



QC Workflow Optimization Working Group

Progress Report
US CONNECT 2026
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Working Group Aims

- 1) The primary aim of our group is to evaluate the industry's current use of "Full Quality Control" (FQC) or "double-coding" to validate deliverables generated for regulatory submissions.
- 2) The secondary aim is to promote alternative approaches to validation, outside of FQC, that maintain high-quality deliverables while reducing the costs (time, effort, resources) associated with validation.



Regulatory Requirements

- Working group reviewed guidance from ICH, FDA, EU, MHRA, PMDA, Health Canada
- **General principles & requirements for validation of statistical analysis**
 - Programs and systems must be accurate, reliable, and consistent with intended performance
 - Data integrity is key – must ensure all data handling and derivations are correct
 - Validation should follow a risk-based approach focusing on intended use
 - Traceability of data transformations and derivations
 - Reproducibility of outcomes
 - Coding standards (e.g. Good Programming Practices)
 - Accurate and thorough documentation
- **MHRA (UK) Good Clinical Practice Guide is only guidance that lists specific techniques for validation of statistical programming (including double-programming)**



Validating Statistical Programs

Statistical programs blur the line between software & statistical analysis

- **Many statistical programs are bespoke for a study**
 - Although general-purpose macros and templates are used, statistical programs are written to match the protocol, data collection, and SAP for a study and evolve over the study's course.
- **Validation goal is to confirm that data is correctly represented in compliant datasets and analyses are executed correctly**
 - Validating study-specific programs for general use is a low priority.
 - Validation is primarily completed by “independent” double-programming.



Why Double Program?

- **Majority of programming groups are risk-averse**
 - Data representation errors are considered “high-risk”, by default
 - Groups resort to “most thorough” validation method (double-programming)
- **Double-programming provides traceability and reproducibility**
 - Easy to show traceability during inspections (e.g. permanent COMPARE outputs)
 - Easy to rerun when you get a new cut of data and identify novel errors.



Issues with Double Programming

- Resource-intensive (two programmers)
- Difficult to maintain “independence”
 - QC Programmer often verifies against production results (rarely, production code)
 - Validation can be an exercise in “reverse engineering” the same results
- Both programmers develop their programs from the same resources (SAP, specifications, source data)
 - When error(s) stem from misunderstandings of the SAP, specs, or source data, they can be hard to detect with double-programming
 - False sense of “confidence”



Risk-Based Validation

- Risk-based approach to validation requires assessment of the *likelihood* and *impact* of a data representation error for each deliverable:
 - Datasets, tables, listings, and figures should be judged individually
 - Validation methodology should vary based on these judgements, with lower risk meriting less resource-intensive methods (e.g. full double-coding, targeted double-coding, code review, output review)
- Risk assessment should be conducted at the study-level by designated stakeholders (e.g. programming lead, statisticians)
 - “Standard” categorizations of risk (across study/compound) can be developed, with time and practice
 - Novel, complex, or unfamiliar study designs may merit a higher risk profile (see *likelihood slide*).



Risk Assessment: Likelihood

- ***Likelihood of data misrepresentation depends on the following:***
 - 1) Complexity of source data
 - 2) Complexity of the output deliverable's structure
 - 3) Complexity of the programming logic for output variables
- Low Likelihood: safety listings, SDTM.PE, ADAM.ADAE; simple source/output data structures and minimal complex derivations.
- Medium Likelihood: safety summary tables, ADAM.ADEG, ADAM.ADVS; simple source data structures but complex derivations or presentation of results.
- High Likelihood: efficacy-related figures, ADAM.ADSL, ADAM.ADTTE; complex derivations or data structure, multiple integrated data sources.



