

Lessons Learned from the QC Process in Outsourcing Model

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ABSTRACT

As more and more companies in the pharmaceutical industry (sponsors) adopt an outsourcing model for clinical studies, improving the quality control (QC) process has become one of the main discussions between sponsors and their vendors, in most cases, the clinical research organizations (CROs).

This presentation discusses the questions often asked by statistical programmers:

- How to improve the communication between sponsors and CROs?
- How to improve the clarity of data and TLF (tables, listings, and figures) specification documents?
- How to manage the QC processes at both sponsors and CROs sites?
- What are the efficient ways to verify CRO's deliveries?

Having worked as a statistical programmer at both pharmaceutical companies and CROs for more than 20 years, the author will share some experiences and lessons learned on these four topics. The paper will present some suggestions on how to improve the quality control process in the outsourcing model. It does not intend to make any judgment on the quality of works produced or process currently used by sponsors or CROs.

INTRODUCTION

In today's pharmaceutical industry, more and more pharmaceutical, biotechnology, and medical device companies (sponsors) adopt outsourcing models in conducting clinical studies, which include statistical analyses and SAS® programming. The scope of outsourcing statistical analyses may include statistical analysis plans, shells for TLF (tables, listings, and figures), datasets such as SDTM, derived datasets like ADaM, and TLF output. This paper will only discuss the quality control related to these processes.

Figure 1 shows a typical process flow for producing statistical analysis results for clinical studies, regardless of underlying business model. In an outsourcing model, preparation of specification documents may be done by sponsors or/and CROs, depending on the contract. However, in most of cases, the majority of production work related to datasets or/and TLF are done by CROs. Before the delivery of output, CROs use the QC process that was agreed upon with the sponsor to assure the quality of works. Nevertheless, there is always some degree of verification performed by sponsors on all or selected output delivered by CROs. This is done not only to ensure the quality of output, but also to help sponsors verify their derivation logic/algorithms used in analyses.

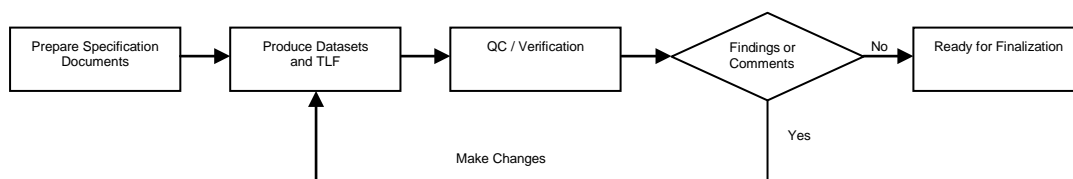


Figure 1

In outsourcing models, some of the main responsibilities of programmers at sponsor's site are to oversee and manage the timeline of CRO's deliveries, to review specification documents, and to verify datasets and TLF generated by CROs to ensure the quality of the output. Their challenges are to implement the following practices:

- A clear and efficient communication path throughout the project between sponsor and CRO
- Very well documented Specifications (such as statistical analysis plan, data specification, TLF Shells)
- A good QC process implemented at both sponsor and CROs site that would minimize timeline and resource strain
- Building up a collaborative and trusting team work environment

In the remainder of the paper, I will share some lessons learned in these areas.

STREAMLINE COMMUNICATION CHANNELS

Lesson learned #1: Assign key contact persons at both CROs and sponsors

When statistical analyses procedure is one of the components included in outsourcing model, it is common practice to assign a key contact person at both sponsor and CRO site for the project. Depending on the extensiveness of the work involved in the project, sometimes it might be necessary to appoint one contact for statisticians and one for programmers as well.

Due to the business nature of CROs, programmers at CROs are often assigned to projects from different sponsors during the same time period. The sponsors need to understand that, when not managed properly, communicating directly to CRO's individual programmers could cause interruption of their work and ultimately delay delivery. Spontaneous communication (phone conversations or even e-mails) also makes it difficult for tracking the decisions/changes made at the project level and would lead to confusion and miscommunication. Designating the key contact person would help to streamline the communication between sponsors and CROs.

Some sponsors have few, or only one, strategic CRO partners. For those outsourcing models, there are liaisons from each function at both sides and their responsibilities are to help set up and improve business processes at CROs site and to ensure overall quality of CROs deliveries. Different from the liaisons, the key contact for a specific project should be those who are responsible for leading statistical analyses and programming for the specific project and are also involved in day-to-day works related to the project.

The key contacts would be responsible to setup routine joint project meetings to discuss timelines, milestones, and any major issues that arise during the project. Though communications between individuals at both sites are encouraged for detail questions/issues, the key contacts should always be copied or informed on such communications.

Lesson learned #2: Have a version control document to track the changes and updates

After verifying analyses results or reviewing delivered specification documents, it is a good practice that sponsor's key contact consolidates all the comments before sending them out to the CRO. The documents used for tracking the sponsor's comments could also be used by the CRO to summarize the responses and resolutions. Table 1 shows an example of a tabulated document for this purpose in MS Word format. For large or/and complicated projects with more than two scheduled deliveries, many people use Excel files for such documents because it provides the benefits of keeping all comments/resolutions in one file.

