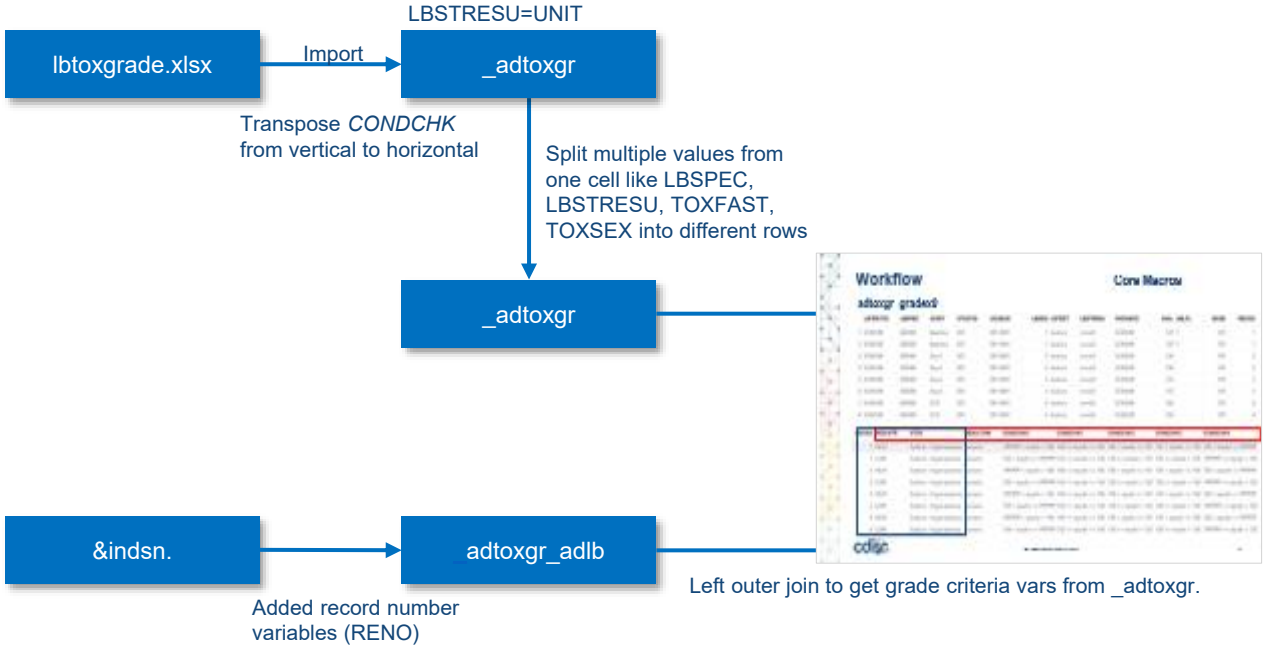
adtoxgr_ adlb

	LBSPEC	AVISIT	STUDYID	USUBJID	LBSEQ	LBTESTCD	LBSTRESU	PARAMCD	AVAL	ABLFL	BASE	RECNO
1	SERUM	Baseline	001	001-0001	1	SODIUM	mmol/L	SODIUM	139	Y	139	1
2	SERUM	Day 3	001	001-0001	2	SODIUM	mmol/L	SODIUM	138		139	2
3	SERUM	Day 6	001	001-0001	3	SODIUM	mmol/L	SODIUM	133		139	3
4	SERUM	EOS	001	001-0001	4	SODIUM	mmol/L	SODIUM	144		139	4

