

A Project Tracking and Analysis Application for Bioequivalence Trials

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ABSTRACT

Pat O'Meara Associates, Inc. performs analysis of clinical trials for pharmaceutical companies. One of the standard tasks is the analysis and reporting of bioequivalence trials. The process of performing the analysis and generating a report involved numerous individual modifications of SAS® programs to fit the specifics of a particular study. Directories and sub-directories to store the programs, data, output, and documents generated for the study were created and managed ad hoc. These process led to problems with consistency, completeness, efficiency, and was unwieldy. The application described is an effort to provide a consistent, efficient, and easy-to-use system for creating project directories and performing efficient analyses and report generation. Extensive use of SAS/AF®, Screen Control Language, and the Macro Facility helped form a cohesive application.

BACKGROUND

Prior to the development of this application, we relied on a system consisting of separate programs, each of which contained the particular study-specific parameters necessary for the task they were assigned to accomplish. These programs would be copied from a central location, modified to fit the particular study parameters, and executed in a particular order to perform the analyses and generate report output. If a modification was omitted or if the execution sequence was not followed properly, the results would not be correct. Also, from study to study, consistency in the way the parameters were defined could vary.

A second aspect of the existing process was that the subdirectory structure was created ad hoc. This also led to inconsistencies in directory definitions and naming. The existing process led to consistency and execution problems and required an

inordinate amount of quality control to assure the final product was acceptable.

We identified several major needs to be addressed by a new process. First, consistency in parameter definitions and directory nomenclature. This would help reduce the quality control time because all persons involved would be looking for the same thing and expecting a certain result. It would also aid in reducing programming errors by avoiding manual manipulation of the code. The code would be static and the system would define the parameter values. Second, efficiency needed to be increased. Reduction of the number of iterations necessary to produce a result and an easy to use system would give us a more marketable product by reducing turn-around time.

The specifications for the system were relatively simple. The system would be based in the SAS system. We began under Version 6.11 for Windows and migrated to Version 6.12 for Windows. The programming also began under Windows 3.1.1 and moved to Windows 95. Input and output capabilities needed to be compatible with Microsoft® Word and Excel software packages. For pharmacokinetic analysis, WinNonlin™, Standard Edition, Version 1.1 was our software of choice.

Based on the specifications, the following SAS software modules were used in the application: SAS/AF®, SAS/ACCESS®, SAS/FSP®, SAS/GRAPH®. Extensive use of Screen Control Language (SCL) and the Macro Facility were also used in the development of the application.

Some terms that will be used in the remainder of the paper are:

Screen or Frame: a SAS/AF screen used for selection or entry of parameters or to control execution.

Widget: a functional unit within a Frame. Example: a text entry box.

Program: a module of open SAS code or SCL code used to complete a certain task.

Macro: a set of commands meant to be used repetitively. Written using the SAS Macro Facility. May or may not contain macro variables.

Global: macro variables which are used throughout the entire application.

Local: macro variables which are used only within a particular program or macro.

Horizontal file or data set: a file or data set that lists sampling times are separate fields with a record. Records are data for one subject on one study period.

Vertical file or data set: a file or data set that has sampling time and concentration as variable fields and each record is data for one subject, one period, and one sampling time.

PROJECT SPECIFICATION SCREENS

The project specifications are entered into the application through the Project Definition, Set Up New Project, Study Design Information, and Select Project screens.

The Project Definition screen contains a radio box widget, where you select either to work with a defined project or to set up a new project. A push button widget to exit the system is also available as this is the entry and exit point for the system. In all subsequent screens, the Next Screen push button moves on to the next frame in the sequence and executes any behind the scenes processing, Previous Screen goes back one frame without processing, and Exit System brings you back to Project Definition in order to exit the system.

The Set Up New Project screen is where you enter, or select, the client name, project name, and drug name. Also, short form mnemonics for client and project are entered to be used in the directory set-up. For the client name, you may enter a new value or select from a pop-up menu of existing clients. If an existing client is selected, the previously defined mnemonic for the client directory is automatically filled in.

The Study Design Information screen begins the process of defining study parameters. First, the study type is selected as either Crossover or Parallel Group. If Crossover is selected, the five boxes immediately above the push buttons are uncovered. You then select whether WinNonlin is to be used and designate the number of compounds of interest, study periods, treatments, treatment sequence groups, subjects enrolled and subjects completed. Selection of the Next Screen push button causes the standard directory structure to be created and returns to the Project Definition screen. Now the project can be selected as a defined project. Defined projects are selected via the Select Project screen. This screen is similar to the Set Up New Project screen, except that both the client name and project name can be selected from pop-up menus. When these two parameters are selected, the other three are automatically selected. If a project has already been worked on, the fields will have that study's parameters from the current values of the global macro variables. New values may be selected or the current ones used.

