DEBUGGING THE RELATIONSHIP OF NCI - CTCAE IN LABORATORY AND ADVERSE EVENTS DATA

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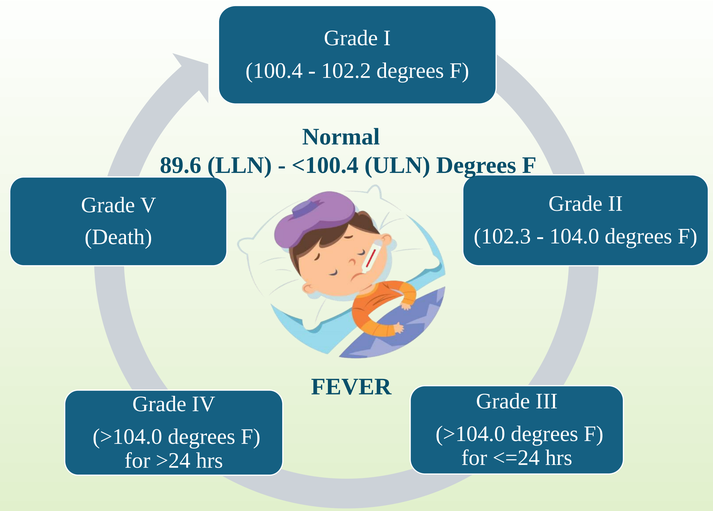
Abstract

The Common Terminology Criteria for Adverse Events (CTCAE) is a pivotal standardized grading system utilized in clinical trials to evaluate the severity of adverse events (AEs) associated with medical treatments. This system categorizes AEs into five grades, from 1 (mild) to 5 (fatal), based on their impact on patient health and daily functioning. The CTCAE enables consistent communication among healthcare professionals regarding treatment-related toxicities, thereby enhancing patient safety and guiding treatment decisions.

The latest version, CTCAE V5.0, introduces a complex approach by considering baseline data for toxicity grading, thereby improving accuracy and consistency in adverse event classification. This paper discusses the integration of CTCAE grading within clinical trial data, particularly focusing on the relationship between laboratory test results and adverse events and provides illustrative examples of uni-directional and bi-directional toxicity assessments. Through this exploration, the paper underscores the significance of the CTCAE in clinical research, highlighting the abnormal laboratory data carried to adverse event data.

Introduction

Accurate assessment and classification of adverse events (AEs) in clinical trials are essential for patient safety and treatment efficacy. The CTCAE has been widely adopted as a standardized system to evaluate and grade the severity of AEs. This grading will also enhance the ability to identify potential patterns of laboratory toxicities and thus improve the clinical decision-making. However, the relationship between laboratory findings and adverse events is a crucial focus, as abnormal lab results often precede or correlate with the onset of AEs. This paper explores the connection between laboratory findings and adverse event data, with particular emphasis on how abnormal laboratory results are incorporated into the adverse event data.



Laboratory Data

Uni-directional Toxicity

subject	paramcd	avisit	adt	aval	anrlo	anrhi	ablfl	atox	atoxgr	btoxgr	anrind	shift1
1001	ALP	Baseline	2023-07-02	120	40	129	Y		0	0	Normal	
1001	ALP	Week 10	2023-09-09	210	40	129		Alkaline phosphatase increased	1	0	High	Normal - High
1001	ALP	Week 30	2024-02-17	580	40	129		Alkaline phosphatase increased	2	0	High	Normal - High
1001	ALP	Week 32	2024-03-02	220	40	129		Alkaline phosphatase increased	1	0	High	Normal - High

Table 1. Laboratory data indicating elevated ALP toxicity

Bi-directional Toxicity

subject	paramcd	avisit	adt	aval	anrlo	anrhi	ablfl	atox	atoxgr	btoxgr	anrind	shift1
1001	HGB	Baseline	2021-08-20	124	115	158	Y		0	0	Normal	
1001	HGB	Week 3	2021-09-23	96	115	158		Anemia	2	0	Low	Normal - Low
1001	HGB	Week 26	2022-02-19	107	115	158		Anemia	1	0	Low	Normal - Low

Table 2. Laboratory data indicating hemoglobin declined

subject	paramcd	avisit	adt	aval	anrlo	anrhi	ablfl	atox	atoxgr	btoxgr	anrind	shift1
1001	HGB	Baseline	2023-06-18	132	115	158	Y		0	0	Normal	
1001	HGB	Week 8	2023-08-29	164	115	158		Hemoglobin increased	1	0	High	Normal - High
1001	HGB	Week 30	2024-01-12	180	115	158		Hemoglobin increased	2	0	High	Normal - High
1001	HGB	Week 34	2024-02-10	210	115	158		Hemoglobin increased	3	0	High	Normal - High

Table 3. Laboratory data indicating elevated hemoglobin

Adverse Events Data

subject	aeterm	aetoxgr	aesoc	aestdtc	aeendtc
1001	Alkaline phosphatase increased	2	Investigations	2024-02-17	2024-02-27
1001	Anemia	2	Blood and lymphatic system	2021-09-30	2021-12-02
1001	Hemoglobin increased	1	Blood and lymphatic system	2023-09-05	2023-12-02
1001	Hemoglobin increased	2	Blood and lymphatic system	2024-01-19	2024-02-03
1001	Dizziness	3	Blood and lymphatic system	2024-02-08	
1001	Hemoglobin increased	3	Blood and lymphatic system	2024-02-10	

Table 4. : Laboratory toxicities are captured in adverse event.

