

Metadata Driven Approach for Data Handling of Toxicity Grade

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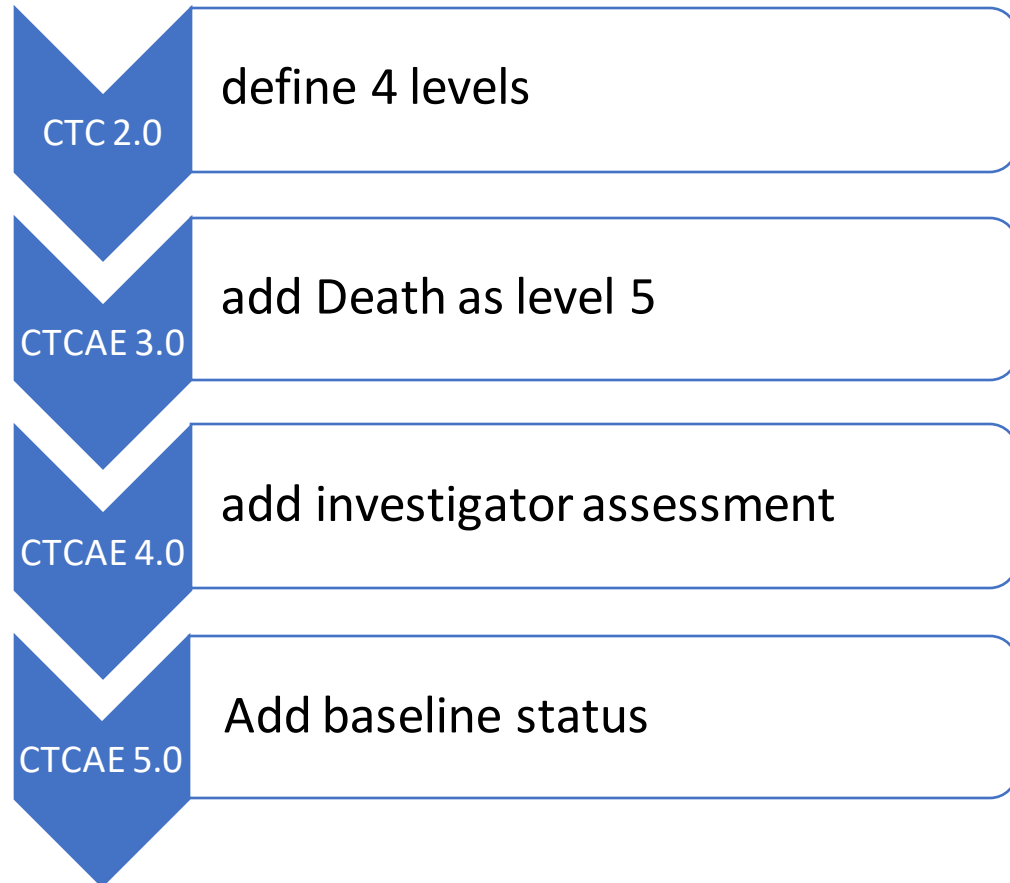
Contents

- Introduction
- Build Metadata from CTCAE
- Design Macro to Assign Grade
- Summary

Lab toxicity grade shows degree of abnormality

LBNRIND	Reference Range Indicator	Indicates where the value falls with respect to reference range	Exp
LBTOX	Toxicity	Description of toxicity	Perm
LBTOXGR	Standard Toxicity Grade	Toxicity grade value using a standard toxicity scale	Perm