Workflow

Core Macros

%adtoxgr



Workflow

Core Macros

adtoxgr_gradex0

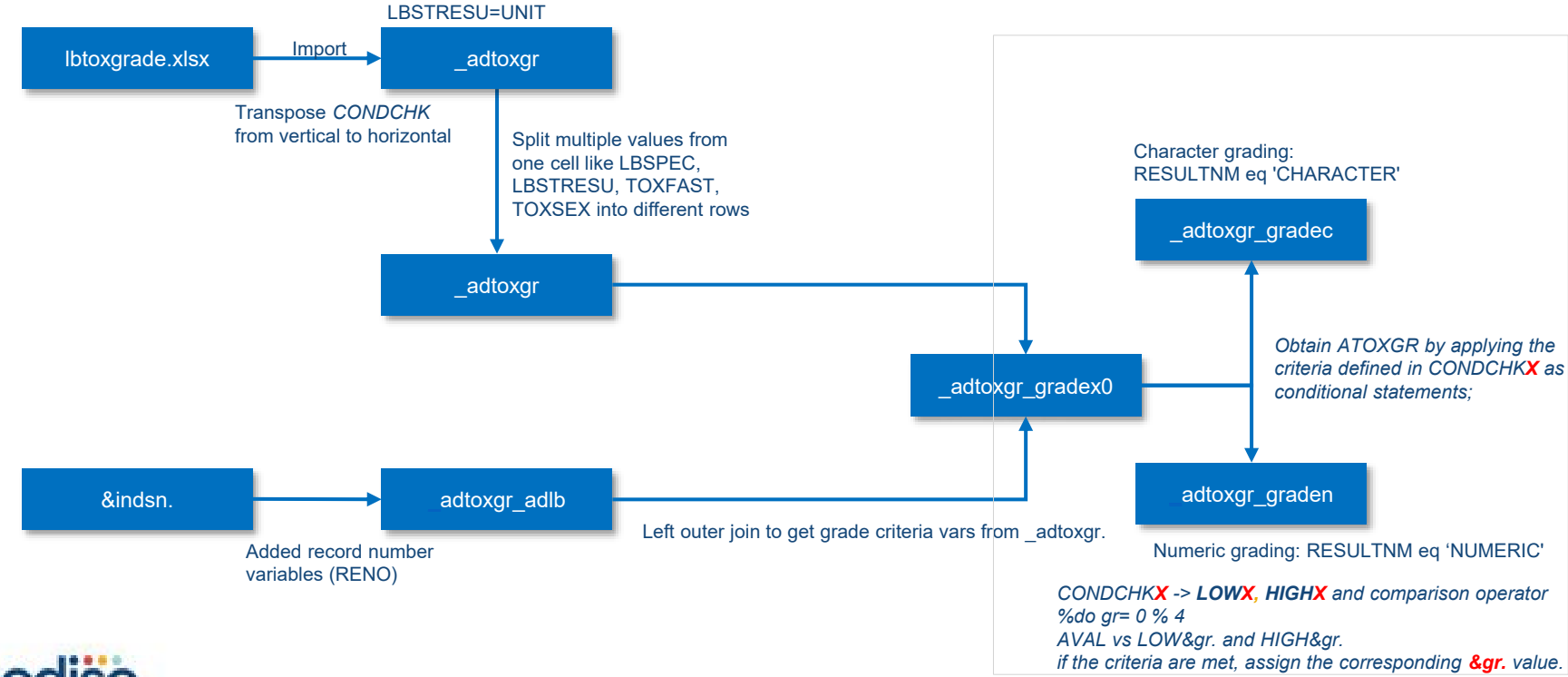
	LBTESTCD	LBSPEC	AVISIT	STUDYID	USUBJID	LBSEQ	LBTEST	LBSTRESU	PARAMCD	AVAL	ABLFL	BASE	RECNO
1	SODIUM	SERUM	Baseline	001	001-0001	1	Sodium	mmol/L	SODIUM	139	Y	139	1
2	SODIUM	SERUM	Baseline	001	001-0001	1	Sodium	mmol/L	SODIUM	139	Y	139	1
3	SODIUM	SERUM	Day 3	001	001-0001	2	Sodium	mmol/L	SODIUM	138		139	2
4	SODIUM	SERUM	Day 3	001	001-0001	2	Sodium	mmol/L	SODIUM	138		139	2
5	SODIUM	SERUM	Day 6	001	001-0001	3	Sodium	mmol/L	SODIUM	133		139	3
6	SODIUM	SERUM	Day 6	001	001-0001	3	Sodium	mmol/L	SODIUM	133		139	3
7	SODIUM	SERUM	EOS	001	001-0001	4	Sodium	mmol/L	SODIUM	144		139	4
8	SODIUM	SERUM	EOS	001	001-0001	4	Sodium	mmol/L	SODIUM	144		139	4

