

PP08 Quality Control and Validation – More than Just PROC COMPARE

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Introduction

In clinical trials, QC of the deliverables created as results of the statistical analysis process traditionally relies on the **principle of independent validation** by others. In the typical notion of validation (that of datasets or TLFs), this concept manifests itself as independent programming of the output using the same inputs. The presumption is that an independently developed program, using the **same inputs** and requirement specifications, which **yields the same outputs**, serves as validation on the aspects of the deliverable that the independent programming replicates.

This “getting match” approach is often relatively easy to automate, e.g. by using SAS® PROC COMPARE, which leads to individuals, and at times organisations, becoming **too reliant on electronic checks** and neglecting other elements of QC.

Within the PhUSE working group Standard Analyses and Code Sharing, a white paper provides an in-depth review of best practices for robust QC, including checks used by CRO and pharma sponsor organisations in clinical trials. This poster leverages the content of the white paper to summarise how **both manual and electronic QC checks** can be applied for each category of deliverables: analysis dataset specifications, analysis datasets, TLFs, and eSubmission.

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Individual Dataset/TLF

Validation of the individual outputs often involves electronic comparison of results independently derived, e.g. via PROC COMPARE. While this is an important aspect of validation, there are many elements where PROC COMPARE fails to capture issues in the produced output.

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Table 1.2 Summary of Demographic Characteristics and Baseline Characteristics Safety Population					
		ACTV01 10 mg (N=28)	ACTV01 20 mg (N=27)	Placebo (N=30)	Overall (N=85)
Sex	n	28	27	30	85
	Female	7 (25%)	9 (33%)	20 (67%)	36 (37%)
	Male	21 (75%)	18 (67%)	10 (33%)	49 (50%)
Age (yrs)	n	28	27	30	85
	Mean	53.2	50.1	52.9	52.2
	SD	9.17	10.43	13.01	12.19
	Median	61.0	53.0	51.5	53.5
	Min.	35	33	32	32
	Max.	72	65	71	72
Ethnicity	n	28	26	30	84
	Hispanic Or Latino	3 (11%)	0	3 (10%)	6 (6%)
	Not Hispanic Or La	25 (89%)	26 (96%)	27 (90%)	78 (90%)
Height (cm)	n	28	27	30	85
	Mean	170.90	171.18	177.12	173.18
	SD	6.986	9.913	11.433	8.944
	Median	170.35	172.05	171.05	171.15
	Min.	151.0	153.2	152.1	151.0
	Max.	185.3	185.4	188.6	188.6
Weight (kg)	n	28	27	30	85
	Mean	83.24	84.78	85.26	84.44
	SD	9.674	14.561	16.761	13.483
	Median	81.35	82.60	85.60	81.60
	Min.	68.1	68.6	59.6	59.6
	Max.	100.	114.	98.9	114.
Note: Baseline is defined as the last valid measurement prior to randomization.					

Electronic Checks

- PROC COMPARE of datasets (or display datasets)
- Check for missing data
- Check logs for unacceptable messages

Manual Checks – Datasets

- Alignment with specification/requirements
- Character strings contain text which is factually correct and meaningful, is spelled correctly, is in the required case
- Units of measure align with results
- Numeric and character variable pairs are consistent
- Data falls within defined value ranges
- Rounding and truncation of numeric values is appropriate
- Precision of decimals

Manual Checks – TLFs

- Population Ns
- Verify analysis population is correct
- Calculations embedded in footnotes
- Text in column headers
- Truncation of character results
- Rounding of numeric values
- Precision of decimals
- Categorical grouping of continuous values
- Data falls within defined axis ranges
- Footnotes consistent with mock shells
- Sort order of rows
- Column order

Analysis package

All analysis datasets and TLFs need to be validated as a complete package. PROC COMPARE remains vital in this part of the process, but additional manual steps are essential as well. Checks performed may repeat those at the individual component level to ensure programs execute as expected.

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Table 2.2 Summary of All Adverse Events by Treatment Safety Population					
Inconsistent label with Table 1.2		Activumab 10 mg (N=28)	Activumab 20 mg (N=27)	Placebo (N=30)	Inconsistent N with Table 1.1 Overall (N=85)
System Organ Class Preferred Term					
ANY EVENT		14 (50%)	18 (67%)	15 (50%)	47 (55%)
Gastrointestinal disorders					
Any event		14 (50%)	12 (44%)	9 (30%)	35 (41%)
Change of bowel habit		10 (36%)	8 (30%)	11 (37%)	29 (34%)
Diarrhoea		9 (32%)	11 (41%)	6 (20%)	26 (31%)
Gastrointestinal pain		7 (25%)	7 (26%)	4 (13%)	18 (21%)
Nausea		6 (21%)	5 (19%)	1 (3%)	12 (14%)
Vomiting		3 (11%)	7 (26%)	0	10 (12%)
Eye disorders					
Any event		10 (36%)	8 (30%)	11 (37%)	29 (34%)
Conjunctival haemorrhage		10 (36%)	8 (30%)	11 (37%)	29 (34%)
General disorders and administration site conditions					
Any event		6 (21%)	5 (19%)	1 (3%)	12 (14%)
Infusion site pain		6 (21%)	5 (19%)	1 (3%)	12 (14%)
Investigations					
Any event		3 (11%)	7 (26%)	0	10 (12%)
Lipase increased		3 (11%)	7 (26%)	0	10 (12%)
Nervous system disorders					
Any event		1 (4%)	0	1 (3%)	2 (2%)
Somnolence		1 (4%)	0	1 (3%)	2 (2%)
Note: sNumSubj. experienced no adverse events in the study.					

