Cue the word QC- All you need to know!

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ABSTRACT

Drug development is complex and critical decisions are made daily based on data. Validation and Quality Control (QC) are essential steps to assure the data source is authentic. In real world, with instream reporting we often deal with unclean data. We must consider a risk based approach to determine what level of QC is required for all the data reporting components involved in a study. Quality is obviously paramount, but to achieve this we need to identify a set of robust quality control techniques and processes. QC starts with understanding and clearly inventorying your data. Assigning the right people to perform validation is crucial. If proper steps are in place and qualified stakeholders are identified, including clinical, statistical and programming leads, to perform the validation then you can meet your timelines, survive an audit, skip the CAPA (Corrective and Preventative Action), and successfully obtain regulatory approval.

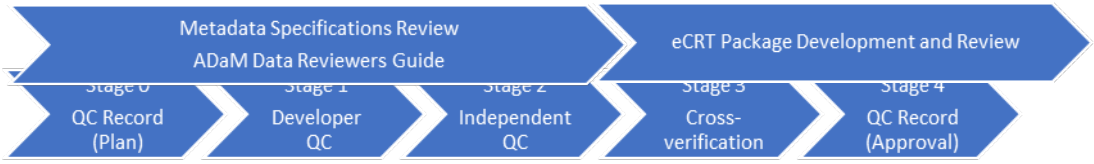
This paper covers a risk based approach and the different stages of QC. Paper will cover checks, responsibilities and accountabilities at each stage. This paper will be helpful to all levels of programmers in the drug development industry.

INTRODUCTION

This paper describes the process for the quality control (QC) of results (datasets, tables, listings, figures, patient profiles, CRF listings, statistical analyses) produced by programmers and statisticians to support study reporting of phase I-IV clinical trials data to ensure that the information is complete, internally consistent and accurately reflect the data collected/provided.

STAGES OF QC

Quality Control (QC) of results (Datasets, Tables, Listings and Figures) consists of the following stages:



Stage 0: Identification of QC Coordinator and drafting of QC Record
Stage 1: Developer Testing and QC
Stage 2: Independent QC
Stage 3: Cross Verification
Stage 4: Final “QC Record” approval and archival

Analysis Data Reviewers Guide (ADRG) is developed in parallel with the analysis dataset creation and validation. It is finalised after Stage 4 QC is complete but prior to Primary Study Report Complete.

Stage 0:

During this stage the lead programmer identifies a QC coordinator. A QC record is drafted to jot down the validation process related details. This is an important stage, and it needs careful consideration in identifying the appropriate resources to perform validation/QC. One needs to take in to account the experience level and the skill set of the person assigned to this task so we can ensure right people are assigned to tasks. Less experienced people are often assigned to QC tasks. Though this may seem logical, there is a higher chance of quality being compromised inadvertently due to the lack of experience and skill set of the people involved. Assigning an experienced programmer to carry out validation is one way to avoid pitfalls.

Stage 1:

At this stage a lead programmer for the study develops the reporting components that are required for a study. Lead programmer responsible must have a thorough understanding of the study, analysis plan and it's reporting requirements. Programs must be set up using defensive programming techniques with ability to spot data collection issues, CDISC mapping issues following good programming practice guidance. Evaluating the results programmed for plausibility and consistency with the source data is required on an ongoing basis as the study accumulates data. This stage is a critical stage in the QC process. The developer is responsible for checking his/her own work before it is passed on to the next stage (Stage 2).

Stage 2:

Independent QC is performed by a person(s) other than the author of the program that produced the results. Be sure that this person has adequate knowledge and skills to perform the task(s). It is recommended to assign this task to an experienced programmer. Independent QC programmer must set up validation programs independently. This involves creating validation programs to the specification of the reporting component that is described in the Analysis Plan rather than programming to match what was produced by the lead programmer at Stage 1.

The following table recommends the independent QC method that should be applied to each data reporting component (Ex: Dataset, Table, Listing, Figure, Stat Output, eCRT package).

Independent QC Method Table:

Independent QC Method		Standard Code: Level 1					Non-Standard Code: Level 2					
Key: D=Dataset; T=Table; L=Listing; F=Figure		D	T	L	F		D	T	L	F	Stat Output	eCRT Package
1. Parameter review			X	X	X				X			
2. Code review									X			
3. Log review		X	X	X	X		X	X	X	X	X	
4. Double-programming (new or existing code)		X					X	X			X	
5. Simple frequency counts (e.g. proc freq)			X					X				
6. Execute Pinnacle 21 checks (or equivalent)		X					X					
7. Visual QC of data against dataset/TLF		X	X	X	X		X	X	X	X	X	
8. Metadata specifications review		X					X					X
9. ADRG review		X					X					X

Note: "T" is referring to tables without formal statistical analyses.