RECNO	INDICATR	ATOX	RESULTNM	CONDCHK0	CONDCHK1	CONDCHK2	CONDCHK3	CONDCHK4
1	HIGH	Sodium - Hypernatremia	numeric	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
1	LOW	Sodium - Hyponatremia	numeric	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
2	HIGH	Sodium - Hypernatremia	numeric	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
2	LOW	Sodium - Hyponatremia	numeric	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
3	HIGH	Sodium - Hypernatremia	numeric	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
3	LOW	Sodium - Hyponatremia	numeric	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125
4	HIGH	Sodium - Hypernatremia	numeric	-999999 < resultn < 144	144 <= resultn <= 145	145 < resultn <= 147	147 < resultn <= 150	150 < resultn <= 999999
4	LOW	Sodium - Hyponatremia	numeric	134 < resultn <= 999999	132 <= resultn <= 134	130 <= resultn < 132	125 <= resultn < 130	-999999 <= resultn < 125

Workflow

Core Macros

%adtoxgr



Workflow

Core Macros

adtoxgr_graden

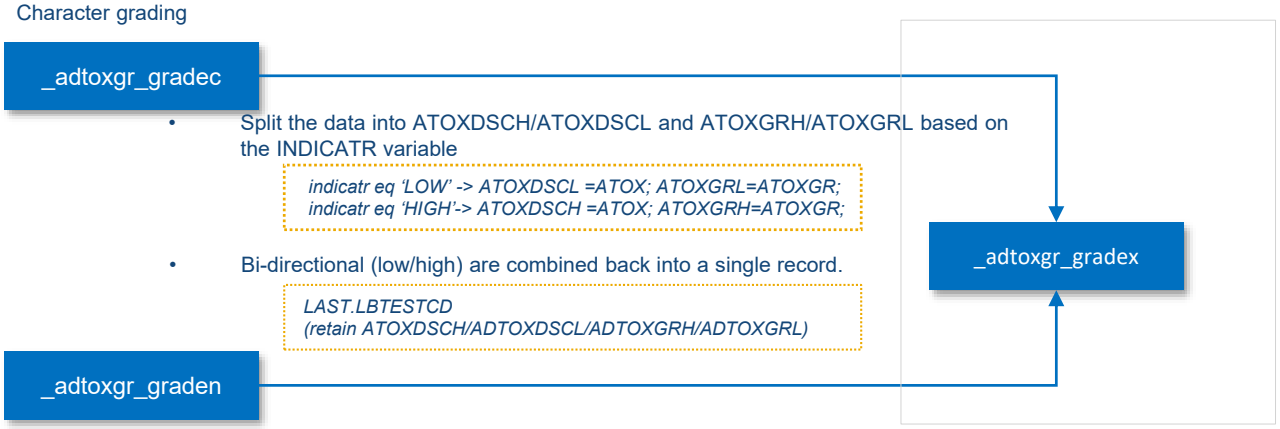
	LBTESTCD	LBSPEC	AVISIT	STUDYID	USUBJID	LBSEQ	LBTEST	LBSTRESU	PARAMCD	AVAL	ABLFL	BASE	RECNO
1	SODIUM	SERUM	Baseline	001	001-0001	1	Sodium	mmol/L	SODIUM	139	Y	139	1
2	SODIUM	SERUM	Baseline	001	001-0001	1	Sodium	mmol/L	SODIUM	139	Y	139	1
3	SODIUM	SERUM	Day 3	001	001-0001	2	Sodium	mmol/L	SODIUM	138		139	2
4	SODIUM	SERUM	Day 3	001	001-0001	2	Sodium	mmol/L	SODIUM	138		139	2
5	SODIUM	SERUM	Day 6	001	001-0001	3	Sodium	mmol/L	SODIUM	133		139	3
6	SODIUM	SERUM	Day 6	001	001-0001	3	Sodium	mmol/L	SODIUM	133		139	3
7	SODIUM	SERUM	EOS	001	001-0001	4	Sodium	mmol/L	SODIUM	144		139	4
8	SODIUM	SERUM	EOS	001	001-0001	4	Sodium	mmol/L	SODIUM	144		139	4