Table 1
Verification/QC Issue Log

Protocol Number	DRUGXXX
Study Number	101
Milestone	100% Blinded
Delivery Date	01/31/2015

1. General Comments:

Deliverable Name	Commented by	Comments	CRO's Response/Resolution
ADSL	Smith K	1. xxxxxxxx 2. xxxxxxxx	1. xxxxx 2. xxxxx
Table 1.1	Smith K	1. xxxxx 2. xxxxx	1. xxxxx 2. xxxxx

WELL DOCUMENTED SPECIFICATION

Lesson learned #3: Improve the clarity of data and TLF specification documents

For insourcing models, sometimes programmers would be able to generate derived datasets and TLFs by directly referring to the SDTM specification (SPEC) and statistical analysis plan (SAP). This is especially common for sponsors who have a very well documented SOP, or for small organizations where statisticians and programmers share a lot of responsibilities. It seems like everyone knows what he/she is doing. Or if not, the person who knows is

very likely sitting in the next cube.

In outsourcing models with statisticians and programmers in different office locations and different companies, programmers from CROs may have little knowledge of the project background. Therefore sponsors should make every effort to improve information sharing. Specification like data SPEC, SAP, and TLF shells are crucial documents. Before production of datasets and TLF is started, statisticians and programmers at the sponsor's site should work closely with internal team members from other functions to make sure these specification documents have been thoroughly reviewed and finalized before they are submitted to the CRO. No matter who would be responsible for generating these documents, statisticians and programmers from both sides should carefully discuss and review these documents and resolve any major issues.

Sometimes it would be even beneficial to annotate TLF shells. Below is an example:

Appendix 16.2.4.1
Informed Consent and Demography

COND ^T	BIRTHDT	AGE	ETHNIC	RACE1C-RACE6C	HEIGHT	WEIGHT	D_BMI
Date of Consent	Date of Birth DDMMYYYY	Age (years)/ Gender	Ethnicity: Hispanic or Latino?	Race(s)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²) (a)
Treatment: DRUG-XXX							
Site: 0001							
Subject #: 001 Age: 41 Gender: Female Race: White Weight: 77.5 (kg)							
DDMMYYYY	DDMMYYYY	XX/X	Yes/No	XXXXXXXXXXXXXXXXXXXX	XXX	XXX.X	XXX.X
				XXXXXXXXXXXXXXXXXXXX			
				XXXXXXXXXXXXXXXXXXXX			

Input Data Set: D_DEMOG
 Selection Criteria: CONDT not missing

This practice would be beneficial for handling complicated TLFs and o help CRO programmers have a clear understanding on the relationship between data SPECs and TLF shells.

Lesson learned #4: Sponsors to provide consistency on analysis standard

Sponsor statisticians and programmers should be consistently compliant to their analysis standards. Whenever a deviation must be made, it should be documented and shared with CROs. Below lists a few commonly discussed analysis standards:

1. Data handling rules such as missing values, missing or incomplete dates collected, and definition of baseline or post dose measurements.
2. Titles and footnotes used across many TLFs, such as footnotes related to baseline, treatment emergent adverse events (TEAE), etc.
3. Statistical reporting standards such as rules for rounding, decimal points displaying for analysis results
4. Derivation standard used in ADaM SPEC

It is not uncommon that the SAP or TLF shells need to be modified or new variables or TLFs added. These specification documents should be updated and reviewed by both sites periodically and in a timely manner. The changes and updates should also be documented for a better tracking.

BUILDING A COLLABORATIVE AND TRUSTING RELATIONSHIP

Lesson learned #5: Share and understand partner's quality control process and standards.

One of the main objectives for outsourcing model could be cost reduction. However, poor QC process management causes multiple changes/updates of datasets and outputs, and leads to timeline delays and increasing budgets.

CROs and sponsors should discuss and understand their partner's quality control processes and standards. It is important that programmers at CROs are trained to understand and follow sponsor's quality control standards. For sponsors and CROs that have established a long-term partnership, this should be done on an ongoing basis and liaisons at both sites are responsible to monitor this process. If the contract is signed on a project basis, CROs should make sure any employees assigned to the projects are trained before the start of the project.

Sponsors want to ensure there is a well documented QC process at CROs before actual production work starts.

Quality control relies on risk-based management. Errors or mistakes always live within our lives and works. Understanding the CRO's QC process and providing better training to the CRO's team members would help to boost the sponsor's confidence level on the products received from CROs. Therefore, the amount of verification/review works would be reduced at sponsor's site.

Lesson learned #6: Delivering and finalizing unique sets of important output first

When planning milestone delivery from CROs, sponsors may request CROs deliver the unique sets of important TLFs first. For example, in a project in which analyses are done for different subject populations, it would be more efficient to deliver *all* output only after major verification/review findings of output are resolved from the *first* selected population. This strategy could also be applied to a situation when there is a large quantity of TLFs that shared similar formats, such as summary tables for TEAE, related TEAE, Serious TEAE, etc.

Lesson learned #7: CROs to provide sponsor the transparency of their analysis processes

We understand that using well-developed and validated macros for production work can greatly improve the efficiency, quality, and consistency of the statistical analysis outputs and data sets. Programmers from CROs should help sponsors better understand global macro systems implemented for the project.

If the current project is very similar to a previous one that CRO had worked on, programmers from both sites should discuss the possibility of carrying works and experience from previous project to the new project.

CROs are encouraged to discuss and share the QC plan with sponsors during the planning stage. The QC plan usually provides detail information such as QC methods (independent programming, code review, visual checks, and cross checks) and QC coverage (full or partial QC).

A QC check list from CROs could also be used to help sponsors gain clear pictures of QC work conducted at the CRO site.

In dealing with large and complicated data, programmers from both sites may need to exchange SAS® codes and log files to resolve QC issues.

CONCLUSION

In outsourcing models, building a cooperative and trusting team work environment is always a critical factor to the success of project. Both sponsors and CROs should strive hard to cooperate with each other by establishing an efficient and flexible communication channel, understanding and implementing standards and processes at both sites, and providing each other a clear and organized documentation system.

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