

PROGRAMMER'S SAFETY KIT: Important Points to Remember While Programming or Validating Safety Tables

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ABSTRACT

With many global pharmaceutical companies/ CRO's outsourcing their work, there is a need of qualified professionals to do the clinical programming job. In order to build clinical programming capabilities, there is a requirement of well designed trainings. The training module generally consists of rigorous SAS trainings followed by trainings on Safety/ Efficacy modules. This paper will provide a checklist for reporting or validation of safety data in the pharmaceutical domain. With the help of this checklist, programming or validation can become relatively easy. Amateurs in clinical programming and especially programmers without a background of clinical domain might find these guidelines to be very useful. Moreover, the safety outputs across various studies are more or less similar. Using a standard checklist can ensure accuracy and efficiency in reporting.

INTRODUCTION

As per the pharmaceutical industry standards, all outputs should be validated by independent programs. During validation, the basic and minimal necessity is to match the numbers in both the outputs. Apart from that, there are other important aspects to be checked. Column alignment, decimal precision, page break issues are some of them. To avoid missing out on crucial points, if there is a checklist for each table, then that would make our job relatively easy. We just need to ensure that we follow each and every point from the checklist to be absolutely sure that the output created is up to the mark. In a rare situation, it can also happen that the validation numbers match exactly with the original, but they both are wrong! If a comparison is made with a third reference, this mistake can be avoided. The third reference can be another related summary table or listing. The checklist that is provided in this paper would touch on all these aspects and more. This checklist should be used as a tool by both the output creation programmer and the validation programmer to ensure quality output creation and effective validation, respectively.

SOME COMMON CHECKS TO FOLLOW:

- 1) All the tables should be validated using independent programs/ programmers.
- 2) Summary tables should be cross-checked with corresponding listings, wherever applicable.
- 3) Values can be cross-checked with other relevant tables.
E.g. Individual Adverse Events (AE) table can be checked against the Overview of Adverse Events (AE) table.
- 4) Check whether the precision of descriptive statistics is as mentioned in the requirements document and Statistical Analysis Plan (SAP). Generally, percentages are displayed up to one decimal (51.0%, 25.0%). Exceptions can be values such as 100.0 or 0.0 which are mostly presented as 100 or 0. Descriptive statistics generally are represented with the following decimal precision: Minimum and Maximum equal to raw data precision, Mean and Median equal to one decimal more than raw data precision, Standard deviation equal to 2 decimals more than raw data precision.
- 5) For frequencies, a few percentages can be checked randomly from each treatment group. PROC SQL is preferred while checking counts. Percentages related to subject counts should not exceed 100%. For summary statistics, median and mean should lie between minimum and maximum. Standard deviation should not be negative. Identify any outliers and investigate if required. Some other basic checks include p-values to be between 0 and 1, the value of estimate should lie between the lower and upper confidence interval.
- 6) Appropriate footnotes should be present. If the denominator is other than the treatment group "N", then it should be mentioned in the footnote. Summary tables should have reference to listings. Cross-check the reference listings. All the abbreviations and symbols used in outputs should have corresponding footnotes.
- 7) Check for consistency across tables. Treatment group "N", Treatment column headers, format of summary statistics, alignment of counts and percentages etc.
- 8) Other visual checks include page break, wrapping/ truncation of text, page numbers, which will vary from each output. This needs to be checked carefully.
- 9) Ensure that the latest data is used for reporting. Also, if there is a data cut-off specified, then ensure that appropriate conditions for the same are present in your SAS program.

These general checks are supposed to be checked for each output programming or validation. In addition to this, there are certain table specific checks which are listed below.

	TRT-A (N = XX)	TRT-B (N = XX)
Number of subjects randomized	xx	xx
Number (%) of subjects in Safety population	xx (xx.x%)	xx (xx.x%)
Number (%) of subjects in Intent-to-Treat population	xx (xx.x%)	xx (xx.x%)
Number (%) of subjects who completed the study	xx (xx.x%)	xx (xx.x%)
Number (%) of subjects who discontinued from the study	xx (xx.x%)	xx (xx.x%)
Primary Reason for Discontinuation		
Adverse Event	xx (xx.x%)	xx (xx.x%)
Withdrawal by Subject	xx (xx.x%)	xx (xx.x%)
Lost to Follow-up	xx (xx.x%)	xx (xx.x%)
Xxxx	xx (xx.x%)	xx (xx.x%)

