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Implementing Laboratory Toxicity Grading for CTCAE Version 6 and Beyond

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ABSTRACT

CTCAE Version 6.0 has been released, further clarifying toxicity grade terms and definitions from Version 5.0. However, CTCAE is not the only standard for toxicity grading. Other criteria also exist, including the grading criteria from the Health and Human Services Division of AIDS (DAIDS) for adult and pediatric adverse events, as well as the FDA guidance on the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. We will show a flexible method for deriving CTCAE grades that can handle cases where the grading derivation requires information external to the lab value itself, such as the FDA toxicity grading guidance, as well as any existing version of CTCAE, including versions up to 6.0.

INTRODUCTION

In 2019, we published a paper regarding the use of CALL EXECUTE in SAS in tandem with an Excel spreadsheet containing chunks of code to automate the derivation of toxicity grades for lab values. In that paper, all programming was performed in SAS, and the Excel spreadsheet containing toxicity grade derivations was populated manually. In this paper, we have gone one step further by taking an existing Excel spreadsheet containing toxicity grade definitions, such as the official CTCAE toxicity grade spreadsheet, and automatically remapping the official toxicity grade derivations into the machine-readable code presented in 2019. We will present proof-of-concept code for this purpose in both SAS and R, and we expect this approach to be replicable in other programming languages as well. This method of deriving toxicity grades can be used for other non-CTCAE toxicity grading criteria as well. While the CTCAE toxicity grades can be found in an Excel spreadsheet that can be read directly, other toxicity grading criteria, such as the DAIDS or FDA grading for FDA guidance on the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials, the criteria are available for download as a PDF and not an Excel spreadsheet. The conversion from PDF to Excel is still manual, but the program to calculate the toxicity grades still works once the grading derivations have been included in the Excel spreadsheet.

INITIAL GRADING DOCUMENTS

First, let's look at the initial documents that show the criteria for the toxicity grades themselves. These documents vary by the organizational body providing the guidance. A few examples are described below.

CTCAE

CTCAE toxicity grading criteria for both versions 5.0 and 6.0 are conveniently available to download in Microsoft Excel .xlsx format, which can then be imported directly into R, SAS, or any other language that can import Excel files. One row from this spreadsheet for the MEDDRA term "Blood bilirubin increased" is shown below. Note that only the criteria for a toxicity grade of 1 is displayed due to space limitations, and that the original document has definitions for toxicity grades 2 through 4 as well:

Table 1: CTCAE v5.0 Excel Spreadsheet for Blood bilirubin increased – Toxicity Grade 1

MedDRA_Code	MedDRA_SOC	MedDRA_Term	Grade1
10005364	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal

A similar spreadsheet is available for CTCAE v6.0. Note the subtle change in text in the Grade 1 definition:

Table 2: CTCAE v6.0 Excel Spreadsheet for Blood bilirubin increased – Toxicity Grade 1

MedDRA_Code	MedDRA_SOC	MedDRA_Term	Grade1
10005364	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal or less than normal; 1.0 - 1.5 x baseline if baseline was >ULN

DAIDS OR FDA GRADING FOR FDA GUIDANCE ON THE TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Unfortunately, toxicity grading for the DAIDS or FDA grading for FDA guidance on the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials were only available in PDF format, and not an importable Excel spreadsheet. Examples of criteria from the PDF documents are shown below:

Table 3: DAIDS Grading Example from PDF Document

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA

Table 4: Grading for FDA Guidance on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Grading Example from PDF Document

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0

The process for importing these criteria into SAS or R still starts with the manual creation of an Excel spreadsheet containing these criteria. However, the automated process for grade calculation still works for these grading criteria once the Excel spreadsheet is created. Examples are shown below:

Table 5: DAIDS Grading Example After Manual Excel Creation

Parameter	Direction	Unit	Grade1	Grade2	Grade3	Grade4
Acidosis				7.3 <= Result & Result < LLN	Result < 7.3 with no AE with AESLIFE = 'Y'	Result < 7.3 with AE with AESLIFE = 'Y'
Albumin	Low	g/dL	3.0 <= Result& Result < LLN	2.0 <= Result & Result < 3.0	Result < 2.0	
Albumin	Low	g/L	30 <= Result & Result < LLN	20 <= Result & Result < 30	Result < 20	

Notice the highlighted items for toxicity grades 3 and 4, where the existence of an AE with AESLIFE = 'Y' is part of the derivation. The sponsor is responsible for deciding how to incorporate this information into the lab data used to calculate the grades. One possible solution would be to bring the variable AE.AESLIFE into the lab data before deriving the toxicity grades. In that case, the machine-executable formula for toxicity grade 3 would be: Result < 7.3 & AESLIFE ne 'Y'.

