Comparability of CTCAE Grading and Clinical Significance in Abnormal Clinical Laboratory Results

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Overview

In clinical trials, laboratory data is a key element of the safety profile for the treatment being studied. When local labs are used, there may be a large amount of variance in determining clinically significant (i.e., investigator determined) abnormal lab values in the reporting of adverse events (AEs). Many clinical trials are moving towards the use of grading scales such as the National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) to provide standard ranges and implement suggested grading across clinical sites.

Rho, Inc. has developed a macro to incorporate the CTCAE grading criteria into laboratory analysis datasets. The CTCAE grading is complex and encompasses a wide variety of laboratory tests making this macro extremely useful.

Using clinical trials data from studies in the Immune Tolerance Network (ITN) project this poster explores the differences in AEs generated by CTCAE and those generated by clinical significance alone across local sites. The ITN is currently routinely using CTCAE criteria in the majority of their ongoing autoimmune trials. Discussion will be presented on various reporting techniques and the distribution and comparability of abnormal clinical laboratory results across sites. The above macro will also be described in detail.

CTCAE Automated Grading Macro

The CTCAE grading macro developed at Rho, Inc. requires minimal user input to efficiently grade abnormal lab values based on the CTCAE. Once the user converts the laboratory values to the units specified in the CTCAE guidance, they are only required to input the name of the dataset to be graded, the name of the variable that specifies the lab parameter, the variable that contains the lab values, the variable that contains the lab units, and the variables that contain the upper and lower limits of normal (ULN and LLN). Then the user can pick the individual laboratory tests to grade and grade them using a SAS data step. The data should be in the following structure:

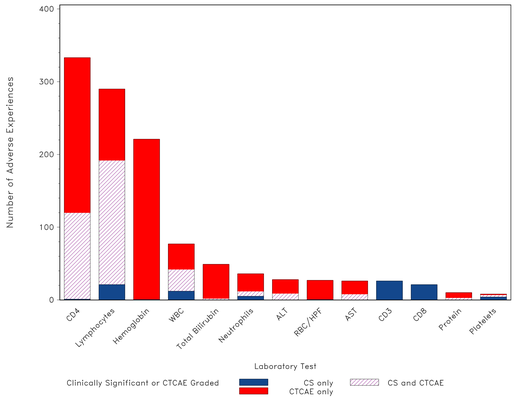
Subject ID	Lab Name	Lab Value	Lab Units	Lab LLN	Lab ULN
001001	ALT	86.00	U/L	10.00	60.00

For the Laboratory test ALT, the CTCAE grading criteria states that a value between the ULN and 3XULN is considered a grade 1 adverse event. Thus for the input above, the following variables will be output by the CTCAE macro:

Subject ID	Lab Name	Lab Value	__crith	__gradeh	__grade
001001	ALT	86.00	>ULN-3 x ULN	1	1

The macro will grade based on high lab values, low lab values, or based on a comparison to the baseline value of the lab test. If there are multiple CTCAE criteria, the macro will output the most severe grade as the variable __grade.

Comparison of CTCAE and Clinically Significant Lab Values



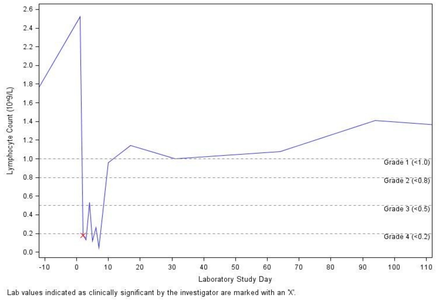
The figure above displays the distribution of lab values classified as adverse events (AEs) for a variety of lab tests. As shown above, there is a large disparity in the classification of AEs based on which method is used. For example, CD3 and CD8 are not specified according to the CTCAE criteria, thus all AEs are only captured by clinical significance. On the other hand, Hemoglobin values that are slightly outside the normal ranges are graded as AEs in the CTCAE criteria, however they were not determined to be clinically significant by the site investigators.

The three figures to the right compare investigator determined clinical significance versus grading lab tests based on CTCAE criteria. The figures illustrate the pros and cons of both clinical significance and CTCAE grading.

