TATA CONSULTANCY SERVICES
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Analysis of LAB dataset

Toxicity Grades

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PALS
Pharma Academy of Learning and Sharing

Agenda

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- Understanding Grades
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NCI CTC Grades

- One of the key ways of analyzing laboratory data includes classifying results into severity grades based on National Cancer Institute (NCI) Common Terminology Criteria (CTC) for Adverse Events.
- While most clinical trials report laboratory results based on normal range criteria (is the result lower or higher than what is considered “normal”), oncology trials take that analysis to the next degree of specificity.
- It is not enough to report where select laboratory results are too high or too low, it is important to report the degree of “lowness” or “highness.”
- For example, if a patient’s hemoglobin results are 6.0 mmol/L, is that merely abnormal or is the patient near death?
- In an indication such as oncology where patients are often *expected* to have abnormal laboratory results, it is important to know how abnormal the abnormal result actually is.

Understanding Grades

- Events are graded on a scale of one to five with one meaning “mildly abnormal” and five meaning “death.”
- When applying these grades to laboratory results, grade zero is often used to indicate “normal” or “not a concern” while grade five is not applicable.
- It is important to note that not all laboratory tests have CTC grade criteria available.
- In addition, some laboratory tests provide two sets of grades – one set for values that are too low and another set for values that are too high.
- It is also worth noting that the criteria are not all defined in the same way. Some criteria are simply multiples of the upper or lower bound of the normal range, as for the term Creatinine increased, while others combine normal range limits with fixed values as the other terms above.

Grades

- Grade 1-> Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2-> Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3-> Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4-> Life-threatening consequences; urgent intervention indicated.
- Grade 5-> Death related to AE.

- Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Example of CTC grades

Blood and lymphatic system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					

Programming using SAS

- One example of a simple approach to assigning CTC criteria for three tests (calcium, creatinine, and platelets) is presented below.
- The key variables in the labs data set are as follows:

☞lbtest : The name of the laboratory test

☞ lbstresn: The laboratory result in standard units

☞ lbstresu: The name of the unit for lbstresn

☞ lbstnrlo: The lower bound of the normal range

☞ lbstnrhi: The upper bound of the normal range.

Lbstresn, lbstnrlo and lbstnrhi are all numeric variables reporting values in the same unit (as indicated by lbstresu).

☞ Lbtoxgr is the name of the variable that will contain the CTC grade.

Sample code for CTC grading

Challenges and Solutions

- **DIFFERENT UNITS OF MEASURE**

Solution: Ensure that results are converted in standrad unit of reporting before you apply CTC grade criteria.

- **MISSING NORMAL REFERENCE RANGES**

Solution: Many CTC criteria use the lower (LLN) and/or upper (ULN) bounds of the normal range and this missing information may prevent CTC criteria from being applied. Based on the number of records with missing normal ranges, default normal ranges may need to be used in cases where the ranges from the local laboratory are not available.

- **ROUNDING WITH UNIT CONVERSION**

Solution: When converting results from one unit to another, the new result will often have many more decimal places than the original. It is rare for summary reports to show results with more than three decimals, often two decimals is the maximum shown. It is important to decide if converted results should be rounded before or after applying CTC criteria as it can affect how the data are reported.

Challenges and Solutions (Contd…)

- **OVERLAPPING RANGES**

Problem: For example, the bounds for platelet

grade one are >= 75 x 103/UL to LLN – what if the LLN for a particular laboratory is 75? That would make the bounds for grade one 75 to 75 and the bounds for grade two 50 to 75. If a patient has a lab result of 75, that result may be coded to either grade one or grade two if the method of assigning grades does not take this into account

	Grade 1	Grade 2
Condition	>= 75 x 103/UL to LLN	50 - 75
If LLN=75	>=75 x 103/UL to 75	50-75
Lab result=75	Should I assign Grade 1 as LLN =75 and condition for Grade 1 is satisfied	Should I assign Grade 2 as my lab result is 75 and it lies in the range 50- 75
This is called problem of Overlapping results		

Reference paper for Reading

- Thank You