Program name: <SAS program name>

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Table 1: Subject Disposition (Randomized Subjects)

✓CHECKS FOR TABLE 1: SUBJECT DISPOSITION (RANDOMIZED SUBJECTS)

1. Check the number of subjects randomized against the randomization file provided by the sponsor/statistician.
2. Summation of number of subjects who “Completed the study” and who “Discontinued from the study” should be equal to the total number of randomized subjects.
3. Check if summation of the number of subjects under different reasons for withdrawal is equal to the number of subjects who discontinued.
4. The safety population counts can be cross-checked against the drug exposure table. Since mostly safety is defined as the population which has been administered a minimum of one drug. There can be deviation in this definition which needs to be checked carefully in the SAP.
5. The number of subjects who have discontinued due to AE should match the number of subjects in the “Any Adverse Event leading to Study Discontinuation” row in the Overview of Adverse Events table (Table 4).
6. For the subjects who are not included in “Safety” and “Intent-to-Treat” populations, ensure they are eliminated due to “criteria not satisfied” and not due to any programming error.
7. Treatment group “N” should not be more than subjects randomized.

	TRT-A (N = XX)	TRT-B (N = XX)
AGE (years)		
N	Xx	xx
Mean	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
<65 years, n (%)	xx (xx.x%)	xx (xx.x%)
≥65 years, n (%)	xx (xx.x%)	xx (xx.x%)
HEIGHT (cm)		
N	Xx	xx
Mean	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
WEIGHT (kg)		
N	Xx	xx
Mean	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
SEX		
Female	xx (xx.x%)	xx (xx.x%)
Male	xx (xx.x%)	xx (xx.x%)
ETHNICITY		
Hispanic or Latino	xx (xx.x%)	xx (xx.x%)
Non Hispanic or Latino	xx (xx.x%)	xx (xx.x%)

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Table 2: Summary of Subject Demographics

✓ **CHECKS FOR TABLE 2: SUMMARY OF SUBJECT DEMOGRAPHICS**

1. Check if the “n” count in each category is consistent.
E.g. Summation of the two gender categories/ summation of race categories should add up to the “n” in the AGE category, etc. None of the categories should ideally have missing values.
2. Check if the AGE/ WEIGHT min, max is in accordance with the inclusion criteria defined in the protocol.
E.g. In obesity studies, the minimum and maximum weight would be listed in the “Eligibility criteria” section, to check the entry criteria for a subject.
3. All category text displayed in the body of the table should match with the text collected on CRF.
E.g. “Hispanic or Latino”, “Non Hispanic or Latino” etc.
4. Check if the measurements are in the same unit. If the HEIGHT is collected in “cm” and “m”, then unit conversion is needed while summarizing the data. This applies for other parameters like WEIGHT as well.

ATC Class Preferred Term	TRT-A (N = XX)	TRT-B (N = XX)
ATC Class 1	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)
Etc...		
ATC Class 2	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)
Etc...		

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Table 3: Summary of Prior/ Concomitant Medications

✓CHECKS FOR TABLE 3: SUMMARY OF PRIOR/ CONCOMITANT MEDICATIONS

1. The definition of prior/ concomitant should be consistent with SAP.
2. If prior/ concomitant medications flag is derived in the table program itself, check for partial dates handling as per the rules mentioned in the SAP.
3. Medications can be either prior or concomitant. Make sure that they are not marked as both.
4. Since the WHO dictionary has four ATC term variables, make sure the correct ATC class variable is used from the WHO Dictionary.
5. Ensure there are no "Uncoded" terms in the data after the Database Lock (DBL). If there are, bring this to the notice of study statistician.

	TRT-A (N = XX)	TRT-B (N = XX)
Any adverse event	xx (xx.x%)	xx (xx.x%)
Any related adverse event	xx (xx.x%)	xx (xx.x%)
Any serious adverse event	xx (xx.x%)	xx (xx.x%)
Any related serious adverse event	xx (xx.x%)	xx (xx.x%)
Intensity		
Mild	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)
Any adverse event leading to study discontinuation	xx (xx.x%)	xx (xx.x%)
Any adverse event leading to death	xx (xx.x%)	xx (xx.x%)

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Table 4: Overview of Adverse Events

