

## Challenge the Specs

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### ABSTRACT

Programmers, when programming tables, listings or figures (TLFs) for a clinical trial, often begin with a diagram or shell of how the display should look. Programmers need to identify the elements that are needed to produce the TLF display. Those elements, which we will call specifications, or specs for short, can be identified through a variety of documents that define the clinical trial. This paper will review an adverse event (AE) table shell and create the specs needed through a review of the documents available in a clinical trial. This paper teaches how to create the specs, and, more importantly, if the specs are already created teaches how to analyze them and the supporting documents to ultimately challenge the specs.

### INTRODUCTION

A table of AEs by relationship to study drug is a common safety report. Through examples from clinical trial documents such as the protocol, statistical analysis plan (SAP), analysis database specifications, annotated case report forms (CRF), etc., this paper shows how that information is used to create or challenge the specs for this AE table. Our end result will be a fully specified document that includes all elements needed to understand and program this AE table.

### REVIEWING THE SHELL

Look over the shell for programming items and ask yourself the questions below:

Start top left – Who is the client? What protocol is this?

Title – What is the main variable being analyzed and how? Need a variable, such as gender to page by?

Sub-titles – What is the population? Is there additional data set subsetting indicated?

Column names – What variables are displayed? What variables need to be concatenated or modified to fit the display format?

Row headers – Does the data come from one data set or many? Do you need an indexing or category variable for sort order and formatting the display?

Data – What values are you displaying? – Summary statistics, counts, confidence intervals, p-values, etc. What procedures will you need to analyze the data? Sort order?

Footnotes – Contains details that should not be overlooked. Any flagging that needs to be done, for example a lab listing that states, "All abnormal labs are marked with an \*." Footnotes may define your data even more, or have additional processing that you need to do, such as counting a patient once at each level of summarization for the AE table.

**ADVERSE EVENT SHELL EXAMPLE**Client: ABC Pharma  
Protocol: 123-4

Page x of y

Table 14.3.3.3  
Summary of All Adverse Events by Relationship to Study Drug  
(Safety Sample)

System Organ Class [a] High Level Term Preferred Term	Study Drug #1 (N=xxx)					
	Not Related	Related			Total	
	Possible	Probable	Missing	Definite		
Total Number of AE Episodes	xxx	xxx	xxx	xxx	xxx	xxx
Number of Patients With at Least One Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High Level Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High Level Term #2						
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High Level Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...						
...						

Note: The total number of AEs counts all AEs for all patients. At each level of patient summarization, a patient is counted once for the most related event if the patient reported one or more events. If the relationship of an AE is missing, the AE is counted as "Related." Percentages are based on the total number of patients in each treatment group.

[a] System organ class from Medical Dictionary for Regulatory Activities (MedDRA) version 7.0.

Source Data: Listing xxx

**REVIEW THE PROTOCOL**

The protocol provides the study's main objective, drug or device being studied and the design of the trial from the client's point of view. Our example study of ABC Pharma compares the client study drug to an existing medication to cure an eye infection, therefore, expect 2 treatments to be displayed in the table. The protocol states that approximately 200 adults and children were enrolled in a multi-center, randomized, double-masked, parallel clinical trial. For a draft delivery, this table will be programmed on masked treatments.

**ADVERSE EVENTS AS DESCRIBED IN THE PROTOCOL**

The protocol states that if the patient has the infection in one eye at the first visit and then the other eye becomes infected then it is recorded as an AE. This means there probably will be a lot of eye related AEs.

The protocol further defines what constitutes an AE and to where it should be reported. An appendix spells out for the investigators the definition of each relationship category. Most of the protocol text relates to the clinical part of the study, but it may also affect how the analysis AE data set is programmed.

## **REVIEW THE STATISTICAL ANALYSIS PLAN**

The SAP states how to perform the statistical analyses. This document provides information that can be put in the general specs and discusses the presentation of each type of analyses. From the general discussion of AEs it is discovered that only treatment emergent AEs are summarized. This is not apparent from the shell, but is central to the data being presented in the table.

### **ADVERSE EVENTS BY RELATIONSHIP IN THE SAP**

The SAP description of the AE table states the following:

#### **RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG**

An overall summary of AEs by relationship to study drug will be presented separately for each study drug. The relationships will address the possibility that the study drug caused the event. The possible grades of relationships are "Not Related," "Unlikely," "Possible," "Probable," "Missing," and "Definite." If a patient reports multiple occurrences of the same AE, only the most strongly related occurrence would be presented. Adverse events (AEs) with missing relationship will be counted in the summary table as related, but will be presented with a missing relationship. Percentages will be calculated based on the number of patients in the Safety sample.

A look back at the shell for the relationship categories shows that "Unlikely" is missing, therefore another column is needed. The SAP also states to sort the relationships to pick up the most related one.