Reconciliation Data

subject	aeterm	aetoxgr	aesoc	aestdtc	aeendtc	Scnerios
1001	Alkaline phosphatase increased	2	Investigations	2024-02-17	2024-02-27	lab collection date and AE reported date are equal
1001	Anemia	2	Blood and lymphatic system	2021-09-30	2021-12-02	lab collection date is earlier than AE reported date
1001	Dizziness	3	Blood and lymphatic system	2024-02-08		lab collection date is after AE reported date and ae reported term is not equal to toxicity term
1001	Hemoglobin increased	3	Blood and lymphatic system	2024-02-10		lab collection date and AE reported date are equal

Table 5. Reconciliation dataset displaying the comparison between adverse events and laboratory results

Programming Approach

Events counts from ADAE & ADLB datasets

```
proc sql noprint;
      create table aelb as
      select a.subjid, a.atox, a.atoxgr, a.adtm, a.adt, a.trta,  a.paramcd, a.aval, a.anrlo, a.anrhi, a.anrind, a.ssfl,
            b.subjid as subj, b.aeterm, b.aedecod, b.aellt, b.aesoc, b.astdt, b.aendt
      from out.adlb as a
      left join (select subjid, aeterm, aedecod, aellt, aesoc, astdt, aendt from out.adae where not missing(aellt)) as b
      on a.subjid=b.subjid and a.atox=b.aellt and b.astdt <= a.adt <= b.aendt
      where a.ssfl="Y" and a.trta ne "" and a.atox ne "";
quit;
```

Events counts from ADLB datasets

```
proc sql noprint;
      create table ctcae_lb as
      select a.subjid, a.atox, a.atoxgr, a.adtm, a.adt, a.trta,  a.paramcd, a.aval, a.anrlo, a.anrhi, a.anrind, a.ssfl,
            b.ctcaev5_0_soc, b.ctcaev5_0_aeterm, b.grade1, b.grade2, b.grade3, b.grade4, b.grade5, b.ctcaev5_0_aeterm_definition
      from out.adlb as a
      left join ctcaev5_0 as b
      on a.atox=b.ctcaev5_0_aeterm
      where a.ssfl="Y" and a.trta ne "" and a.atox ne "";
quit;
```

Tabular Representation of Clinical Laboratory Events

ATOX	AESOC	AEDECOD	TRT1_Gr1	TRT1_Gr2	TRT1_Gr3	TRT1_Gr4	TRT2_Gr1	TRT2_Gr2	TRT2_Gr3	TRT2_Gr4
Anemia	Blood and lymphatic system disorders	Anaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Alkaline phosphatase increased	Investigations	Blood alkaline phosphatase increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Hyperkalemia	Metabolism and nutrition disorders	Hyperkalaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Hypokalemia	Metabolism and nutrition disorders	Hypokalaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Summary of Clinical Laboratory Events by MedDRA System Organ Class, Preferred Term and CTCAE Grades

		Treatment 1 N=XX				Treatment 2 N=XX			
System Organ Class	preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Anaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Investigations	Alanine aminotransferase increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Aspartate aminotransferase increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Blood alkaline phosphatase increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Blood bilirubin increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Blood creatinine increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Gamma-glutamyltransferase increased	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Metabolism and nutrition disorders	Hyperkalaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Hypocalcaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Hypokalaemia	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Renal and urinary disorders	Chronic kidney disease	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Renal failure	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Conclusions

The integration of MedDRA (Medical Dictionary for Regulatory Activities) terms into the CTCAE framework has revolutionized the connection between clinical adverse events and laboratory data. By mapping laboratory toxicity findings to MedDRA terms, raw results are transformed into actionable clinical events, improving both the accuracy and consistency of reporting. This approach enhances treatment impact analysis and facilitates real-time monitoring of the relationship between treatment-related laboratory toxicities and adverse events. It also improves the quality of adverse event data, providing greater insight into the safety profile of the drug. Ultimately, this integration establishes a standardized bridge between adverse events and laboratory data, supporting better decision-making, enhanced safety surveillance, and optimizing the safety and efficacy of therapies in clinical practice.

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