By identifying the different methods involved in the validation process and choosing appropriate method to validate different components, a risk based approach is used to determine what level of validation is needed to various reporting components. Standard code in the table above refers to a set of validated code that are released by a company upon successful User Acceptance (UAT) and Validation Testing. Issues identified at Stage 2 must be clearly documented with accountabilities, dates and must be communicated to the individual who conducted Stage 1 of the QC process (Developer). Upon resolving the issues identified, the developer then passes the rectified reporting components to Stage 2 QC. All resolutions must be clearly documented and tracked and archived at Clinical Study Report (CSR) sign off to facilitate any audits.

Metadata Specifications Review Stage:

This stage begins at Stage 0 and ends when the independent validation, Stage 2 is complete. Both the developer (during the development stage) as well as the independent QC programmer (during Stage 2) are responsible for reviewing the metadata specifications. Metadata specifications document is a living document and may need to be updated past the initial review and finalization stage as applicable. Metadata specification is the back bone of the analysis datasets. It is recommended to create and review detailed metadata specifications (ADaM specifications) prior to creating analysis datasets (ADaM datasets) at study start and maintain the documents with needed updates throughout the study. This will reduce the time needed to review define.xml at the end of the study when the CRT package is created.

During review of the metadata specifications:

- Review the specification to make sure that it follows the CDISC standards for dataset structure per the current implementation guidelines.
- For variables that include controlled terminology (CT), crosscheck the values with source dataset as well as analysis plan requirements for completeness.
- Check if Value Level Metadata (VLM) has been used appropriately and the information is accurate. VLM is very useful if different derivations of AVAL/AVALC exists for each new parameter in an analysis dataset (ADaM)
- If analysis flags, visit windowing, on-treatment/off-treatment categorization are included in the ADaM datasets check to make sure the derivation algorithms are consistent with the Analysis Plan.

Stage 3:

This stage begins after Stage 2 and Metadata Specification Review Stage of the QC process is complete. This stage involves Cross Verification. Cross checking all results for consistency, across all reporting components. This means comparing analysis datasets to source datasets, verifying analysis results (Tables, Listings, Figure, Patient Profiles, CRF Listings) to analysis datasets for accuracy. Inconsistencies across tables, inappropriate analysis (e.g. Convergence Issues), data errors, formatting errors, data display specification errors can all be detected at this stage. Any errors that slipped through Stage 2 of the QC process must be identified at this stage. Stage 2 complete doesn't necessarily mean that your analysis is accurate. This is your last chance to detect and rectify any errors before the study analysis is finalized (SAC, Statistical Analysis Complete). Stage 3 review requires an inquisitive mind. Stage 3 may involve independent programming, evaluating the analysis package for accuracy and completeness. Stage 3 QC must be performed by an experienced individual who has a thorough knowledge of the study, usually by the study statistician. All issues identified at Stage 3 must go through Stages 1 and 2 of the QC process. A final Stage 3 sign off occurs when all results are final and the study declares SAC. Issues identified at Stage 3 must be clearly documented with accountabilities, dates and resolutions and archived at Clinical Study Report (CSR) sign off to facilitate any audits.

eCRT Package Development and Review Stage (ADaM):

This stage starts when the analysis datasets have passed independent validation (Stage 2) and continues until the study's Clinical Study Report (CSR) is finalized.
At this stage:

- Verify all analysis datasets have transport files
- Verify data definition file includes all datasets and is consistent with the content of the transport files
- Where datasets have been split, compare the split files against the source file to verify all variables and records are present
- Verify data definition file is consistent with the metadata specification (all definitions are present and correct and all references to external sources are valid and linked correctly including links to annotated Case Report Form (aCRF), and Analysis Data Reviewer's Guide)
- Verify data conformance issues are included from Pinnacle 21 checks or equivalent (where applicable) following the last creation of the DEFINE file
- Verify traceability between variables used in data display to the variables in the analysis datasets

ADaM Data Reviewers Guide (ADRG): To evaluate the thoroughness of ADRG the following checks are recommended.