INDICATR	ATOX	LOW0	HIGH0	ATOXGR	LOW	HIGH	LOW1	HIGH1	LOW2	HIGH2	LOW3	HIGH3	LOW4	HIGH4
HIGH	Sodium - Hypernatremia	-999999	144	0	-999999	144	144	145	145	147	147	150	150	999999
LOW	Sodium - Hyponatremia	134	999999	0	134	999999	132	134	130	132	125	130	-999999	125
HIGH	Sodium - Hypernatremia	-999999	144	0	-999999	144	144	145	145	147	147	150	150	999999
LOW	Sodium - Hyponatremia	134	999999	0	134	999999	132	134	130	132	125	130	-999999	125
HIGH	Sodium - Hypernatremia	-999999	144	0	-999999	144	144	145	145	147	147	150	150	999999
LOW	Sodium - Hyponatremia	134	999999	1	132	134	132	134	130	132	125	130	-999999	125
HIGH	Sodium - Hypernatremia	-999999	144	1	144	145	144	145	145	147	147	150	150	999999
LOW	Sodium - Hyponatremia	134	999999	0	134	999999	132	134	130	132	125	130	-999999	125

Workflow

Core Macros

%adtoxgr



- ATOXGR represents the worst case for two directions and equivalent to ATOXDSCH/ATOXDSCL for one direction

Workflow

Core Macros

_adtox_gradex

	AVISIT	STUDYID	USUBJID	LBSEQ	LBTESTCD	LBSTRESU	LBSPEC	PARAMCD	PARAM	AVAL	ABLFL	BASE
1	Baseline	001	001-0001	1	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	139	Y	139
2	Day 3	001	001-0001	2	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	138		139
3	Day 6	001	001-0001	3	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	133		139
4	EOS	001	001-0001	4	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	144		139

ATOXDSCL	ATOXDSCH	ATOXGR	ATOXGRL	ATOXGRH	ATOXGRN	ATOXGRLN	ATOXGRHN
Sodium - Hyponatremia	Sodium - Hypernatremia	0	0	0	0	0	0
Sodium - Hyponatremia	Sodium - Hypernatremia	0	0	0	0	0	0
Sodium - Hyponatremia	Sodium - Hypernatremia	1	1	0	1	1	0
Sodium - Hyponatremia	Sodium - Hypernatremia	1	0	1	1	0	1

Workflow

Core Macros

%adtoxgr

Character grading:
RESULTNM eq
'CHARACTER'

_adtoxgr_gradec

- Split the data into ATOXDSCH/ATOXDSCL and ATOXGRH/ATOXGRL based on the INDICATR variable

indicatr eq 'LOW' -> ATOXDSCL =ATOX; ATOXGRL=ATOXGR;
indicatr eq 'HIGH'-> ATOXDSCH =ATOX; ATOXGRH=ATOXGR;

- Bi-directional (low/high) are combined back into a single record.

LAST.LBTESTCD
(retain ATOXDSCH/ADTOXDSCL/ADTOXGRH/ADTOXGRL)

_adtoxgr_graden

Numeric grading

_adtoxgr_gradex

Derive baseline toxicity grade vars: BTOXDSCH/BTOXDSCL and BTOXGRH/BTOXGRL

&outdsn.