CTCAE is a descriptive terminology for adverse events with grading scale

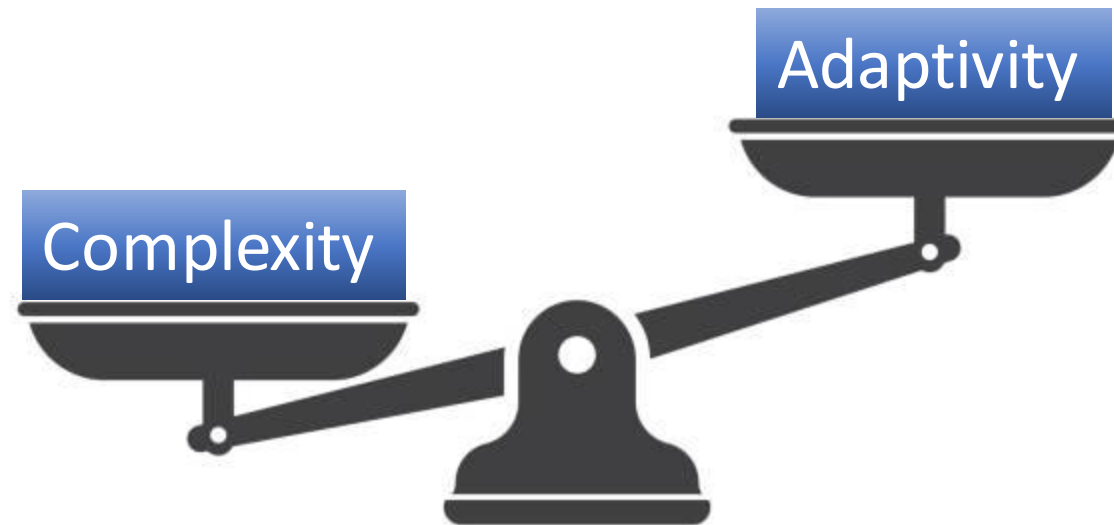


1	Mild
2	Moderate
3	Severe
4	Life-threatening
5	Death

CTCAE 5.0 grading scales contain quantitative ranges and investigator assessments

CTCAE TERM (TESTCD)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Activated partial thromboplastin time prolonged (APTT)	>ULN - 1.5 x ULN normal range	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-
Hyperkalemia (K)	>ULN - 5.5 mmol/L value with unit	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Alkaline phosphatase increased (ALP)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal range vary with baseline	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 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	-

Deriving toxicity grade from CTCAE is quite challenging



Contents

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Macro Variables are defined to interpret CTCAE grades

R	Result (LBSTRESN)
U	Unit (LBSTRESU)
LLN	Lower limit of normal (LBSTNRLO)
ULN	Upper limit of normal (LBSTNRHI)
VISN	Visit number (VISITNUM)
B	Result at baseline
BULN	Lower limit of normal at baseline
BLLN	Upper limit of normal at baseline
BVISN	Visit number at baseline

Abnormal at baseline: (&B[^]=. AND &BULN[^]=. AND &B > &BULN AND &VISN > &BVISN)

baseline exist

out of range

post baseline visit

CTCAE criteria are interpreted into SAS syntax

	Activated partial thromboplastin time prolonged	APTT
Grade 1	>ULN - 1.5 x ULN	(&ULN ^= .) AND (&ULN < &R AND &R <= 1.5*&ULN)
Grade 2	>1.5 - 2.5 x ULN	(&ULN ^= .) AND (1.5*&ULN < &R AND &R <= 2.5*&ULN)
Grade 3	>2.5 x ULN; bleeding	(&ULN ^= .) AND (&R > 2.5*&ULN)
	Hyperkalemia	K
Grade 1	>ULN - 5.5 mmol/L	(&ULN ^=.) AND ("&U"="mmol/L" AND &ULN < &R AND &R<= 5.5)
Grade 2	>5.5 - 6.0 mmol/L; intervention initiated	("&U"="mmol/L" AND 5.5 < &R AND &R<= 6)
Grade 3	>6.0 - 7.0 mmol/L; hospitalization indicated	("&U"="mmol/L" AND 6 < &R AND &R<= 7)
Grade 4	>7.0 mmol/L; life-threatening consequences	("&U"="mmol/L" AND &R > 7)

	Alkaline phosphatase increased	ALP
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	((&ULN^=.) AND (&B=. OR &BVISN >= &VISN OR &BULN=. OR &B <= &BULN) AND (&ULN < &R AND &R <= 2.5*&ULN)) OR ((&B^=. AND &ULN^=.) AND (&BULN^=. AND &B > &BULN AND &VISN > &BVISN) AND (2*&B <= &R AND &R <= 2.5*&B))
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	((&ULN^=.) AND (B=. OR &BVISN >= &VISN OR &BULN=. OR &B <= &BULN) AND (2.5*&ULN < &R AND &R <= 5.0*&ULN)) OR ((&B^=. AND &ULN^=.) AND (&BULN^=. AND &B > &BULN AND &VISN > &BVISN) AND (2.5*&B < &R AND &R <= 5.0*&B))
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	((&ULN^=.) AND (&B=. OR &BVISN >= &VISN OR &BULN=. OR &B <= &BULN) AND (5.0*&ULN < &R AND &R <= 20.0*&ULN)) OR ((&B^=. AND &ULN^=.) AND (&BULN^=. AND &B > &BULN AND &VISN > &BVISN) AND (5.0*&B < &R AND &R <= 20.0*&B))
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	((&ULN^=.) AND (&B=. OR &BVISN >= &VISN OR &BULN=. OR &B <= &BULN) AND (&R > 20.0*&ULN)) OR ((&B^=. AND &ULN^=.) AND (&BULN^=. AND &B > &BULN AND &VISN > &BVISN) AND (&R > 20.0*&B))

