

Quality Assurance of Outsourced Programming

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Agenda

- Outsourcing Challenges
- What I Mean By Quality Assurance
 - Quality Assurance vs. Quality Control
 - Scope of Quality Assurance
- Reasons Sponsors Performing QA/QC
- Best Practices for Quality Assurance
- Case Studies
- Your Thoughts and Experiences

Outsourcing Challenges

- Knowledge transfer / training
- Multiple handoff of instructions
- Statistical Analysis Plans (SAPs) not always clear and sometimes finalized late
- Programming rules may be changed late in study
- Often no programming specs
- Expectations between Sponsor and CRO, e.g.
 - Number of ad-hoc reports
 - CRO cross-checking and Statistician review of Tables, Listings, and Figures (TLFs)
 - Structure/organization of SAS programs
 - File formats

The Problem with Programming



Wife: “Please go to the store and buy a bottle of milk. If they have eggs, buy 6.”

The programmer goes to the store and returns with 6 bottles of milk.

Wife: “Why did you buy 6 bottles of milk????”

Programmer: “Because they had eggs.”

Quality Assurance vs. Quality Control

- Quality Assurance (QA) is a check on process
- Quality Control (QC) is check for specific results
 - Can range from high-level review to full reproduction of results
 - “Acceptance Checking” or “Review”
- Most sponsors use combination of QA and some QC
 - New outsourcing relationships: Recommend QA and some QC
 - Move towards QA-only as relationship matures
 - Use judgment/experience to decide how much QC to do
 - Recommend a risk-based approach
 - Prioritize QC based on importance and difficulty
 - Do not duplicate CRO’s work

Scope of Quality Assurance

- **Scope:** Analysis results and CDISC compliance
- Deliverables to Review
 - Statistical Analysis Plans and TLF shells (if outsourced)
 - SDTM mappings and datasets
 - ADaM specifications and datasets
 - Annotated TLF Shells (nice to have)
 - Annotated with dataset and variable names and programming notes
 - TLFs
 - Cosmetics matter too (misspellings, titles, footnotes)
 - eCRT package
 - Annotated CRF, Define, Reviewers Guides, Analysis Results Metadata
 - OpenCDISC report and explanations

Reasons Sponsors Perform QA/QC

- Analyses must be accurate
- Sponsor is accountable for accuracy of analyses
- Assess knowledge transfer and training needs
 - Are SAP and specs being interpreted same way?
 - Is communication working?
 - Is CRO team knowledgeable of CDISC and therapy area
 - Are sponsor standards and conventions clear?
- Pitfalls
 - Don't want to replicate CRO's work
 - May contribute to Us-Them Mentality

Best Practices for Quality Assurance

- **Goals:**

- Continuous review/feedback loop with lots of communication
- Move towards QA-only for long-term outsourcing arrangements

- Clear Process and Expectations

- Create timeline with scheduled times for review of deliverables
- Review in batches with staggered deliveries
- Review deliverables only after they are QCed by CRO
- Include adequate time for sponsor reviews
- Start reviews early

Best Practices for Quality Assurance

- Example Timelines

Task	Due Date	CRO	Sponsor
Create ADaM dataset Specs	dd-mon-yy	X	
CRO Touchpoint: Review ADaM dataset Specs	dd-mon-yy		X
Update ADaM dataset specs w/changes	dd-mon-yy	X	
Program and QC ADaM datasets	dd-mon-yy	X	
CRO Touchpoint: Review ADaM datasets	dd-mon-yy		X
Update ADaM datasets w/changes	dd-mon-yy	X	
Run OpenCDISC for ADaM datasets, explain all errors and warnings	dd-mon-yy	X	
CRO Touchpoint: Review OpenCDISC & explanations	dd-mon-yy		X

Best Practices for Quality Assurance

- Talk a lot – Ask Questions
- Document issues and verify corrective action
 - Reduce risk of miscommunication/misunderstanding
 - Documentation is evidence of sponsor oversight
- If issues found, make adjustments to QA plan
 - More discussions of algorithms
 - May want to perform more QC

Case Study #1

- CDISC, CRO Systems, New Relationship

- CDISC submission for leukemia drug
 - Multiple studies, ISS, ISE
 - CRO worked on their systems
 - Very tight timelines and complex algorithms
 - All programming had to be done in parallel
 - New relationship between CRO and sponsor team
 - Different CRFs and data formats for studies
- Original Plan for QA/QC
 - Review all deliverables in-stream on staggered basis
 - Reprogram Key Analyses