Unresolved macro variable

Electronic Checks

- Same as individual datasets/TLFs
- Compliance with standards such as Pinnacle 21®

Manual Checks – Datasets

- Same as individual datasets/TLFs
- Relationships between datasets
- Common variables have same values and attributes in different datasets

Manual Checks – TLFs

- Same as individual datasets/TLFs
- Count checks across TLFs (e.g., listing vs table or table vs figure)
- Alignment with planned analysis
- Consistency of representation (fonts, treatment labels)
- Consistency of figure representation (colors, symbols, lines)
- No planned, but missing, outputs
- No unplanned/legacy files included

Date-Time Stamps

- Raw data > SDTM > Analysis Dataset > TLFs
- Order within analysis datasets
- Specification > Program > Output
- Production > Independent QC



Standard Analyses
and Code Sharing

eSubmission

Similar to PROC COMPARE for validation of datasets and TLFs, eSubmission validation can myopically rely on Pinnacle 21®, which focuses on validating define.xml against XML schema, FDA/PMDA validation rules and implementation of controlled terminology. It does not check meaningfulness and comprehensiveness of the information, nor verify content of the Analysis Data Reviewer's Guide and other documents.

Variable	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
ETHNIC	Ethnicity	text		ETHNIC • "NOT HISPANIC OR LATINO" = "Not Hispanic or Latino"	Predecessor: DM.ETHNIC Codelist does not include all collected values per CRF
ETHNICN	Ethnicity (N)	integer		ETHNICN • 1 = "HISPANIC OR LATINO" • 2 = "NOT HISPANIC OR LATINO"	Derived Numeric representation of ETHNIC
ASUBMR	Analysis Subject Information	text	24		Derived Concatenation of SUBID, AGE, SEX variables, abbreviated RACE (W = White, A = Asian, B = Black or African American, N = American Indian or Alaska Native), TST (if subject was screen failure) via comma for reporting purposes
COMPFL	Completers Population Flag	text		No Yes_Responses • "N" = "No" • "Y" = "Yes"	Derived Concatenation of SUBID, AGE, SEX variables, abbreviated RACE (W = White, A = Asian, B = Black or African American, N = American Indian or Alaska Native), TST (if subject was screen failure) via comma for reporting purposes Incorrect derivation
SAFL	Safety Population Flag	text		No Yes_Responses • "N" = "No"	Derived Subjects who died with the study and had at

AVAL	Analysis Value	Root	5	Predecessor: VLSUBSTR Use Reviewer's Guide for more information about the variable Reviewers Guide 100
PABANDP	PABANDP (Diastolic Blood Pressure)	integer	2	Predecessor: VLSUBSTR
PABANDP	PABANDP (Pulse Rate)	integer	2	Predecessor: VLSUBSTR
PABANDP	PABANDP (Respiratory Rate)	integer	2	Predecessor: VLSUBSTR
PABANDP	PABANDP (Systolic Blood Pressure)	integer	3	Predecessor: VLSUBSTR

ADRG requires separate review

Incorrect origin

eSubmission package content

- All expected datasets (XPT files) are included
- Only relevant files and nothing extra are included
- No empty (with zero records) datasets present
- Datasets greater than 5 gigabytes in size are split into smaller datasets
- All file names in lower case

Define.xml

- Spelling and grammar
- Dataset order
- All derived variables have clear and sufficient comments and derivations
- Proper use of ORIGIN
- Readability of comments
- Codelists and Value Level Metadata implementation
- Links to external files lead to the correct places within the documents

Analysis Data Reviewer's Guide

- Technical properties: PDF version, bookmarks, hyperlinks, fast web view etc.
- All required sections of the document are present and numbered appropriately
- Correctness of data standards and dictionaries specified
- Study Description is phrased in relation to data structure, is sufficient and supported with graphical representation of the study design if needed
- The list of Key variables is present and checked against the data and define.xml
- All datasets are listed
- All special derivation methods such as visit windowing or processing of incomplete dates should be fully described and cross-checked vs the SAP and define.xml
- Variable names should be checked against data (XPT files) and define.xml
- The results of automated validation checks are fully and clearly explained