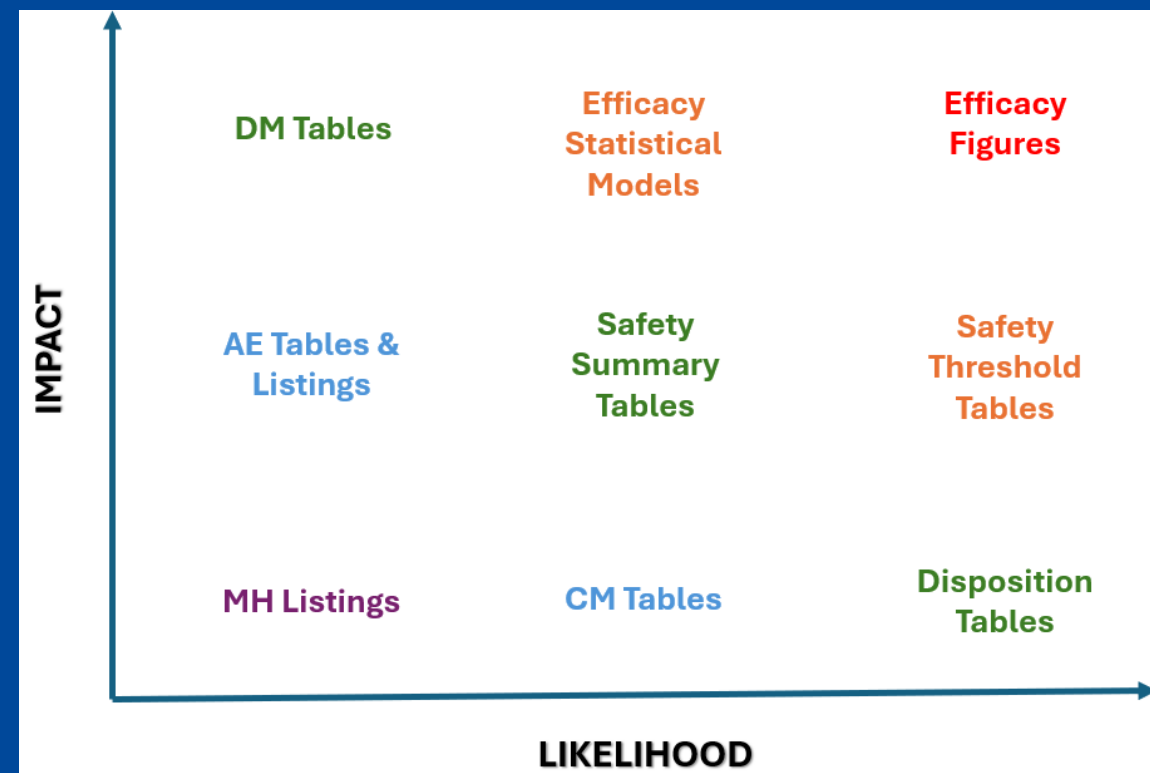
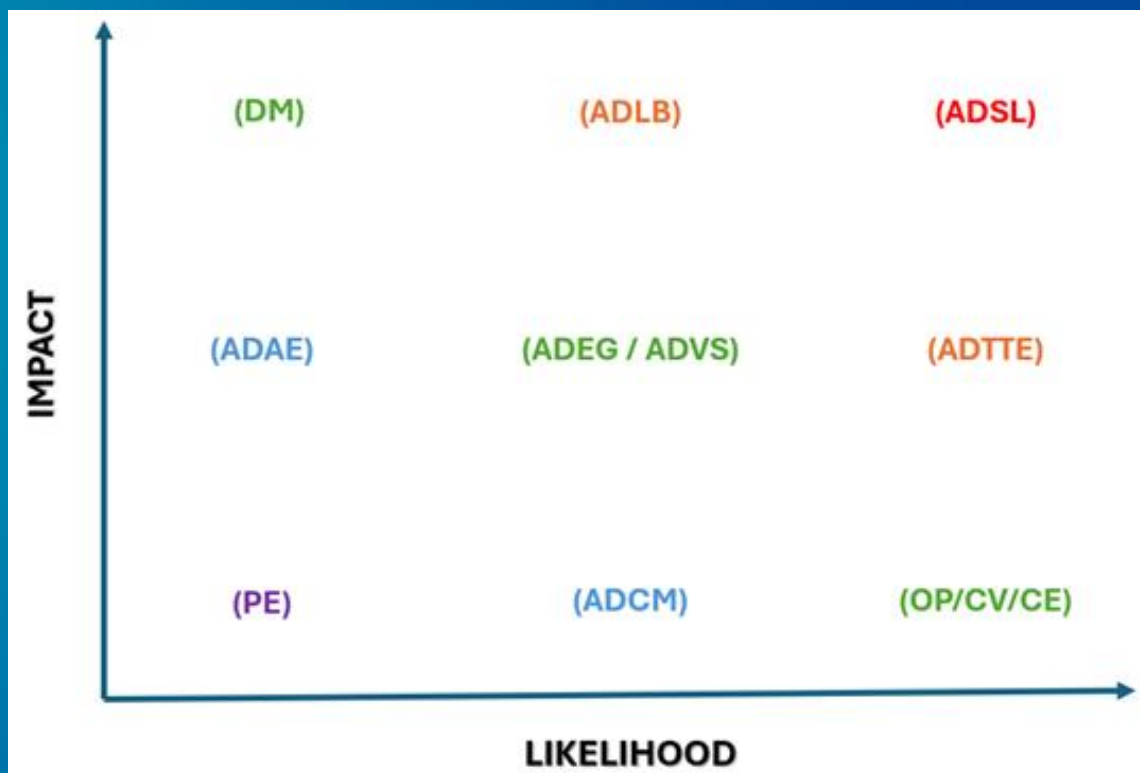
Risk Assessment: Impact

