

Statistical Programming Workflow Process Improvement at Fujisawa USA

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Abstract

In an effort to reduce time to production of an NDA, an evaluation of quality and efficiency of statistical programming at Fujisawa USA was undertaken by the company with the assistance of DataCeutics, Inc. This paper describes the evaluation process, the opportunities for improvement which were identified, and implementation of changes. A combination of procedural and technical changes led directly to substantially increased quality, decreased production time and reduced staffing needs.

History

Fujisawa USA, a US subsidiary of a large Japanese company, was formed in the late 1980's. The company was tasked with the clinical development of drugs to facilitate human organ transplantation. Clinical trials involving transplant patients tend to be rather complex due to a very sick patient population with disease complications. The studies were noteworthy in the following ways:

- C Studies were long, up to three years in duration.
- C Large volume of data was collected at each visit, with 18 to 24 scheduled visits.
- C Multiple unscheduled visits occurred.
- C There were multiple safety and efficacy end-points.
- C Several supporting safety studies conducted in from Europe and Japan were included.

Because of these characteristics NDA programming and analysis required a large planning, coordination and manpower effort. In support of this effort staffing of the Statistical Programming group at Fujisawa USA was increased from two to over ten programmers in a six month period. This rapid expansion resulted in inefficiencies in the statistical programming process as the pace and range of work out-paced the development of standard procedures and methods. Following completion of an NDA for the first indication, Fujisawa USA embarked on a project to improve the programming process. The project started in May of 1995 and was completed in nine months.

Project Strategy

The project was conducted in two phases. In the first phase an analysis of the current environment was performed to identify potential areas of improvement and submit recommendations to Fujisawa USA management. In the second phase an implementation team was selected and recommended changes were made to the statistical programming work process.

An outside vendor, DataCeutics Inc., was selected to perform the analysis and propose improvement recommendations. An outside vendor was selected for several key reasons:

- C Vendor's expertise in statistical programming work flow analysis.
- C Lack of available Fujisawa USA resources.
- C Vendor's ability to provide an unbiased analysis.

The first phase spanned three weeks. During this time the vendor was on site interviewing staff, reviewing work processes and reviewing the computing environment. A report was produced and presented to the Fujisawa USA management team. The report included a review of the existing work flow process using a current process map (a sample page is in Appendix 1), and recommendations for changes to work process and the computing environment. The current process map describes the statistical programming process and interactions between staff members.

Recommendations for changes to the Fujisawa USA statistical programming defined two primary goals:

- C Build quality into the process.
- C Reduce the time needed to produce the clinical study report output.

These goals would be accomplished by:

- C Automating repetitive manual processes.
- C Eliminating unnecessary and repetitive steps from the overall process.
- C Modifying and standardizing processes or

software use.

The report was reviewed by management and most of the recommendations were accepted. A team from Fujisawa USA and DataCeutics, Inc was selected to implement the second phase of the plan.

Improvement Opportunity Areas

Five target areas identified by DataCeutics as improvement opportunities are outlined below. A project plan addressing all of these areas was developed.

Implementation of the project spanned a period of eight months. For each area, meetings were held with the team and/or users to define or review the new processes.

1. Departmental Processes - Changes in operational processes focused on development of a more rigorous analysis plan and summary table specifications early in the study in an effort to begin the programming process as soon as data was first available, and to reduce the cycles of programming and revisions. A Proposed Process Map was created describing the work flow utilizing the improvements implemented as an outcome of all recommendations. This was used to provide a clear vision of future work flow. Changes implemented include:

- C Delivery of a statistical analysis plan before data is collected. The plan includes analysis dataset, summary table and analysis specification.
- C Safety review and analysis plans were combined.
- C The number of data quality reviews and the volume of custom programming to support them were reduced.
- C The programming process was initiated using first cut of data.
- C A single review of patient listings, summary table & graphics is now conducted.
- C A program validation step was added.
- C Recommended completion of programming and validation before final database lock.
- C Eliminated production of 'CRF tabulations' in favor of standard patient listings.

2. Access to Clinical Data - An automated process for extracting data from the Sybase clinical data management system was implemented. Automated processes developed by DataCeutics replaced manual coding of SAS pass-through SQL procedures and format library creation.

- C A formats dictionary was created in the Sybase system.
- C The Sybase data dictionary was used automate the production of SAS SQL pass-through code.
- C Use of SAS/Access enabled direct access to raw data.
- C The new automated processes were validated.

3. Statistical Computing SAS Programming Environment

- A comprehensive programming environment was designed with a standard project directory structure applying to all projects and protocols. Documentation and training were provided to programmers and statisticians.