Using clinical significance alone allows an investigator flexibility in determining which lab values are truly abnormal and should be reported as an AE, especially for labs not outlined in the CTCAE grading criteria. The investigator can factor in subject medical history and contributing factors into his or her decision to report an AE. However, investigators can differ greatly in what they consider a significant lab value to be and this results in inconsistency in the reporting and grading of AEs.

The CTCAE criteria define a set grading scale and make recording and querying for AEs much more consistent. The CTCAE grading criteria allow for interpretation across sites, since AEs are collected using the same method. This is especially important when trying to analyze and interpret safety results at the end of a study. However, CTCAE grading can be complex and issues such as overlapping ranges can create problems during the grading process.

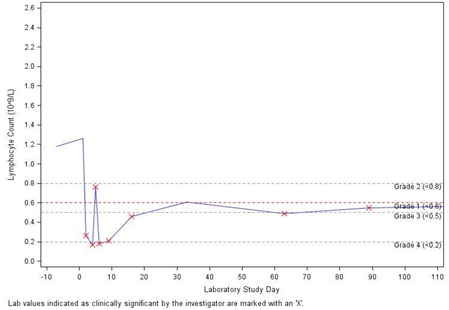
Lab Values Over Time: CTCAE Grading vs. Clinical Significance



Lab values indicated as clinically significant by the investigator are marked with an 'X'.

In the figure above, only the initial Grade 4 decrease in lymphocytes was marked as clinically significant by the investigator. Using clinical significance alone, an investigator has the ability to make the decision on what lab tests are AEs and can factor in subject medical history and values over time when determining AEs. However, using CTCAE grading allows for consistency in both reporting and grading of the AEs, regardless of whether the investigator thinks the value was clinically significant.

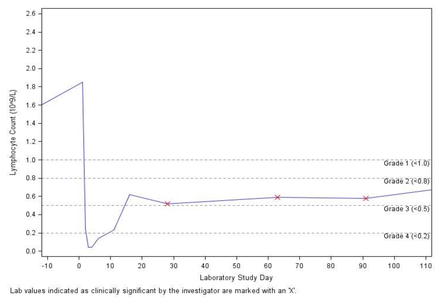
Lab Values Over Time: CTCAE Grading vs. Clinical Significance



Lab values indicated as clinically significant by the investigator are marked with an 'X'.

In the second figure, almost every decrease in lymphocyte counts, including the initial drop to Grade 4, has been marked as clinically significant by the investigator. Similar to the first figure above, it's clear there is no uniformity in classifying which lab values are AEs using clinical significance. This figure also shows some of the complexity of the CTCAE grading scale. In this example the site lower limit of normal (0.6 10^9/L) actually falls below the CTCAE specified Grade 2 limit (0.8 10^9/L), making the definition of Grade 1 vs. Grade 2 complex.

Lab Values Over Time: CTCAE Grading vs. Clinical Significance



Lab values indicated as clinically significant by the investigator are marked with an 'X'.

In the third figure, the initial Grade 4 decrease in lymphocyte counts has not been marked as clinically significant by the investigator. There is no real gradient of determining clinical significance and this makes interpreting AEs across sites difficult. Using CTCAE grading allows for consistency in reporting and interpretability across sites, since AEs are recorded using the same method, which sites can easily implement.

Lessons Learned

To ensure the best possible collection of AEs related to abnormal laboratory values the discussion should begin during the protocol development process. The following topics should be discussed prior to study start up:

- Importance of consistency in reporting across sites. Make sure all investigators are in agreement/aware of grading scales being used for study.
- Discuss appropriate CRF designs for capturing accurate data.
  - Clarify on the CRF what constitutes reporting an adverse event.
  - Align lab units on CRF with CTCAE grading criteria units, if possible.
- Clearly define what labs should be reported as AEs during protocol development. For example:
  - Only report Grade 2 or higher AEs.
  - Only report AEs for specific lab values of interest (e.g. liver function tests).
- Discuss how labs will be graded and recorded as AEs:
  - Determine if the study will use clinical significance, CTCAE grading or another grading scale.
  - For lab tests not having CTCAE grading criteria, will clinical significance be used or will an appropriate grading scale be derived by the study team.

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