- ***Impact* of data misrepresentation is dependent on “downstream” datasets and/or “terminal” outputs and their role in regulatory decision making.**
- Low Impact:
 - SDTM.MH; often limited role in ADaM-level datasets and safety- & efficacy-related outputs.
 - TFLs with limited role in regulatory decisions.
- Medium Impact:
 - ADAM.ADEG or ADAM.ADVS, with a direct role in safety-related outputs.
 - Safety tables, figures, and/or listings.
- High Impact:
 - ADAM.ADSL, with a direct impact on all safety- and efficacy-related outputs.
 - Efficacy tables, figures, and/or listings.



Risk Matrix

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COMMUNITY ENGAGEMENT & NEXT STEPS

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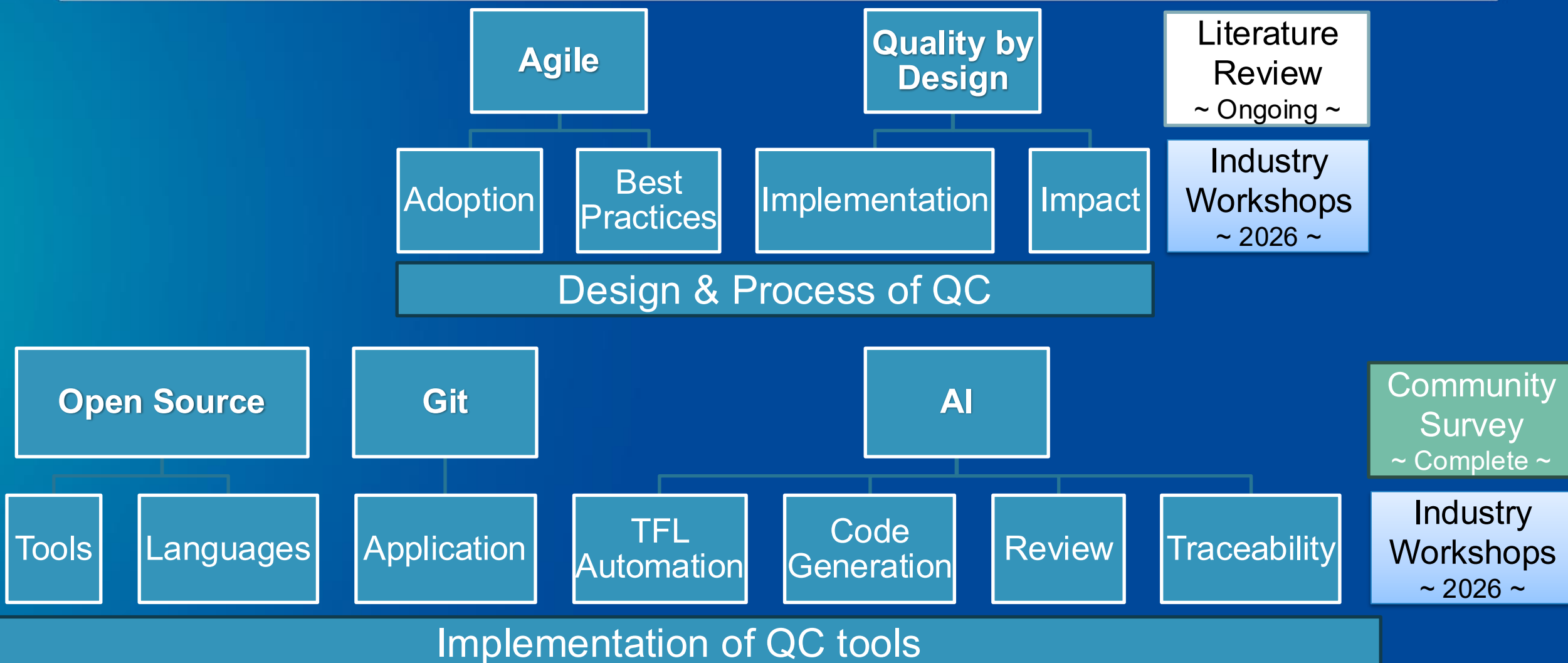
- Collaborative Approach to Industry Transformation
- Completed:
 - ✓ Public survey (48 responses) - December 2025
 - ✓ Regulatory landscape analysis
 - ✓ Risk-based framework development
 - ✓ Literature review methodology established
- Planned:

Timeline/Event	Purpose	Outcome
Q1 2026: PHUSE US Connect	Paper Presentation: Introduce community to the Project	State of the Union: QC processes
	Workshop: Build new QC strategies, Validate survey findings	Initial guidance framework
Q3 2026: PHUSE EU Connect	Workshop: Refine findings	Consolidated recommendations
Q1 2027	White paper development	Comprehensive best practices



EXPLORING LATEST TRENDS

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LITERATURE REVIEW FRAMEWORK

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- Systematic Examination of Recent Advances (2023-2025)
- **Research Question:**
 - 'What is the effect of AI, Open-Source, GIT, Agile, and QbD on Statistical Programming Quality Control?'
- **Information Sources:**
 - PubMed, Google Scholar, Lexjansen, PHUSE Archive, PharmaSUG, ScienceDirect, AI tools (Perplexity, ChatGPT)
- **Quality Assurance:**
 - Validation per PRESS2015 Guideline for peer review
- **Timeline:** Results to be synthesized in 2026 and integrated into final white paper





CONCLUSION & CALL TO ACTION

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Industry Asks:

- Implement risk-based validation strategies (Double Programming for high-risk outputs only)
- Evaluate AI/automation tools against FDA guidance framework
- Pilot emerging technologies (open-source, Git workflows, Agile)

Join Us: Participate in PHUSE 2026 workshops to shape next-generation QC practices

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THANK YOU!

Regulatory Background

- **ICH and other guidance distinguish between software/system validation and validation of statistical analysis**
 - E.g. *ICH Harmonised Guideline for Good Clinical Practice E6(R3)* has separate sections for *Computerized System Validation* and for *Statistical Programming and Data Analysis*
- **Software/system validation – Out of Scope**
 - Techniques such as unit testing, integration testing, regression testing and software development life cycle
- **Validation of statistical analysis – In Scope**
 - Regulatory guidances emphasize adherence to ICH statistical principles and data integrity (e.g. providing traceability of data transformations and derivations).
 - Recommended techniques include independent double-programming; checks of output against raw data or data listings; and review of code/programming



Regulatory Requirements

Agency	Guidance on Validation of Statistical Analysis
FDA	Aligns to ICH Guidance
EMA	Aligns to ICH Guidance • EMA mandates specific validation requirements for clinical trial data, focusing on the integrity, accuracy, and reliability of data generated and computerized systems used in trials
MHRA	Provides approaches to validation of statistical programming:- does not require specific techniques • Independent programming (dual programming and comparing output) • Detailed checks of output against raw data or data listings combined with review of code/programming (essentially computer system validation). It is expected that the programmers writing code will undertake checks to confirm that the programme is functioning correctly. • Use of previously validated code or macros • Checks and retention of any logs produced by the statistical software to ensure the code runs correctly • Checks on accuracy and quality of any new variables/data sets derived from final data sets provided at the end of the data management process • Review of any formulae in spreadsheets (where used for analysis)



Regulatory Requirements

Agency	Guidance on Validation of Statistical Analysis
PMDA	• Mandatory engine-based validation using a specific version of Pinnacle 21 Enterprise to assess SDTM and ADaM datasets for CDISC compliance, with all Errors/Rejects resolved or justified. • Use of validated code and macros, along with traceable programming practices documented through define.xml, SDRG, and ADRG to ensure reproducibility and transparency. • Risk-based quality control, prioritizing validation of critical outputs (e.g., primary endpoints, population flags) and key derived datasets. • Independent programming or peer review of key analyses and outputs to confirm accuracy, especially where results drive regulatory decisions. • Thorough log review and program documentation, ensuring clean execution, traceability of derivations, and alignment with the Statistical Analysis Plan (SAP).
Health Canada	