- Source SDTM(s) clearly identified in each ADaM(s) specification
- Comparison of number of observations between SDTM and ADaM datasets, do they match your analysis dataset expectation?
- If non-SDTM datasets (ex: Protocol Deviation spreadsheet, Adverse Events of Special Interest reference dataset) are used in ADaM, check ADRG has a detailed description of the source data.
- If analysis flags are included in the ADaM a description of them detailing their purpose is clearly provided in ADRG
- Any derivations from the Study Analysis Plan or any additional data handling techniques not included in the Analysis Plan should be clearly documented and justified.
- All unresolved issues from Pinnacle 21 report must be clearly listed providing clear explanation of why the issue is left unresolved.
- Check to make sure ADRG table of contents matches the relevant ADRG template (PHUSE) and that all the hyperlinks work.
- Make sure the required naming convention for the reviewer's guide meets regulatory agency guidelines (ex: For FDA submission the file naming convention is adrg.pdf)

REAL LIFE EXAMPLES

Below are a few real-life examples where the errors were detected at various stages of QC. Some errors were unfortunately, only discovered by the regulatory agencies. By implementing a rigorous Quality Control process through the different stages of QC these errors can be detected early and avoided in the future.

Incorrect Medical History Listing Delivered to FDA and PMDA

A Medical History Listing contained a column titled "Ongoing". The Medical History analysis dataset had a variable to indicate if condition was Ongoing. But listing program did not check for the correct data values, so the Ongoing column in the listing was incorrect. No medical conditions were flagged as Ongoing in the listing

The issue was discovered by PMDA during submission review.

How Can we prevent a problem like this in the future?

- Stage 2 QC must include visual review of the dataset, understand your variable values
  - PROC FREQ and PROC MEANS are useful tools for reviewing datasets
  - PROC FREQ would have shown values contained in a variable.
- Stage 2 and Stage 3 QC should both consider whether the display makes sense
  - A review of the medical history listing should have raised questions – is it really likely that not a single subject in the study had an ongoing medical condition?

Blinded Biomarker Data in LAB Dataset After DBF

Some biomarker data are not delivered until after DBF because it has potential to unblind subjects. At time of SAC delivery, team discovered that the LAB dataset contained blinded T-cell biomarker data (see table below).

The issue was found during Stage 3 QC.

VISITNUM	VISIT	LBDT	LBACTTM	LBTESTCD	LBSTRESN	LBSTUNIT	LBSTNRLO	LBSTNRHI	LBORRES
40.00	YEAR 1 WEEK 4	10MAR2015	12:30	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
50.00	YEAR 1 WEEK 8	08APR2015	11:00	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
60.00	YEAR 1 WEEK 12	05MAY2015	10:30	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
60.01	UNSCHEDULED	08JUN2015	11:05	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
90.00	YEAR 1 WEEK 24	29JUL2015	12:23	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
120.00	YEAR 1 WEEK 36	14OCT2015	11:35	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
150.00	YEAR 1 WEEK 48	13JAN2016	11:20	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
160.00	YEAR 2 WEEK 4	16FEB2016	14:05	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
512.00	DOUBLE BLIND EXIT	24MAY2016	13:55	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
520.00	FOLLOW-UP	11AUG2016	11:10	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
40.00	YEAR 1 WEEK 4	28AUG2014	10:45	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
50.00	YEAR 1 WEEK 8	25SEP2014	10:10	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
60.00	YEAR 1 WEEK 12	23OCT2014	9:25	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
90.00	YEAR 1 WEEK 24	15JAN2015	11:00	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
120.00	YEAR 1 WEEK 36	10APR2015	9:30	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
150.00	YEAR 1 WEEK 48	29JUN2015	10:03	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
160.00	YEAR 2 WEEK 4	27JUL2015	11:05	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
210.00	YEAR 2 WEEK 24	16DEC2015	9:45	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
512.00	DOUBLE BLIND EXIT	15JUN2016	10:25	CD3+_BLC	.	GI/L	0.8400000	3.0600000	BLINDED
520.00	FOLLOW-UP	03AUG2016	10:40	CD3+ BLC	.	GI/L	0.8400000	3.0600000	BLINDED

How Can we prevent a problem like this in the future?