Table 6: Grading for FDA Guidance on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Grading Example After Manual Excel Creation

Parameter	Sex	Grade1	Grade2	Grade3	Grade4
Hemoglobin (g/dL)	F	(11 <= Result & Result <= 12) |(-1.5 <= Result-Base & Result-Base < 0)	(9.5 <= Result & Result <= 10.9)| (-2.0 <= Result-Base & Result-Base <= -1.6)	(8.0 <= Result & Result <= 9.4) |(-5.0 <= Result-Base & Result-Base <= -2.1)	Result < 8.0 or Chang Result-Base e < -5.0

Notice that these criteria are dependent on sex. The sponsor is responsible for deciding how to incorporate this information into the lab data used to calculate the grades. One possible solution would be to bring the variable SEX into the lab data from ADSL before deriving the toxicity grades.

PROGRAM TO REMAP INITIAL GRADES TO EXECUTABLE CODE

Once the grading criteria are in an Excel spreadsheet, the text can be rearranged into machine-readable code that can then be imported and executed in SAS or R.

EXAMPLE

For example, for CTCAE v5 Bilirubin Increased, we get the following definition for Toxicity Grade 2:

">1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal"

This contains two statements: one for when baseline is normal, and one for when baseline is abnormal. Within each normality level, there are two statements. In SAS, we would break these up into a "normal" statement and an "abnormal" statement, process them into a machine-executable format, and then concatenate them together. Below is SAS code showing how to transform the "normal" statement into a machine-executable format:

Figure 1: SAS Code to Convert a CTCAE Toxicty Grade Definition into a Machine-Executable Format

```
var = '>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal';


part1 = scan(var,1,';');


if prxmatch('/baseline.*\snormal/',part1) > 0
        then
                do;
                        part1a = substr(part1,find(part1,'if'));
                        stm1a = prxchange('s/if baseline.*\snormal/Base <= ULB/',1,part1a);
                        part1b = prxchange('s/if baseline.*\snormal//',1,part1);
                                stm1b = prxchange('s/>ULN - (.+) x ULN/ULN < Result & Result <=
                                $1*ULN/',1,part1b);
                        stm1 = strip(stm1b)||' & '||strip(stm1a);
                end;
```

This code outputs the string "(ULN < Result & Result <= 1.5*ULN & Base <= ULB) | (1.0*Base < Result & Result <= 1.5*Base & Base > ULB)". The code to format the "abnormal" statement is similar, and they can be concatenated to create the following complete machine-executable code for CTCAE v5 Bilirubin Increased Toxicity Grade 2:

(ULN < Result & Result <= 1.5*ULN & Base <= ULB) | (1.0*Base < Result & Result <= 1.5*Base & Base > ULB)

The code below mimics the SAS code above in R:

Figure 2: CTCAE v5 Bilirubin Increased – Toxicity Grade 2 Criteria in Machine-Executable Format

```
vv <- ">ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was
abnormal"


part1 <- sub("(.+);(.+)","\\1",vv);
if (grepl("baseline.*\\snormal",part1)) {
  part1a = sub("(.+)if(.+)" , "\\2",  part1)
  stm1a = sub("baseline.*\\snormal","Base <= ULB ",part1a);
  part1b = sub("(.+)if(.+)" , "\\1",  part1)
  stm1b = sub(">ULN - (.+) x ULN","ULN < Result & Result <= \\1*ULN",part1b)
  stm1 = paste0(trimws(stm1b),' & ',trimws(stm1a))
  }
```

CODE EXECUTION AND TOXICITY GRADE DERIVATION

Once the spreadsheet containing executable code has been imported, the action of calculating the toxicity grades themselves can be performed in SAS using CALL EXECUTE, or in R using the built-in functions eval(), parse(), for example: str <- "2^3"; eval(parse(text=str)), will produce 8 as a result.

Richard Allen's paper "Creating a Function for Lab Toxicity Grading using PROC FCMP" from PharmaSUG China in 2019 outlines a process for executing the code by using PROC FCMP to create custom functions in SAS. In that process, the grading criteria are coded into the custom functions themselves for each individual parameter. Our PharmaSUG paper "Implementing Laboratory Toxicity Grading for CTCAE Version 5" from 2019 outlines how to execute the code using CALL EXECUTE in SAS. The advantage of our system is that by having the toxicity grading stored separately in an Excel document, someone who is familiar with labs, but not necessarily with programming, can review and maintain the toxicity grading criteria without having to update any programs.

CONCLUSION

The process outlined here of taking an input Excel spreadsheet containing toxicity grading criteria, transforming those criteria into machine-readable code, and then importing that code and executing it is extremely powerful and flexible. With the use of regular expressions, mapping one toxicity grading criteria from source to machine-executable will easily facilitate the mapping of any other toxicity grading criteria with similar formatting. The conversion from source to machine-executable only needs to be processed whenever the toxicity grading criteria are updated, due to a new version from a regulatory agency, or a study with special needs calling for more specific toxicity grade criteria. Storing the machine-executable code in an Excel spreadsheet outside of the program makes review and maintenance accessible for non-programmers.

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