✓CHECKS FOR TABLE 4: OVERVIEW OF ADVERSE EVENTS

1. Make sure all AE's have been included, i.e. none of the AE's are excluded due to partial/ incorrect date format.
2. Ensure that AE's with AETERM = "NONE" or "NO ADVERSE EVENT" are not counted.
3. Count for "Any related adverse event" should be less than or equal to count for "Any adverse event".
4. Read the SAP carefully while summarizing by severity/ relationship to the study drug. In some situations subjects are counted only once under maximum severity/ relationship. In some other situations, a subject is counted in all severity/ relationship categories wherever applicable. This condition should be checked in the SAP and there should be a corresponding footnote to explain the same. Also, make sure the intensity of an adverse event is not null. Generally if the intensity is null, it considered as "Severe", provided it is an AE post drug administration. Else severity is considered as "Mild". Same is the case with relationship to study drug. Check this with the study statistician.
5. Number of subjects with "Any adverse event leading to study discontinuation" should match with "Adverse Event" row in disposition table (Table 1).
6. Check the number of subjects with corresponding AE listing, if possible. Double check serious adverse event (SAE) counts.

System Organ Class Preferred Term	TRT-A (N = XX)	TRT-B (N = XX)
Number (%) of subjects with any drug related adverse event	xx (xx.x%)	xx (xx.x%)
System Organ Class 1	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)
Etc...		
System Organ Class 2	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)

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Table 5: Summary of Adverse Events by System Organ Class and Preferred Term

✓CHECKS FOR TABLE 5: SUMMARY OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM

1. Cross check the numbers against Overview of Adverse Events table (Table 4).
2. Check the sorting order. Sorting usually takes place in the descending order of "N" in the active group, followed by the "N" in Placebo group. Or else sorting can be done by arranging the System Organ Class (SOC) terms alphabetically.
3. Check if the denominator should be count of subjects from "Subjects with any drug related adverse event" or the "N" from treatment headers.
4. Ensure there are no "Uncoded" terms in the data after the DBL. If there are, bring this to the notice of the study statistician.
5. Appropriate footnotes should be present.
E.g. Footnotes for Treatment Emergent Adverse Event (TEAE), medical dictionary used etc.

Parameter (unit)	Baseline	End of Study	Change from Baseline
Parameter (unit)			
N	xx	xx	xx
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Min, Max	xx,xx	xx,xx	xx,xx

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Table 6: Summary and change from baseline of Laboratory Parameters/ ECG/ Vital Signs

✓CHECKS FOR TABLE 6: SUMMARY AND CHANGE FROM BASELINE OF LABORATORY PARAMETERS/ ECG/ VITAL SIGNS

1. Number of subjects at “End of Study” should be less than or equal to “Baseline” subject counts. Number of subjects at “Change from baseline” should be less than or equal to minimum of {number of subjects at “Baseline”, number of subject at “End of Study”}.
2. Check for the uniqueness of records. In this situation there should be one record per subject, per visit, per parameter. If more than one record exists, check with study statistician about selection method of the required record. We can consider either the average, worst case scenario or selecting earliest record or latest record which is closest to the target visit day.
3. Text to numeric conversion is recommended in order that no data is lost.
E.g. if there are values like “< 0.01” (less than the lower limit of quantification - LLOQ), then 0.1 is used for analysis.
4. Proper footnote should be present to define baseline.
5. Check if the values are in the same unit, else unit conversion is essential.
6. Ensure that correct unit is displayed against each parameter.

			TRT-A (N = xx)		
Parameter (unit)	Visit	Result	Baseline		
			Low	Normal	High
Erythrocytes (unit)	Week 4	Low, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Normal, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		High, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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Table 7: ECG/ Physical Examination/ Laboratory Shift Tables

✓CHECKS FOR TABLE 7: ECG/ PHYSICAL EXAMINATION/ LABORATORY SHIFT TABLES

1. Sum of numbers in the shift table, at a particular visit should tie up with total number of subjects "N" in a particular treatment. There can be a situation where a subject has baseline record but does not have any post baseline record. In such a situation "Missing" category should be added in the table so that the table counts add up to "N". Else, if "Not Done" category is collected on the CRF, then instead of "Missing" category, "Not Done" category is introduced in the table.
2. Proper footnote should be present to define baseline.
3. Ensure that correct unit is displayed against each parameter.

CONCLUSION

Maintaining high efficiency without compromising quality is a necessity in the CRO/ Pharmaceutical industry. This paper enables easy facilitation of the same.

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