Metadata is created to store SAS syntax of CTCAE grades

CTCAE Term	TESTCD	DIR	G0	G1	G2	G3	G4
Hyperkalemia	K	&R>ULN	&ULN ^=. AND &U="mmol/L"	(&ULN ^=.) AND ("&U"="mmol/L" AND &ULN < &R AND &R<= 5.5)	("&U"="mmol/L" AND 5.5 < &R AND &R<= 6)	("&U"="mmol/L" AND 6 < &R AND &R<= 7)	("&U"="mmol/L" AND &R > 7)
Hypokalemia	K	&R<LLN	&LLN ^=. AND &U="mmol/L"	(&LLN ^=.) AND ("&U"="mmol/L" AND 3 <= &R AND &R< &LLN)		("&U"="mmol/L" AND 2.5 <= &R AND &R< 3)	("&U"="mmol/L" AND &R < 2.5)

Contents

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Macro input arguments

indata	Input dataset
outdata	Output dataset
where	Subset of input dataset
ctcae	CTCAE metadata
subject	Subject identifier variable (USUBJID)
testcd	Lab test code variable (LBTESTCD)
R	Result variable (LBSTRESN)
U	Unit variable (LBSTRESU)
ULN	Upper limit variable (LBSTNRHI)
LLN	Lower limit variable (LBSTNRLO)
VISN	Visit number variable (VISITNUM)
BLFL	Baseline flag variable (LBXOBFL)

Baseline variables are defined and merge with input dataset

SUBJECT	TESTCD	R	U	LLN	ULN	VISN
001	K	4.4	mmol/L	3.5	5	1.01
001	K	3.9	mmol/L	3.5	5	2.01
001	K	3.3	mmol/L	3.5	5	3.01
002	K	4.2	mmol/L	3.5	5	1.01
002	K	4.3	mmol/L	3.5	5	2.01
002	K	5.3	mmol/L	3.5	5	3.01

Grading level macro variables are evaluated to assign toxicity grade

CTCAE Term	TESTCD	DIR	G0	G1	G2	G3	G4
Hyperkalemia	K	&R>ULN	&ULN ^=. AND &U="mmol/L" K_UPPER_G0	(&ULN ^=.) AND ("&U"="mmol/L" AND &ULN < &R AND &R<= 5.5) K_UPPER_G1	("&U"="mmol/L" AND 5.5 < &R AND &R<= 6) K_UPPER_G2	("&U"="mmol/L" AND 6 < &R AND &R<= 7) K_UPPER_G3	("&U"="mmol/L" AND &R > 7) K_UPPER_G4
Hypokalemia	K	&R<LLN	&LLN ^=. AND &U="mmol/L" K_LOWER_G0	(&LLN ^=.) AND ("&U"="mmol/L" AND 3 <= &R AND &R< &LLN) K_LOWER_G1		("&U"="mmol/L" AND 2.5 <= &R AND &R< 3) K_LOWER_G3	("&U"="mmol/L" AND &R < 2.5) K_LOWER_G4

Toxicity grade are assigned for valid records

SUBJECT	TESTCD	R	U	LLN	ULN	VISN	B	BLLN	BULN	OBSID	TOX	TOXGR
001	K	4.4	mmol/L	3.5	5	1.01	4.4	3.5	5	1		0
001	K	3.9	mmol/L	3.5	5	2.01	4.4	3.5	5	2		0
001	K	3.3	mmol/L	3.5	5	3.01	4.4	3.5	5	3	HYPO	1
002	K	4.2	mmol/L	3.5	5	1.01	4.2	3.5	5	4		0
002	K	4.3	mmol/L	3.5	5	2.01	4.2	3.5	5	5		0
002	K	5.3	mmol/L	3.5	5	3.01	4.2	3.5	5	6	HYPER	1

Contents

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Thank you very much

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