- ATOXGR represents the worst case for two directions and equivalent to ATOXDSCH/ATOXDSCL for one direction

Workflow

Final Dataset

	AVISIT	STUDYID	USUBJID	LBSEQ	LBTESTCD	LBSTRESU	LBSPEC	PARAMCD	PARAM	AVAL	ABLFL	BASE
1	Baseline	001	001-0001	1	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	139	Y	139
2	Day 3	001	001-0001	2	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	138		139
3	Day 6	001	001-0001	3	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	133		139
4	EOS	001	001-0001	4	SODIUM	mmol/L	SERUM	SODIUM	Sodium (mmol/L)	144		139

ATOXDSCL	ATOXDSCH	ATOXGR	ATOXGRL	ATOXGRH	ATOXGRN	ATOXGRLN	ATOXGRHN	BTOXGR	BTOXGRN	BTOXGRL	BTOXGRLN	BTOXGRH	BTOXGRHN
Sodium - Hyponatremia	Sodium - Hypernatremia	0	0	0	0	0	0	0	0	0	0	0	0
Sodium - Hyponatremia	Sodium - Hypernatremia	0	0	0	0	0	0	0	0	0	0	0	0
Sodium - Hyponatremia	Sodium - Hypernatremia	1	1	0	1	1	0	0	0	0	0	0	0
Sodium - Hyponatremia	Sodium - Hypernatremia	1	0	1	1	0	1	0	0	0	0	0	0

Workflow

Core Macros

%adbilitox: used to update the grade of Bilirubin when ALT or AST tests are abnormal.

Laboratory Test / Toxicity Term	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)	Implementation Notes
Chemistry					
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN	
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN	Any increase in Liver Function Test is defined as grade 1 or higher for AST and/or ALT increase by factor.
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN	This grading is applied to all Bilirubin measurements where the condition for grading as per the line above is not met.

The above data is sourced from: https://www.fda.gov/media/73679/download

QC

LBTESTCD	LBTEST	LBSPEC	TOXFAST	TOXSEX	UNIT	INDICATR	TOXTERM	RESULTNM	TOXGRD	CONDCHK
AST	Aspartate Aminotransferase	SERUM, PLASMA, SERUM OR PLASMA			ANY	HIGH	AST - increase by factor	numeric	0	-999999 < resultn <= 1.0*ULN
AST	Aspartate Aminotransferase	SERUM, PLASMA, SERUM OR PLASMA			ANY	HIGH	AST - increase by factor	numeric	1	1.0*ULN < resultn <= 2.5*ULN
AST	Aspartate Aminotransferase	SERUM, PLASMA, SERUM OR PLASMA			ANY	HIGH	AST - increase by factor	numeric	2	2.5*ULN < resultn <= 5.0*ULN
AST	Aspartate Aminotransferase	SERUM, PLASMA, SERUM OR PLASMA			ANY	HIGH	AST - increase by factor	numeric	3	5.0*ULN < resultn <= 10.0*ULN
AST	Aspartate Aminotransferase	SERUM, PLASMA, SERUM OR PLASMA			ANY	HIGH	AST - increase by factor	numeric	4	10.0*ULN < resultn <= 999999

```
for(i in 1:nrow(tox_criteria)) {
  if(C.INDICATR == "LOW") {
    qc.adlb <- qc.adlb %>%
      mutate(ATOXGRLN = ifelse(CONDITION[i],TOXGRD[i],ATOXGRLN),
        ATOXDSCL = ifelse(CONDITION[i],TOXTERM[i],ATOXDSCL))
  }else if(C.INDICATR == "HIGH") {
    qc.adlb <- qc.adlb %>%
      mutate(ATOXGRHN = ifelse(CONDITION[i],TOXGRD[i],ATOXGRHN),
             ATOXDSCH = ifelse(CONDITION[i],TOXTERM[i],ATOXDSCH))
  }
}
```

Thank You!