



Cue the word QC – All you need to know

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Agenda

- **Background**
- **Review Stages of QC**
- **Real Life Examples**
- **Q & A**

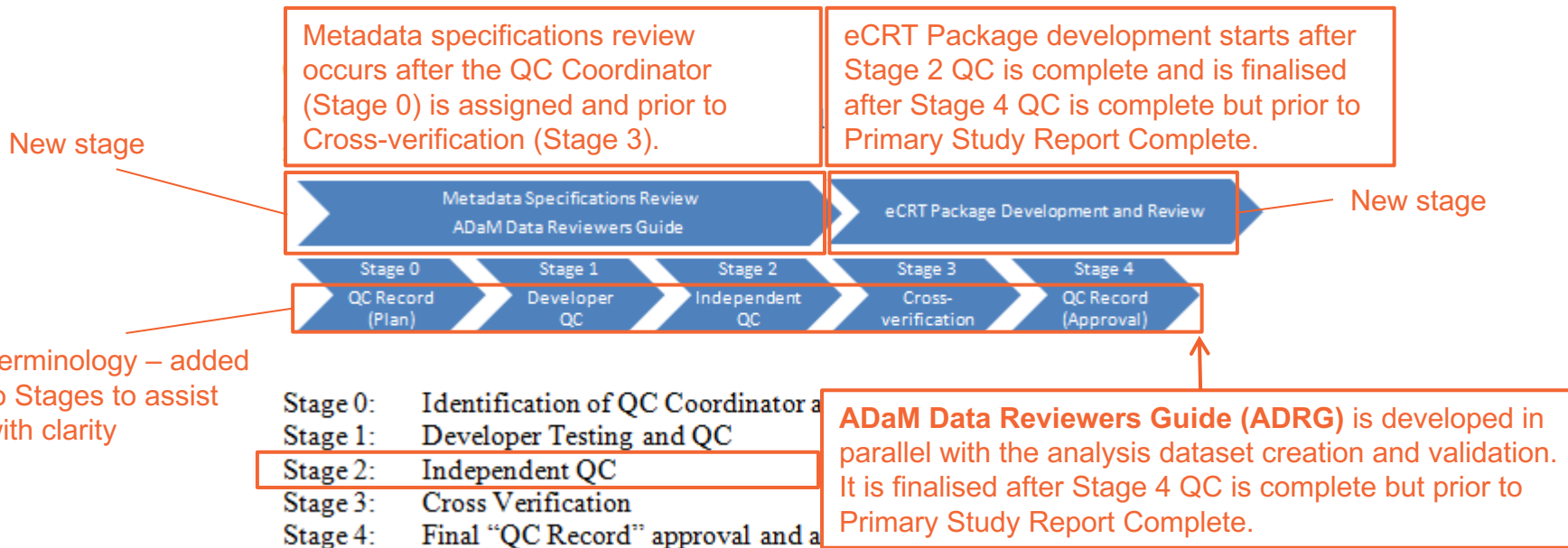
Background: MHRA & CDQA findings



Recent Medicines and Healthcare Products & Clinical Data Quality Audit findings revealed the following:

- QC Record template was not mandatory
- QC comments history was not always retained
- QC program logs weren't always saved and archived
- Creation and the QC programs were not version controlled
- Lack of documentation for eCRT QC process
- RAP didn't have sufficient clarity regarding derivations of key endpoints
- Decisions to skipping levels of QC or performing reduced level was QC was not clearly documented

QC Stages



Stage 0: Identification of QC Coordinator and Drafting of QC Record



- ❑ Identify the QC coordinator (Lead Programmer/Lead Statistician)
- ❑ Draft the QC Record prior to start of any QC activities (QC Coordinator)
- ❑ Assign QC activities and update QC record throughout the QC process (QC Coordinator)

Note: Take into account experience and skill levels so right people are assigned to tasks

- e.g. Have experienced programmers QC work of junior programmers
- e.g. Assign complex QC to senior programmers

Stage 1: Developer QC



1. Verify programs conform to Good Programming Practices (E.g. program header block, internal program comments, modification history)
 2. Verify log contains no error messages or warnings unless there is a valid reason
 3. Verify the analysis datasets satisfy the applicable data standards
 4. Verify results for plausibility and consistency with source data and that they represent function defined in RAP/SAP
 5. (If applicable) Verify the log contains no model specific warnings or notes that may impact any statistical analysis
 6. (If applicable) Verify statistical analysis conforms to model specifications as defined in RAP and that results in table match results in program execution list file from the direct statistical model output
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Stage 2: Independent QC Method Table



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					
	D	T	L	F	D	T	L	F	Stat Output	eCRT Package
<i>Key: D=Dataset; T=Table; L=Listing; F=Figure</i>										
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.