## **READ THE GENERAL SPECS FOR YOUR STUDY**

The general specs is a study specific document drawn up to cover items across all the TLFs being programmed. They can include how numbers are formatted, how to display the treatments, how to calculate your column header counts, etc. Always review this document to achieve consistent formatting with all of the study's TLFs. The general specs for this study says "When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts." Put this condition in the programming code since the AE table presents counts and percentages.

## **REVIEW THE ANALYSIS DATABASE SPECIFICATIONS**

The analysis database specs documents the derived variables needed for the AE table. The derived variables SAFETY and TMTEMG are used to subset the AE data set when records are first read in to the program. The values needed to subset the data are spelled out in these specs, so that TMTEMG = 1 should be selected, not TMTEMG = 0, to subset the AE data set. Notice in the derivation of the variable TMTEMG the description from the protocol about the second eye getting infected and being reported as an AE.

**TMTEMG VARIABLE DESCRIPTION IN THE ANALYSIS DATABASE SPECS**

AE	TMTEMG	<p>Treatment Emergent Event – char</p> <p>'1' = 'Yes'</p> <p>'0' = 'No'</p>	<p>If AETERM is blank then TMTEMG is blank. If AETERM is not missing then derived TMTEMG as follows:</p> <p>If adverse event is not eye specific (EYE = 'NA') then compare AE start date AESTDT to date of first dose global DOSEDATE – if event start date on or after first dose, then event is treatment emergent, TMTEMG = '1', other wise not emergent TMTEMG = '0'.</p> <p>If adverse event is for both eyes (EYE = 'B') and AE start date AESTDT is on or after dosing for either the right or left eyes (RDOSE1 and LDOSE1) then event is treatment emergent, TMTEMG = '1', other wise not emergent TMTEMG = '0'.</p> <p>If adverse event is for right eye (EYE = 'R') and AE start date AESTDT is on or after dosing for right (RDOSE1) then event is treatment emergent, TMTEMG = '1', other wise not emergent TMTEMG = '0'. (If right eye is not dosed, then TMTEMG = '0'.)</p> <p>If adverse event is for left eye (EYE = 'L') and AE start date AESTDT is on or after dosing for left (LDOSE1) then event is treatment emergent, TMTEMG = '1', other wise not emergent TMTEMG = '0'. (If left eye is not dosed, then TMTEMG = '0'.)</p> <p>However, because the spread of bacterial conjunctivitis to the second eye is recorded as an AE and the eye would not as of yet received study drug – if index(AEPREFT, 'Conjunctivitis' 'Conjunctival hyperaemia' 'Erythema' ' Eye Discharge') ne 0 and the AE start date equals the dosing start date for the given eye, then the event will not be considered treatment emergent. If the AE start date is after date of first dosing, then the conjunctivitis event will be treatment emergent.</p>
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**CASE REPORT FORM OR DATABASE SPECIFICATION DOCUMENT**

The remaining variables needed are found in the annotated CRF or a database specification document. AE pages tend to look similar with the investigator entering numbers or checking off boxes that indicate relationship. The decodes for these values are shown in the document and are included in the format catalog. Having the relationship coded numerically provides an easy way to sort the relationships to pick the most related AE if a subject has multiple AEs. Notice here that "Unlikely Relationship" is a choice and should be included on the table.



AESOC  
AEHLT  
AEPREFT

Table 14.3.3.3  
Summary of All Adverse Events by Relationship to Study Drug  
(Safety Sample)

System Organ Class [a] High Level Term Preferred Term	Study Drug #1 (N=xxx)					AEREL Total
	Not Related	Related			Definite	
		Possible	Probable	Missing		
Total Number of Adverse Events	xxx	Unlikely Related (column to left of Possible and under line for Related)			xxx	xxx
Number of Patients With at Least One Adverse Event	xx (xx.x%)				xx (xx.x%)	xx (xx.x%)
System Organ Class #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High Level Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High Level Term #2 Preferred Term #1	DATA: AE where SAFETY='1' and AETERM is not missing and TMTEMG='1'.  At each level (system organ class, high level term and preferred term), sort by the total related number of events in the Study Drug # 1 treatment group					xx (xx.x%)
System Organ Class #2						xx (xx.x%)
High Level Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...						

Note: The total number of AEs counts all AEs for patients. At each level of patient summarization, a patient is counted once for the most related event if the patient reported one or more events. If the relationship of an AE is missing, the AE is counted as "Related." Percentages are based on the number of patients in each treatment group.

[a] System organ class from Medical Dictionary for Regulatory Activities (MedDRA) version 7.0.

Source Data: Listing 16.2.19.1

### CONTACT INFORMATION

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