Case Study #1

- CDISC, CRO Systems, New Relationship

- Challenges Encountered

- Limited time for specs and algorithm questions
- Programmed in parallel but needed to be consistent
- CDISC issues
 - Many team members new to CDISC
 - SDTM domains for Oncology and leukemia very new
 - Sponsor CDISC standards being developed
- Did not have proper knowledge transfer of sponsor standards
- Sponsor made major changes close to delivery dates
- Project Management issues
 - Difficulty tracking issues and versions of deliveries

Case Study #1

- CDISC, CRO Systems, New Relationship

- Had to Adjust QA Plan
 - Performed more QC than originally planned
 - Wrote automated checks
 - Structure of SDTM and ADaM datasets
 - Checked consistency across studies
 - Compared datasets in current delivery against datasets in last delivery (not a typical check)
 - Checked TLFs against SAP list of TLFs
 - All TLFs present, titles and TLF number correct
 - Brought in CDISC experts
 - Helpful for new Oncology SDTM domains
 - Enforced firm decisions about CDISC structures

Case Study #1

- CDISC, CRO Systems, New Relationship

- Did not review
 - QC programs
 - CRO's QC Record (until end of contract)
 - SAS programs (until end of contract)

Case Study #1

- CDISC, CRO Systems, New Relationship

- Learnings

- Tight timelines harder with outsourcing
- Sponsor should provide clear info on standards & conventions
- CRO should ask lots of questions
- Takes time to develop outsourcing relationship
 - Sponsor needs to invest time and training
- Late changes are painful!
- Project management important
- When encounter problems, adjust plan

Case Study #2

- CDISC, Sponsor Systems, New Relationship

- CDISC study for lymphoma drug
 - One Phase 3 study
 - CRO worked on Sponsor system
 - Functional Service Provider (FSP) Model
 - New relationship between CRO and sponsor team
 - Team more experienced with CDISC

Case Study #2

- CDISC, Sponsor Systems, New Relationship

- QA/QC Performed
 - Reviewed all deliverables in-stream on staggered basis
 - Prioritize review based on complexity and importance
 - Spent a lot of time reviewing ADaM specs and datasets
 - Reprogrammed Key Analyses
 - Primary and key secondary endpoints, Key safety tables
 - Checked across sampling of domains
 - Spot-checked
 - QC Record
 - A few production programs to ensure CRO used Sponsor standard macros correctly

Case Study #2

- CDISC, Sponsor Systems, New Relationship

- Automated checks – more checks possible
 - Structure of SDTM and ADaM datasets
 - TLFs against SAP list of TLFs and QC Record
 - All TLFs present, titles and TLF number correct
 - RTF files created for all tables
 - Logs for error and warning messages
 - Timestamp of QC program logs vs. production timestamps
 - QC program for every ADaM dataset and TLF

Case Study #2

- CDISC, Sponsor Systems, New Relationship

- Did not review
 - QC programs
 - In FSP model, sponsor could spot-check QC programs to make sure they are independent

Case Study #2

- CDISC, Sponsor Systems, New Relationship

○ Learnings

- CRO on Sponsor's system, possible to check more – be judicious
- Sponsor should provide clear info on standards & conventions
- CRO should ask lots of questions
- Review of ADaM specs not as useful at preventing errors in ADaM datasets and TLFs as we expected
 - Specs sometimes just as general as SAP
 - Can be difficult to identify errors in specs
- Still had CDISC issues
 - CDISC standards open to different interpretations

Case Study #3

- Non-CDISC, Sponsor Systems, Established Relationship

- Oncology supportive care studies outsourced to Preferred Provider CRO
 - CRO works on Sponsor system
 - Non-CDISC – Data in Sponsor's pre-CDISC format
 - Long-established relationship between CRO and sponsor
 - CRO very familiar with Sponsor standards, data format, and systems
 - Perform QA, not QC for these studies
- Learnings
 - Things get better over time
 - Mature relationship requires less sponsor resource
 - Easier with Mature Data Standard

Your Thoughts?

- Your Thoughts (especially on Case Studies)
 - Too Much Sponsor Checking? Or Too Little?
- Your Experiences?