Metadata Specification Review and Validation



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- ❑ Metadata specifications review occurs after the QC Coordinator (Stage 0) is assigned and prior to Cross-verification (Stage 3).
 - ❑ Create and review detailed ADaM specifications prior to ADaM creation at study start and maintain throughout the study. This will reduce the time needed to review define.xml at the end of the study when CRT package is usually created
 - ❑ QC involves - Verify that all expected domains are present , verify consistency with applicable standards, verify consistency of definitions across domains, verify that all RAP-defined derivations and analyses are included, and are consistent with the RAP.
 - ❑ Approval occurs at the latest prior to the start of Stage 3 QC of the results.

Stage 3 QC



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- ☐ Stage 3 QC is done after Stage 2 QC is completed
 - ☐ Cross-check across all results for consistency.
 - ☐ Verify that treatment codes have been assigned correctly.
 - ☐ Verify the statistical analysis.
 - ☐ Verify any changes since Stage 2.
 - ☐ Verify analyses/outputs have been performed in accordance with RAP (or other applicable reporting specification).
 - ☐ Resolve all issues identified during cross verification, including successful QC of any modifications.

QC of eCRT Package



Data Definition File (including transport files) & Data Reviewer's Guide

- ☐ Starts after Stage 2 QC is complete and finalized after Stage 4 is complete (prior to Primary Study Report Complete)
- ☐ Verify all datasets have transport files
- ☐ Verify data definition file (DEFINE) includes all datasets and is consistent with the content of the transport files
- ☐ 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 Study Data Reviewer's Guide, aCRF, and Analysis Data Reviewer's Guide)
- ☐ Where datasets have been split, compare the split files against the source file to verify all variables and records are present

QC of eCRT Package



Data Definition File (including transport files) & Data Reviewer's Guide

- ❑ Check the Keys of page 1 of the ADaM define.xml are unique by doing a PROC SORT with NODUPKEY. The log should show “0 observations with duplicate key values were deleted”
- ❑ For variables that use controlled terminology do a quick PROC FREQ on that variable in SAS for crosschecking against define.xml.
- ❑ If time and budget permit, it is a good idea to get the CRT packages reviewed by a programmer that has never worked on the study. They will see the study in the same way as the external reviewer.
- ❑ Verify data conformance issues are included in ADRG from Pinnacle 21 checks or equivalent (where applicable) based on the FINAL version of the DEFINE file.
- ❑ ADRG should be a living document, start writing ADRG in parallel to you ADaM dataset creation.

QC of eCRT Package



Data Definition File (including transport files) & Data Reviewer's Guide

ADRG Specific Checks:

- ☐ Has the source SDTM(s) for the ADaM been specified?
- ☐ Compare the number of observations in the ADaM with the main source SDTM. Are there more, less or the same? An explanation is useful.
- ☐ Check non-ADaM/SDTM source datasets (eg: Protocol deviation spreadsheet, Adverse Events of Special Interest reference dataset) are described clearly
- ☐ Check ADaM specific analysis flags are described clearly and they are derived consistently
- ☐ Include reasons for deviations from the RAP/SAP.
- ☐ Review Pinnacle21 report to ensure issues not resolved have been appropriately listed
- ☐ Check all hyperlinks work correctly and the TOC matches PHUSE ADRG template
- ☐ The naming convention for ADRG is adrg.pdf

Stage 4 QC



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- Final QC Record approval, this stage occurs when all results are considered final (e.g. for study report approval).
 - Stage 4 signoff is required at the latest by final study report approval.
 - For studies using Pharma TMF system electronic signature process may be required.
 - Verify any changes since Stage 3
 - Verify that the “QC Record” is complete
 - Upon successful completion of this review Lead Programmer/Statistician provides approval and enter Stage 4 completion date in the “QC Record”.
 - QC record is archived after Stage 4 approval