UTILITY SCREENS

The Utilities screen offers a choice of tasks. You can define or modify parameter information, import or export data, view data, analyze data, or run a system validation against stored data. There is also an archive option that has not yet been activated. After execution of the task, control is returned to the Utilities screen.

Selecting to define or modify project information brings up the Project Information screen, which displays all the current definitions of the study parameters. Key

variable names, numbers of periods, treatments, sequence groups, and subjects, limit of quantitation and units of concentration and time, and sampling times are all defined. If you are working with a newly defined study, default values will appear in these fields. For a previously defined project, the values will represent the given values. A second Project Information screen finishes the definition process by defining the expected values for the period, treatment and sequence variables. All default or existing values may be modified. When exiting these screens, a new parameter definition file is created. This file contains macro code defining the values for the study parameter global macro variables. The specification file is included into programs during execution to update the defined values for these variables.

Import Data allows the application to create SAS data sets from other data sources. Currently defined sources are PC-based files and ASCII text files. The orientation of the file, columns that correspond to particular variables, and the formats of key variables are defined. For ASCII files, the field delimiter is also defined. For the PC-based files, the application generates a SAS/ACCESS descriptor and view and reads the data into a data set. A corresponding data set of opposite orientation is also created as the application uses both horizontal and vertical data sets. For the ASCII files, a DATA step with an INFILE statement is generated to read the raw data into a data set. In all files, key variable fields are assumed to be present: subject, period, treatment, and sequence.

View Data uses SAS/FSP to browse the concentration-time or pharmacokinetic (PK) parameter data sets. Two choices of concentration data set are listed: CONCEN1, which is the horizontal set; and CONCEN2, which is the vertical set. The PK parameter data set is created after doing the PK analysis using WinNonlin.

The Analysis Utilities screen offers a choice of doing the PK analysis with WinNonlin or the statistical analysis. Selecting WinNonlin moves you to the WinNonlin screen, where a

choice of editing the WinNonlin command file or running WinNonlin is made. The command file controls the execution of WinNonlin analysis. This file is originally a template that needs to be modified for the particular study. Removing the need to manually edit this file is a pending modification of the application. After the command file has been modified, WinNonlin may be run and the PK parameters computed and stored. When WinNonlin is terminated, the PK parameter data set is generated to be used in subsequent analysis.

The statistical analysis is performed by a set of standardized SAS programs. The programs analyze the PK parameters and generate output files for inclusion in the report. You may select all output, just the statistical output, just the summary tables, or just the graphical figures to be generated. Tables generated include concentration-time tables, PK parameter tables, tables showing the derivation of the AUC(0- ∞) parameter (if necessary), and bioequivalence comparison tables. Figures include mean concentration-time plots in both linear and semi-logarithmic scales, individual concentration-time profiles, and confidence interval plots. The statistical output consists of detailed analysis procedure output and a log of the statistical analysis job.

Exporting Data is similar to the Import Data in that specific data formats are listed. The formats are the same as in Import Data, except that a SAS transport file has been added. Check boxes indicate which data are to be exported and a status box shows the files that are created.

CONCLUSION

The prior process involved manual modification of programs and ad hoc definition of directory structure. This created opportunities for inconsistent definition of parameters and directory nomenclature, necessitated more intense quality control, and led to reduced efficiency and increased turn-around time and number of iterations of processes.

A new system was needed to address the need for more consistent output and ease of use. It also needed to reduce iterations and turn-around time and to alleviate the intensity of the quality control process.

A solution was devised around current program code. The program code was modified to be more generic and to utilize global and local macro variables and code to pass parameter values and to accomplish certain tasks without programmer intervention. An application based in SAS/AF and Screen Control Language was used to control the process, enter parameter values, and perform certain quality control tasks such as review of data and correction of parameter definitions.

The application has been used on several projects and is still in the 'beta' stage of development. Additional functionality, such as archiving of data and automated generation of the WinNonlin command file, remain to be developed. Overall, the application described here has met many of the needs for which it was targeted.

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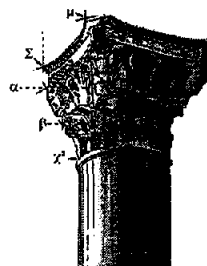
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