- PROC COMPARE is not enough, Stage 2 QC must also include visual review of the dataset
  - PROC FREQ and PROC MEANS are useful tools for reviewing datasets
  - Opening and viewing the dataset would have shown the error

Pneumonia Table with Dummy Hard-Coded Numbers

RAP shell for a Pneumonia table had 3 blocks with notes specifying the data source for the table (see mock table shell below)

When table was pre-programmed, data for 2nd & 3rd blocks were not available. So the programmer only wrote code to derive the first block of the table. The programmer hard-coded dummy numbers to produce the 2nd and 3rd blocks (place-holder code), with the intention of removing the hard-coded numbers when actual study data was available in the future.

The QCer also pre-programmed the QC program for this table. Since data was not available to produce numbers in the 2nd and 3rd blocks, the QCer did not write code to check the 2nd and 3rd blocks in table.

Neither the production nor the QC programmer updated their programs when more data became available

Summary of On-Treatment Pneumonia

	Drug X (N=xxx)	Drug Y (N=xxx)	Drug Z (N=xxx)
Number of subjects with			
Pneumonia	xx (xx%)	xx	xx
Pneumonia and an associated chest x-ray	xx (xx%)	xx	xx
An associated x-ray which shows infiltrates	xx (xx%)	xx	xx
An associated x-ray which does not show infiltrates	xx (xx%)	xx	xx
An associated x-ray with infiltrates unknown	xx	xx	xx
Pneumonia and hospitalised	xx (xx%)	xx	xx
No associated chest x-ray	xx	xx	xx
An associated x-ray which shows infiltrates	xx	xx	xx
An associated x-ray which does not show infiltrates	xx (xx%)	xx	xx
An associated x-ray with infiltrates unknown	xx	xx	xx
Fatal pneumonia	xx	xx	xx
No associated chest x-ray	xx	xx	xx
An associated x-ray which shows infiltrates	xx	xx	xx
An associated x-ray which does not show infiltrates	xx	xx	xx
An associated x-ray with infiltrates unknown	xx	xx	xx
Pneumonia with an onset date within the duration of a severe exacerbation	xx	xx	xx

How Can We Prevent a Problem Like This in the Future?

- Do not hard-code dummy numbers into displays
- If a dataset or display cannot be completed during pre-programming because data is not yet available, document this:
  - Add this status to the QC Record – a dataset or display cannot be ready for Stage 2 QC if it is not yet programmed
  - Write notes to the program log

Stage 3 qc can identify minor errors, e.g. spelling, format errors, outputs that don't make sense, inconsistencies across tables. Below is just one example from a stage 3 finding.

Baseline included in post baseline year interval

Protocol: XXXXXX Page 1 of 1
Population: XXXXXXX

Table x.xx
Worst Laboratory Toxicity Grade by Year Interval: Urinalysis (Double-blind Phase)

Parameter / Worst Grade / Toxicity		Anytime Post Baseline (Placebo: N=52) (Drug X: N=53)	Year 0-1 (Placebo: N=52) (Drug X: N=53)	Year 1-2 (Placebo: N=43) (Drug X: N=33)	Year 2-3 (Placebo: N=14) (Drug X: N=7)	Year 3-4 (Placebo: N=1) (Drug X: N=1)
Urine Total Protein/Creatinine Ratio						
n	Placebo	51	52	42	14	1
	Drug X	52	50	33	7	1
Grade 0	Placebo	24 (xx%)	28 (xx%)	30 (xx%)	8 (xx%)	1 (xx%)
	Drug X	18 (xx%)	23 (xx%)	19 (xx%)	6 (xx%)	0
1	Placebo	21 (xx%)	20 (xx%)	10 (xx%)	5 (xx%)	0
	Drug X	22 (xx%)	21 (xx%)	10 (xx%)	0	1 (xx%)
2	Placebo	3 (x%)	3 (x%)	0	1 (x%)	0
	Drug X	3 (x%)	3 (x%)	3 (x%)	1 (xx%)	0

- Evident by more subjects in year 0-1 than in the anytime post baseline summary

How Can We Prevent a Problem Like This in the Future?

- Have an inquisitive mind
- Don't assume the output is correct because it passed stage 2 QC
- Apply some common sense

CONCLUSION

As the saying goes ‘To err is human’. Current industry expectations to accomplish key milestones with limited resources, is contributing to high pressure work environment. Quality Control is often overlooked, almost always lacks the needed funding and appreciation. With experience and thorough knowledge of the deliverable requirements, good quality results are easily accomplished through careful planning and resourcing. This paper discusses planning your quality control process through various stages. Through quoting “real life” examples the paper highlights even with careful scrutiny it is easy to miss things. Addressing the root cause and developing a set of corrective actions to prevent failures will help achieve the desired quality results.