- C Developed separate program development and production environments.
- C Developed a standardized data and library storage structure.
- C Developed a comprehensive SAS Programming Environment Guide containing:
 - directory structures and descriptions
 - data access methods
 - programming tools information
 - program and dataset naming conventions
 - macro development and validation guidelines
 - SAS programming development and validation guidelines
 - procedures for the move to production
- C Trained users.

4. Standard Analysis Dataset Structures - There were different standards for the Statistical/Analysis Database for each compound. These were modified to facilitate data extraction and programming/analysis.

- C Implemented a world-wide standard database structure.
- C Format a user-friendly Standard Statistical/Analysis Database Guidelines document. Expand the contents to include dataset descriptions, references to macros and include rules for creation of datasets.
- C Merged the KEY dosing/patient characteristics dataset with all other datasets to facilitate programming and analysis.

- C Modify the standard variables names to mirror the Sybase item names to facilitate the data extraction process.

5. Utility and Report Macro Library - While some macro-driven reporting was in place, it needed to be expanded and be brought under more structured control.

The following actions were taken:

- C Developed a single macro to access any data that can be used from both VMS and Windows SAS platforms
- C Developed a macro for table-driven appendix/table numbering with automated report headers, footers and numbering
- C Developed a macro to create a table of contents for a report and print the output in the proper order.
- C Purchased DataCeutics report macro library for production of safety summaries and patient listings.
- C Validated the macro library.
- C Developed a comprehensive Macro User Manual and train users.

Results

The new statistical programming process was implemented in late 1995 and used for the second indication for a human organ transplantation enhancement compound. The studies included in first and second indications were very similar. The differences in length of the project, number of resources and total cost show a dramatic increase in efficiency between the first and second indications (see below). A large factor in this decrease in project metrics was the improved statistical programming process.

Project Metrics		
	First Indication	Second Indication
Duration	24 months	9 months
Number of Resources	2 managers 1 statistician 13 programmers	2 managers 4 programmers
Programs*	254	60
Cost	\$2,500,000	\$436,000

* number of programs used to produce the phase 3 pivotal study

Three factors had the most dramatic effect on the improved performance: improved planning, implementation of the Standard Analysis Dataset Structures and use of the Report Macro Library.

Planning

- C All data structures and outputs were defined before the start of programming.

Standard Analysis Dataset Structures

- C Databases were standardized across all studies (Europe, Japan and US).
- C Databases were "user friendly" where they could be used for "quick" analyses by statisticians and with report macros.

Report Macro Library

- C All listings created using a single report macro.
- C 95% of safety tables created using report macros.

Biography

Jay Erdman is the Assistant Director of Statistical Analytical Services at Fujisawa USA. He is responsible for all SAS based statistical and clinical programming in support of regulatory submissions. He has ten years of experience with clinical statistics and statistical programming. He was the leader of the statistical programming process improvement project.

Paul Gilbert is Vice President of DataCeutics, Inc., a consulting group specializing in software solutions, system integration, programming and support in the areas of clinical data management and statistical reporting. His fifteen years experience includes clinical data management, implementing and maintaining Domain/Clintrial, designing SAS based biostatistics reporting systems, managing SAS based NDA programming support, SAS/PH-Clinical implementation and CANDAs integration.



**Figure 1
Sample Process Map**

Site							Ongoing Enroll Patients =====>	Ongoing Fill Out CRF =====>		
Clinical Research	Design Protocol	Review and Finalize Protocol	Design CRF	Review and Finalize CRF		Study Initiation at Site		Review and Finalize Edit Check Specifications	Ongoing Study Monitoring =====>	Review and Finalize Statistical Analysis Plan
Biostatistics	Design Protocol	Review and Finalize Protocol		Review and Finalize CRF	Create Study Randomization		Develop Statistical Analysis Plan	Review and Finalize Edit Check Specifications		Review and Finalize Statistical Analysis Plan
Medical Affairs Central Files										CRFs In-House Ongoing =====>
Data Management		Review and Finalize Protocol	Design CRF	Review and Finalize CRF	Annotate CRF	Review and Finalize Annotated CRF	Design Edit Check Specifications	Review and Finalize Edit Check Specifications		Review and Finalize Statistical Analysis Plan
Statistical Programming		Review and Finalize Protocol		Review and Finalize CRF	Create Study Randomization	Review and Finalize Annotated CRF	Develop Statistical Analysis Plan	Review and Finalize Edit Check Specifications		Review and Finalize Statistical Analysis Plan
Research Computing						Review and Finalize Annotated CRF	Design and Create Database	Design and Create Data Entry Screens	Program Edit Checks	