Driver Macro Version Report



dmv_report_14-MAY-2018_2034.csv [Read-Only] - Excel

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	A	B	C	D	E	F	G	H	I	J
1	Study ID	Reporting Effort	Create Date of Report	Create User of Report						
2	XXXXXX	XXXXX	14-May-18	Jane Doe						
3										
4	Dataset Drivers									
5	Driver Name	Driver Version	Macro Name	Macro Version						
6	adhuuc	2	rc_adhuuc	5						
7	adae	1	ru_getadamdata	1						
8	adsl	1	rc_adsl	3						
9	adae	1	ru_getadamdata	1						
10	adae	1	ru_getadamdata	1						
11	adae	1	ru_getadamdata	1						
12	adhu	2	rc_adhu	2						
13	adae	1	ru_getadamdata	1						
14	adae	1	ru_getadamdata	1						
15	adae	1	ru_getadamdata	1						

Examples: Real-Life Quality Problems

Cue the world – All you need to know

Review of Real-Life Quality Problems



Example:

- Incorrect Medical History Listing Delivered to FDA
 - RAP/SAP and Dataset Specifications Mismatch
 - Table with Dummy Hard-Coded Numbers
- For each problem, we will review following questions and decide on the **Take-Away Messages**
- What went wrong?
 - How can we prevent a problem like this in the future?

Real Life Quality Problems



Incorrect Medical History Listing Delivered to FDA and PMDA

Summary of Problem

- 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.
- This was missed by all stages of QC.

How Was Problem Found?

- The PMDA discovered the problem while reviewing the submission (6 months after filing)

Impact:

- Sponsor has to provide a post submission correction to two regulatory agencies.

Take-Aways?

Real Life Quality Problems



Incorrect Medical History Listing Delivered to FDA and PMDA

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

- Stage 2 QC must include visual review of the dataset
 - PROC FREQ and PROC MEANS are useful tools for reviewing datasets
 - PROC FREQ would have shown what values were contained in the 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?

Real –Life Quality Problems



RAP and Dataset Specifications Mismatch

Summary of Problem

- The primary analysis imputed drop outs as non-responders. The exception to this rule was for subjects who withdrew within 28 days of the expected exit visit. This rule was applicable to most efficacy endpoints, including the primary. **This exception was explained in a different section of the RAP since it applied to multiple endpoints.**
- The '28 day rule' was specified in the RAP but was not included in the dataset specifications.
- Programming was based on the Specifications and no one queried the inconsistency with the RAP.

How Was Problem Found?

- The error was spotted after SAC, during the reporting of a subsequent study, two weeks prior to submission.

Impact:

- 3 subjects incorrectly classified as non responders in the primary analysis.
- Submission was delayed by 4 months.
- All efficacy outputs had to be re-run and the majority of the submission documents had to be updated.

Take-Aways?

Real –Life Quality Problems



RAP and Dataset Specifications Mismatch

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

- Analysis metadata specifications must be QCed against the RAP/SAP
- Stage 2 QC must “verify that the results represent the intended function as defined in the RAP/SAP or other applicable reporting specification where one exists.
- All programmers must read entire RAP/SAP – they cannot limit their reading to specific sections
- Other Suggestions
 - Include cross-references in RAP/SAP to link together related sections
 - Training on efficacy endpoints to ensure all staff understand algorithms
 - Training can include examples/case studies

Real –Life Quality Problems



Table with Dummy Hard-Coded Numbers

Summary of Problem

- RAP shell for a table had 3 blocks with notes specifying the data source for the table (*Fatal/hospitalised categorisation to come from the AE dataset, which will be linked via seq number.*)
- When table was programmed, data for 2nd & 3rd blocks were not available. So the programmer only derived the first block of the table. The numbers in the 2nd and 3rd blocks were dummy hard-coded numbers (place-holder code). QC program did not check 2nd and 3rd blocks in table.
- Also, the SDTM.AESHOSP variable was not captured in any ADaM dataset.

How Was Problem Found?

- Stage 2 QC did not find this problem. Problem was found by Stats during Stage 3 QC.

Impact: Re-run and re-QC of table.

Take-Aways?

Real –Life Quality Problems

Table with Dummy Hard-Coded Numbers



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

With Experience Comes Wisdom

